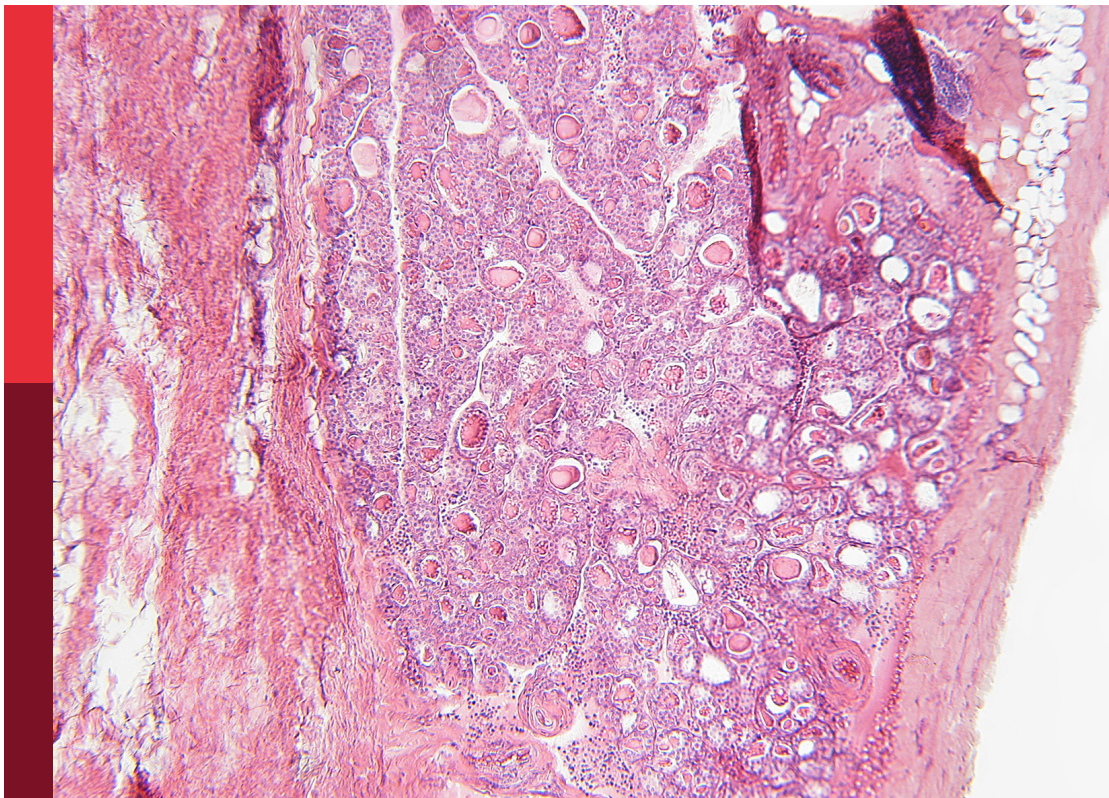
frontiers | Research Topics

Innovation in diabetes self-care management and interventions

Edited by
Edward Zimbudzi, Martha M. Funnell, Hiroshi Okada, and Masahide Hamaguchi

Published in
Frontiers in Endocrinology
Frontiers in Public Health



ISSN 1664-8714
ISBN 978-2-8325-2914-0
DOI 10.3389/978-2-8325-2914-0

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Innovation in diabetes self-care management and interventions

Topic editors

Edward Zimbudzi — Monash University, Australia
Martha M. Funnell — University of Michigan, United States
Hiroshi Okada — Matsushita Memorial Hospital, Japan
Masahide Hamaguchi — Kyoto Prefectural University of Medicine, Japan

Citation

Zimbudzi, E., Funnell, M. M., Okada, H., Hamaguchi, M., eds. (2023). *Innovation in diabetes self-care management and interventions*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-2914-0

Table of contents

frontiers | Frontiers in Endocrinology

TYPE Editorial
PUBLISHED 21 August 2023
DOI 10.3389/fendo.2023.1269437

OPEN ACCESS

EDITED AND REVIEWED BY
Åke Sjöholm,
Gävle Hospital, Sweden

*CORRESPONDENCE
Edward Zimbudzi
edward.zimbudzi@monash.edu

RECEIVED 30 July 2023
ACCEPTED 11 August 2023
PUBLISHED 21 August 2023

CITATION
Zimbudzi E, Okada H, Funnell MM and Hamaguchi M (2023) Editorial: Innovation in diabetes self–care management and interventions. *Front. Endocrinol.* 14:1269437. doi: 10.3389/fendo.2023.1269437

Editorial: Innovation in diabetes self–care management and interventions

Edward Zimbudzi[1,2,3]*, Hiroshi Okada[4], Martha M. Funnell[5] and Masahide Hamaguchi[4]

[1]School of Nursing and Midwifery, Monash University, Melbourne, VIC, Australia, [2]Department of Nephrology, Monash Health, Melbourne, VIC, Australia, [3]School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia, [4]Department of Endocrinology and Metabolism, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [5]Department of Learning Health Sciences, University of Michigan Medical School, Ann Arbor, MI, United States

KEYWORDS

self-management, innovation, diabetes complications, technology, patient-centered interventions

Editorial on the Research Topic
Innovation in diabetes self–care management and interventions

In recent years, the number of patients with type 2 diabetes mellitus (T2DM) has increased. In 2021, it was estimated that 537 million adults worldwide were living with diabetes with the total number projected to rise to 643 million by 2030 (1). In view of this, new innovations including person-centered self-management interventions are needed to prevent new onset of diabetes and the development of complications associated with diabetes. Over the past two decades, a significant number of diabetes self-management education and support programmes have been developed and translated into practice (2). Multiple studies and meta-analyses have shown that these programmes are efficacious and cost-effective in promoting and facilitating self-management and improvements in patients' knowledge, biomedical, behavioural, and psychosocial outcomes have been reported (3–7). Among this array of diabetes self-management education programmes, variations in method of delivery, content, duration, setting, and use of technology and person-centred philosophy need to be acknowledged (2). Most importantly, questions need to be asked regarding the usefulness of some programmes, which are anchored on the traditional provider–patient relationship due to a huge shift towards a paradigm in which individuals with diabetes play a key role in guiding their care, in partnership with health care providers. Within this context, we launched our Research Topic on April 7th, 2022, and invited researchers to submit articles that explore *Innovations and Interventions in Diabetes Self-Management and Interventions.*

This Research Topic reports on new insights, challenges, and future directions regarding innovations in diabetes self-management. The Research Topic generated a lot of interest across a broad range of critical issues resulting in the publication of 13 articles

(all in Frontiers in Endocrinology), involving 113 authors from 7 countries. These articles covered the following themes; (1) use of technology in managing complications of diabetes and (2) novel approaches to optimise diagnosis, monitoring and self-management interventions for people with diabetes.

A first line of research includes contributions examining the use of technology in addressing complications associated with diabetes. One of the complications of diabetes is Erectile Dysfunction (ED) which affects over two-thirds of men (8), and this is normally treated with phosphodiesterase type 5-inhibitors (PDE5is). However, a substantial number of people with ED do not respond to PDE5is necessitating the use of other therapies. Tao et al. show that the combined therapy of low intensity extracorporeal shock wave treatment (Li-ESWT) and vacuum erectile device (VED) is more beneficial to shift turn PDE5is non-responders to responders for moderate impotence men with diabetes than Li-ESWT or VED monotherapy due to their synergistic effect. Diabetic foot ulcers (DFU) are also a well-recognised complication of diabetes. Sousa et al. report on a protocol of a study that aims to develop innovative footwear to prevent DFU, specifically a shoe and sensor-based insole, which will allow for monitoring pressure, temperature, and humidity parameters.

A second stream of research includes studies that focus on novel approaches to optimise diagnosis, monitoring and self-management interventions for people with diabetes. Two studies from Sun et al. and Byeon et al. report on nomograms that can be used to optimize screening of diabetes mellitus in people at risk of diabetes. These two studies address a very important concept that may result in the reduction of the lead time between diabetes onset and clinical diagnosis allowing for prompt multifactorial treatment to be initiated if warranted. Another study established a model using fasting capillary blood glucose (FCG) and postprandial capillary blood glucose (PCG) together to predict HbA1c in patients with T2DM (Yuan et al.). This approach provides an available and convenient way to convert real-time SMBG readings to HbA1c resulting in timely management by people with T2DM. While it is recognised that SMBG is one of the pillars of diabetes management for patients with diabetes, we need to better support our patients in implementing and using the data for daily decision-making from SMBG (9). In relation to this, Lin et al. described the current status of SMBG among pre-diabetes patients and those with T2DM, explored the relationship between SMBG frequency and blood glucose level and analyzed the potential factors that influence patient implementation and use of SMBG based on electronic questionnaires using the information-motivation-behavior model.

In prediabetes, it is known that weight loss can delay the onset or decrease the risk for T2DM, while in established T2DM weight loss improves glycaemic control, with severe calorie restriction even reversing the progression of T2DM (10). In view of this, a study by Almeida et al. show that a technology-enhanced diabetes prevention program is effective in reducing body mass index at 6 months and maintaining these results at 12 and 18 months in a group of primary care patients at risk for developing T2DM. Matsui et al. investigated the association between change in body weight and T2DM remission in Japanese men with new-onset T2DM. A weight loss of ≥5% effectively achieved diabetes remission for those with a BMI ≥25 kg/m^2 and new-onset T2DM.

Exercise is one of the first management approaches advised for patients newly diagnosed with T2DM. Matsushita et al. investigated the effects of physical therapists' exercise instructions among Japanese patients with T2DM. After 8 weeks of follow up, HbA1c levels were significantly better in the intervention group than among the non-intervention group (7.3% [6.8-%–7.9%] vs. 7.4% [7.3%–7.7%], P = 0.04). Additionally, the intervention group had more improved motor skills than the non-intervention group, and the transtheoretical model varied in the intervention group but not in the non-intervention group between before and after intervention.

Feng et al. conducted a randomized double-blind placebo-controlled trial to explore the effects of a highly active α-amylase inhibitor derived from white common bean extract (WCBE) on glucose metabolism and diabetes complications in patients with T2DM. There was a greater reduction in HbA1c levels among patients who received the WCBE compared to those who did not at the end of the 2-month intense intervention (0.660 ± 0.468% vs. 0.222 ± 0.763%, p<0.05) and at the end of the second 2-month intervention (0.721 ± 0.742% vs. 1.059×10-8 ± 0.942%, p<0.05) suggesting that using this dietary supplement can potentially lower HbA1c levels. The proportion of patients with diabetic peripheral neuropathy (measured by the Toronto Clinical Scoring System, TCSS ≥ 6) was significantly lower in the intervention group compared to the control group. Additionally, both the left and right sural sensory nerve conduction velocity slightly decreased among those in the control group and slightly increased in the intervention group suggesting that the intervention may potentially improve complications such as diabetic vasculopathy and neuropathy.

A systematic review from Racey et al. explored the effects of health coaching with adults with T2DM based on patient-reported outcomes, clinical outcomes, provider satisfaction, and cost-effectiveness. Findings from this study suggest that health coaching interventions can have short term impact beyond glucose management on cardiometabolic and mental health outcomes. In another systematic review (Racey et al.), the same authors examined aspects of diabetes health coaching interventions for adults living with T2DM that have been reported using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework to optimize implementation. They found that there is paucity of reporting of the RE-AIM components for diabetes health coaching leading to limited implementation and clinical practice implications that can be drawn.

A study from Moghaddam et al. examined the determinants of quality of life among elderly patients based on problem areas in diabetes (PAID). As expected, they report that treatment barriers, psychological distress related to the burden of diabetes, the type of treatment, and age had a negative impact on the quality of life of elderly patients. Findings from this study reinforce the importance of considering diabetes-specific distress, treatment barriers and patient barriers and preferences when discussing interventions.

Overall, these findings highlight that patient-centered interventions to support self-management of diabetes and its complications are evolving. Notably, it is encouraging to see that a number of these interventions embrace the use of technology. The strengths of these contributions include the use of randomised control trials and systematic reviews and meta-analyses to examine the effect of interventions on outcomes. However, results from some studies may not be generalisable due to the inclusion of people whose BMI was lower than that of other populations. Additionally, the long-term efficacy and safety of some interventions still needs to be ascertained. Nevertheless, we are confident that all the selected studies in our Research Topic bring important perspectives to the understanding of current innovations in diabetes self-management and person-centered interventions.

Author contributions

EZ: Writing – original draft, Writing – review & editing. HO: Writing – review & editing. MF: Writing – review & editing. MH: Writing – review & editing.

Acknowledgments

We sincerely thank all the authors and reviewers who participated in this Research Topic.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* (2022) 183:109119. doi: 10.1016/j.diabres.2021.109119

2. Chatterjee S, Davies MJ, Heller S, Speight J, Snoek FJ, Khunti K. Diabetes structured self-management education programmes: a narrative review and current innovations. *Lancet Diabetes Endocrinol* (2018) 6:130–42. doi: 10.1016/S2213-8587(17)30239-5

3. Hopkins D, Lawrence I, Mansell P, Thompson G, Amiel S, Campbell M, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the UK DAFNE experience. *Diabetes Care* (2012) 35:1638–42. doi: 10.2337/dc11-1579

4. Speight J, Holmes-Truscott E, Harvey DM, Hendrieckx C, Hagger VL, Harris SE, et al. Structured type 1 diabetes education delivered in routine care in Australia reduces diabetes-related emergencies and severe diabetes-related distress: The OzDAFNE program. *Diabetes Res Clin Pract* (2016) 112:65–72. doi: 10.1016/j.diabres.2015.11.002

5. Chrvala CA, Sherr D, Lipman RD. Diabetes self-management education for adults with type 2 diabetes mellitus: A systematic review of the effect on glycemic control. *Patient Educ Couns* (2016) 99:926–43. doi: 10.1016/j.pec.2015.11.003

6. Pillay J, Armstrong MJ, Butalia S, Donovan LE, Sigal RJ, Vandermeer B, et al. Behavioral programs for type 2 diabetes mellitus: a systematic review and network meta-analysis. *Ann Internal Med* (2015) 163:848–60. doi: 10.7326/M15-1400

7. Powell RE, Zaccardi F, Beebe C, Chen XM, Crawford A, Cuddeback J, et al. Strategies for overcoming therapeutic inertia in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* (2021) 23:2137–54. doi: 10.1111/dom.14455

8. Getie Mekonnen E, Yeshita HY, Bishaw Geremew A. Sexual dysfunction among men with diabetes mellitus attending chronic out-patient department at the three hospitals of Northwest Amhara region, Ethiopia: Prevalence and associated factors. *PloS One* (2021) 16:e0256015. doi: 10.1371/journal.pone.0256015

9. Hu Z-D, Zhang K-P, Huang Y, Zhu S. Compliance to self-monitoring of blood glucose among patients with type 2 diabetes mellitus and its influential factors: a real-world cross-sectional study based on the Tencent TDF-I blood glucose monitoring platform. *mHealth* (2017) 3:25. doi: 10.21037/mhealth.2017.06.01

10. Wilding J. The importance of weight management in type 2 diabetes mellitus. *Int J Clin Pract* (2014) 68:682–91. doi: 10.1111/ijcp.12384

frontiers | Frontiers in Endocrinology

ORIGINAL RESEARCH
published: 23 June 2022
doi: 10.3389/fendo.2022.937958

The Efficacy of Li-ESWT Combined With VED in Diabetic ED Patients Unresponsive to PDE5is: A Single-Center, Randomized Clinical Trial

Rongzhen Tao[1†], Jianhuai Chen[2†], Dujian Wang[1], Yunpeng Li[1], Jun Xiang[3], Lei Xiong[1], Junbiao Ji[1], Jie Wu[1], Shuang Zhou[1], Chunping Jia[1], Jianlin Lv[1], Jie Yang[4,5] and Qinglai Tang[1*]*

[1] Department of Urology, The Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing, China, [2] Department of Andrology, Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China, [3] Department of Ultrasound, The Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing, China, [4] Department of Urology, Jiangsu Provincial People's Hospital, First Affiliated Hospital of Nanjing Medical University, Nanjing, China, [5] Department of Urology, People's Hospital of Xinjiang Kizilsu Kirgiz Autonomous Prefecture, Xinjiang, China

OPEN ACCESS

Edited by:
Hiroshi Okada,
Matsushita Memorial Hospital, Japan

Reviewed by:
Nicola Caretta,
University Hospital of Padua, Italy
Noriyuki Kitagawa,
Kameoka Municipal Hospital, Japan

***Correspondence:**
Qinglai Tang
tql7807@163.com
Jie Yang
yj197912@163.com

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

Received: 06 May 2022
Accepted: 23 May 2022
Published: 23 June 2022

Citation:
Tao R, Chen J, Wang D, Li Y, Xiang J, Xiong L, Ji J, Wu J, Zhou S, Jia C, Lv J, Yang J and Tang Q (2022) The Efficacy of Li-ESWT Combined With VED in Diabetic ED Patients Unresponsive to PDE5is: A Single-Center, Randomized Clinical Trial. Front. Endocrinol. 13:937958. doi: 10.3389/fendo.2022.937958

Introduction: Phosphodiesterase type 5-inhibitors (PDE5is) are the first-line treatment for patients with diabetes mellitus-induced erectile dysfunction (DMED), however, some patients are non-responser to PDE5is. We performed a perspective, randomized, comparative study to explore the efficacy of low intensity extracorporeal shock wave treatment (Li-ESWT) combined with vacuum erectile device (VED) in the treatment of DMED patients who were unresponsive to PDE5is.

Methods: One hundred and five eligible patients were randomly divided into three groups: group A (VED), group B (Li-ESWT) and group C (VED plus Li-ESWT). Follow-up was conducted at 4 weeks, 8 weeks and 12 weeks after the end of treatment. The erectile function was estimated by the international index of erectile function-erectile function domain (IIEF-EF), erection hardness score (EHS), sexual encounter profile questions 2 and 3 (SEP2 and SEP3) and global assessment question 1 and 2 (GAQ1 and GAQ2) before and after treatment. The changes of five points in IIEF-EF were calculated as the minimal clinical important difference (MCID), which was considered as the main index of efficacy.

Results: The MCID was achieved in 14.7%, 14.7% and 17.6% patients in group A at the follow up on 4 weeks, 8 weeks and 12 weeks, respectively (36.4%, 39.4% and 36.4% in group B; 36.4%, 51.5%, and 66.7% in group C). There were significant differences in the percentage of MCID cases between group A and group C at the follow up on 12 weeks ($P<0.001$), as well as that between group B and group C ($P=0.014$). Additionally, comparison in MCID within group C showed that there were significant differences between 4 weeks and 12 weeks follow-up ($P=0.014$).

Conclusion: Our findings indicated the combined therapy Li-ESWT and VED was more beneficial to shift turn PDE5is non-responders to responders for moderate patients with

DMED than VED or Li-ESWT monotherapy. Moreover, this study provided evidence that patients with DMED who failed after taking oral PDE5is could attempt to opt for an alternative physicotherapy (Li-ESWT or VED) prior to more invasive alternatives.

Keywords: erectile dysfunction, diabetes mellitus, low intensity extracorporeal shock wave treatment, vacuum erectile device, phosphodiesterase type 5-inhibitors

INTRODUCTION

Diabetes mellitus (DM) is a common disease with a relative high prevalence of 9-11% (1, 2). One-third of patients have a microvascular complication at the time of diagnosis of diabetes, while more than half of male patients with diabetes will eventually develop ED and the treatment rate of ED in younger men with type 2 diabetes is up to four times higher than those without diabetes (3, 4). Phosphodiesterase type 5-inhibitors (PDE5is) are the first-line for these patients. However, clinical studies on effectiveness of oral PDE5i are mainly aimed at patients with mild to moderate diabetes mellitus-induced erectile dysfunction (DMED) (5, 6). Moderate and severe diabetic ED patients who are non-responser to PDE5is have to choose other options or PDE5is combined with novel emerging therapies (7).

In recent years, low intensity extracorporeal shock wave treatment (Li-ESWT), as a strongly-recommended option by increasing experts from various countries in the world, has been becoming a promising and encouraging physical modality, according to its satisfactory efficacy and safety, especially for ED patients with vascular factor (8–10). One double-blind, sham controlled study demonstrated that penile low intensity shock wave treatment was able to shift PDE5is non-responders to responders (11). Nevertheless, the other study on elevating long time effect of Li-ESWT found that the diabetic patients with severe ED who were initially successful had lost the effect of LI-ESWT during two-year follow-up (12). Meanwhile, diabetic patients with moderate to severe ED who were PDE5is non-responders, might be necessary to be received comprehensive management protocol or implantation of penile prosthesis (IPP) to obtain long-term efficacy (13).

Vacuum erectile device (VED), as yet, is simple, reversible and effective second-line therapeutic strategy for patients with PDE5i refused or failed, as well as for diabetic ED patients. Vacuum with a mechanical pump can enlarge penis, maintain penile length, get a non-physiological erection and augment an erection even in difficult-to-treat population (14, 15). Although intracavernosal and transurethal alprostadil is also effective in diabetic patients with ED of mixed aetiology (16, 17), however, the second-line therapeutic management is not usually accepted by patients and/or their sexual partners as a long-term therapeutic measure due to common adverse events such as burning, erythema, pain sensations from patients and vaginal burning or itching from sexual partners. VED could offer a viable alternative to intracavernosal injection, transurethral suppositories or topical administration of vasoactive agents (18).

Based on current conditions that most patients with mild DMED are effective with PDE5is, and those who are ineffective often have significantly improved symptoms after PDE5is combined with Li-EWST or VCD, while non-surgical treatment invalid patients with refractory and severe DMED usually have to receive IPP if they intend to the ideal curative effects, in spite of relatively significant postoperative pain (19). Therefore, initial PDE5is non-response patients with moderate DMED were selected as subjects of this study, and we performed a perspective, randomized, comparative study to explore whether Li-ESWT combined with VED was more effective than Li-ESWT or VED monothepy in the treatment of PDE5is non-responser with moderate DMED.

MATERIALS AND METHODS

Subjects

The subjects of this study were diagnosed with DMED (T2DM) in the urology and andrology clinic of the Affiliated Jiangning Hospital of Nanjing Medical University from October 2019 to September 2021. Their medical history was more than six months and all of them were non-responders after using the maximum tolerated dose of PDE5is along with adequate sexual stimulation for more than 6 times (20). Total of 105 subjects were finally eligible. All patients were randomly divided into three groups with 35 cases in each group: group A (VED), group B (Li-ESWT) and group C (VED plus Li-ESWT).

Inclusive criteria: (1) patients with DMED (T2DM), aged between 20-65; (2) IIEF-EF: 11-16 scores; (3) fixed sexual partner maintaining a normal sexual relationship and trying sexual behavior at least once a week from the beginning to the end of the study; and (4) normal reproductive hormone, and erection hardness score (EHS) ≤ 2 and peak systolic velocity (PSV) < 25cm/s 10-15 min after the intracavernous injection of 10 ug prostaglandin E1 (PGE1).

Exclusive criteria: (1) severe diabetic complications were excluded, such as neuropathy, nephropathy, and retinopathy; (2) mental and psychological diseases, serious cardiovascular (including hypertension) and cerebrovascular diseases, liver and kidney dysfunction, malignant tumors, alcohol dependence and abnormal coagulation function; (3) hepatitis B/hepatitis C/HIV infection, spinal cord injury, genitourinary tract injury, inflammation, and external genital malformations; (4) ED patients with other organic or endocrine factors such as severe thyroid disease, end-stage renal failure, non-diabetic related metabolic diseases (including dyslipidemia), sleep disorders

and other systemic diseases; (5) history of ED related surgery or treatment, such as radical prostatectomy, pelvic radiologic therapy; (6) bleeding disorders and those on anticoagulation therapy.

The age, duration of disorder, body mass index (BMI), IIEF-EF (baseline), EHS (baseline), testosterone, and PSV (baseline) of penile cavernous artery measured by color duplex doppler ultrasound (CDDU) were evaluated in each group of this study. In addition, this study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and approved by local ethical committee (No. 2019-03-026-k01). All patients gave their informed consent to the collection of clinical data in a prospectively maintained database and to the use of these data for research purposes.

Schedule and Protocol

VED: Patients in group A and C were treatment with penile vacuum erectile device (Osbon, Timm Medical Technologies, Eden Prairie, MN, USA). Subjects were made sure to practiced how to use VED successfully by personal tutoring and watching an instructional video before enrollment of the study. Each treatment time was 15 minutes during 9-week trail period, which include repeatedly creating penile erection by pumping gradually and becoming penile softness by releasing vacuum, without the use of tension ring, 3 times a week.

Li-ESWT: Patients in group B and C were treated with electromagnetic type Li-ESWT (HD. ESWO-I, 80mm diameter, focusing probe, Shenzhen Hyde Medical Equipment Co., Ltd. Shenzhen, China). These patients were treated twice a week. After 3 weeks of treatment, they were intermittently treated for 3 weeks and then treated for 3 weeks, a total of 12 times. The treatment parameter was set under the shock pressure 7.5KV and pulse frequency 100 times/min, and the position of treatment was located in the distal, body and crura of each left and right side of penile cavernous body. Each site was impacted 300-400 times, a total of 1800-2400 times.

Li-ESWT plus VED: The treatment protocol of this group integrated that of the above two groups, and the interval between two treatments was necessary to be more than 24 hours.

All patients who participated in the studies were not allowed to receive PDE5is 1 month before and during the study. After the last treatment, they were allowed to consume PDE5is on demand. Schedule and protocol of the study was shown in **Supplementary Figure 1**.

Follow-Up and Assessment of Therapeutic Efficacy

All subjects were assessed at 4 weeks, 8 weeks and 12 weeks after the end of treatment. The efficacy was measured by IIEF-EF, EHS, sexual encounter profile question 2 and 3 (SEP2 and SEP3), Global Assessment Question 1 and 2 (GAQ1 and GAQ2). Effectiveness at 4th, 8th, 12th week follow-up was determined by the score changes of IIEF-EF from baseline according to the minimal clinical important difference (MCID) (21) i.e. an increase of at least 5 points for moderate ED. Mean EHS level and per patient percentage of "yes" responses to SEP2 (successful penetration), SEP3 (successful intercourse), GAQ1 (improving erectile function) and GAQ2 (improving the ability to engage in sexual activity) were investigated as treatment outcomes.

Statistical Analyses

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) software. Firstly, the Shapiro-WilK test was used to test the normality of the initial descriptive data of continuous variables, which were expressed as mean ± SD or median (25%,75% quantile), and were compared using t-test or Mann-Whitney U test, as appropriate. Proportions were expressed as absolute numbers and percentages and compared using the Chi-squared test or Wilcoxon rank sum test as appropriate. The one-way analysis of variance (ANOVA) was performed to compare the mean IIEF-EF score changes with respect to baseline in subgroups A, B, and C. $P<0.05$ was taken to indicate statistical significance. Z-test was used for testing two proportions the with unpooled variance and the power was computed using the normal approximation method by PASS 15.0.5 (NCSS, Kaysville, Utah, USA).

RESULTS

Demographic and Clinical Characteristics of Patients

One hundred patients completed the clinical trial and obtained all data (group A: 34 cases, group B: 33 cases and group C: 33 cases). Baseline characteristics of patients with DMED in three groups were shown in **Table 1**. There were no significant differences in the age, course of ED, BMI, testosterone level, IIEF-EF scores, EHS and PSV values of penile cavernous artery before treatment ($P>0.05$).

TABLE 1 | Baseline characteristics of patients with diabetic erectile dysfunction in three groups.

Parameters	Group A (n = 34)	Group B (n = 33)	Group C (n = 33)	F Value	P Value
Age (mean ± SD, yr)	47.97 ± 5.69	46.70 ± 4.93	48.30 ± 3.49	1.032	0.360
ED Duration (mean ± SD, m)	45.53 ± 21.95	43.88 ± 27.16	45.27 ± 25.06	0.043	0.958
BMI (mean ± SD, points)	23.11 ± 5.99	23.33 ± 4.84	23.99 ± 3.36	0.296	0.744
Baseline PSV (mean ± SD, cm/s)	16.03 ± 2.05	15.86 ± 2.03	15.94 ± 2.36	0.050	0.497
Testosterone (mean ± SD, nmol/l)	15.29 ± 2.74	15.35 ± 2.46	14.85 ± 2.19	0.398	0.436
IIEF-EF (score)	13.38 ± 1.71	13.48 ± 1.62	13.30 ± 1.61	0.101	0.904
EHS (score)	1.82 ± 0.39	1.85 ± 0.36	1.82 ± 0.39	0.060	0.942

The data was analyzed by one-way analysis of variance (ANOVA) with a significance level alpha=0.05. ED, erectile dysfunction; BMI, body mass index; PSV, peak systolic velocity of penile artery; IIEF-EF, international index of erectile function erectile function domain; EHS, erection hardness score.

Comparison of Efficacy Among and Within the Three Groups

The parameters of therapeutic efficacy included the proportion of cases achieving MCID (improving in IIEF-EF score is more than 5 score), the proportion of patients reporting successful penetration (SEP2), the proportion of patients reporting successful intercourse (SEP3), the proportion of cases improving erectile function (GAQ1), and the proportion of cases improving the ability to engage in sexual activity (GAQ2). The difference of parameters of therapeutic efficacy among three groups and within each group at all follow-up time points were shown in **Table 2**.

MCID, a change of 5 IIEF-EF points for moderate ED, was considered as the main index of efficacy, MCID in group A was achieved in 14.7%, 14.7%, and 17.6% of patients at the follow up on 4, 8, and 12 weeks, respectively. In group B, MCID was achieved in 36.4.6%, 39.4%, and 36.4% of patients at the follow up on 4, 8, and 12 weeks, respectively. In group C, MCID was achieved in 36.4%, 51.5%, and 66.7% of patients at the follow up on 4, 8, and 12 weeks, respectively. The differences among the groups in MCID were shown in **Table 3**.

The results of MCID differences within and between groups showed that the combination therapy was more beneficial than VED monotherapy at 12 weeks follow-up (P<0.001), and the power was 0.997 at a significance level of 0.05. Meanwhile, the combination therapy was more effective than Li-ESWT monotherapy at 12 weeks follow-up (P=0.014), although the power was 0.734 at a significance level of 0.05. The results of comparison within the combination therapy group showed that there were significant differences in MCID between 4 and 12 weeks of follow-up (P=0.014; **Table 4**), and the power was 0.824 at a significance level of 0.05.

There were significant differences among there groups in the mean IIEF-EF scores and EHS, as well as SEP2 and GAQ1 at the 8th and 12th week follow-up. Additionally, there were significant differences in the average IIEF-EF scores and EHS between pre & post-treatment in each group (P<0.001), and at all follow-up time points in Group C (P=0.013), however, no differences were found at all follow-up time points in Group A and Group B (**Table 2** and **Figure 1**). There were no significant differences in SEP2, GAQ1 and GAQ2 among three groups at the 4th week follow-up, except for SEP3. Moreover, there were no remarkable differences in SEP3 and GAQ2 among three groups at the 8th and 12th week follow-up, and in the mean IIEF-EF scores and EHS at the 4th week follow-up.

Comparison of Complications Among Three Groups

During treatment and follow-up, there were no moderate and severe penile pain or local ecchymosis cases in all patients. The 2 cases of mild pain and 1 case of mild local ecchymosis recovered without special management in each group. There were no marked differences in therapeutic complications among three groups.

TABLE 2 | The differences of parameters of therapeutic efficacy among three groups and within each group at various follow-up points.

Parameters	Follow-up	Group A	Group B	Group C	Chi-square value	P value
MCID (yes%,n)	4w	14.7%, 5	36.4%, 12	36.4%, 12	5.112	0.078
	8w	14.7%, 5	39.4%, 13	51.5%, 17	10.392	0.006*
	12w	17.6%, 6	36.4%, 12	66.7%, 22	17.038	<0.001*
	Chi-square value	0.148	0.086	6.066		
	P value	0.929	0.958	0.048*		
SEP2	4w	29.4%, 10	45.5%, 15	42.4%, 14	2.054	0.358
(yes%,n)	8w	26.5%, 9	42.4%, 14	57.6%, 19	6.655	0.036*
	12w	29.4%, 10	39.4%, 13	66.7%, 22	10.016	0.007*
	Chi-square value	0.096	0.248	4.009		
	P value	0.953	0.883	0.135		
SEP3	4w	8.8%, 3	18.2%, 6	27.3%, 9	12.786	0.002*
(yes%,n)	8w	8.8%, 3	18.2%, 6	21.2%, 7	2.087	0.352
	12w	8.8%, 3	21.2%, 7	24.2%, 8	3.042	0.219
	Chi-square value	–	0.130	0.330		
	P value	–	0.937	0.848		
GAQ1	4w	35.3%, 12	51.5%, 17	45.5%, 15	1.831	0.400
(yes%,n)	8w	32.4%, 11	45.5%, 15	63.6%, 21	6.626	0.036*
	12w	35.3%, 12	45.5%, 15	66.7%, 22	6.843	0.033*
	Chi-square value	0.087	0.324	3.580		
	P value	0.957	0.850	0.167		
GAQ2	4w	14.7%, 5	27.3%, 9	36.4%, 12	3.830	0.147
(yes%,n)	8w	14.7%, 5	36.4%, 12	36.4%, 12	5.112	0.078
	12w	14.7%, 5	36.4%, 12	39.4%, 13	5.810	0.055
	Chi-square value	–	0.818	0.086		
	P value	–	0.664	0.958		

*The proportions were expressed as percentages and compared using the Chi-squared test. MCID(yes%): The percentage of patients meeting MCID≥ 5 score; SEP2(yes%): The percentage of patients reporting successful penetration; SEP3(yes%): The percentage of patients reporting successful intercourse; GAQ1 (improving erectile function), GAQ2 (improving the ability to engage in sexual activity). *P<0.05, there were statistically significant difference.*

TABLE 3 | The differences of chi-square statistical outcome in percentage of MCID cases between each two groups.

groups	4-week follow-up		8-week follow-up		12-week follow-up	
	Chi-Square	P value	Chi-Square	P value	Chi-Square	P value
Group A vs. Group B	4.148	0.042*	5.195	0.023*	2.986	0.084
Group A vs. Group C	4.148	0.042*	10.288	<0.001*	16.542	<0.001*
Group B vs. Group C	–	–	0.978	0.323	6.066	0.014*

*The data of percentages was compared by the Chi-squared test. *P<0.05, there were statistically significant difference.*

TABLE 4 | The differences of chi-square statistical outcome in percentage of MCID cases between each two various follow-up points.

Follow-up	Group A		Group B		Group C	
	Chi-Square	P value	Chi-Square	P value	Chi-Square	P value
4th week vs. 8th week	–	–	0.064	0.800	1.538	0.215
4th week vs. 12th week	0.108	0.742	–	–	6.066	0.014*
8th week vs. 12th week	0.108	0.742	0.064	0.800	1.567	0.211

*The data of percentages was compared by the Chi-squared test. *P<0.05, there were statistically significant difference.*

DISCUSSION

Over the past few decades, accumulating evidences demonstrated that the occurrence and development of DMED possibly involved in multifactorial pathogenesis including metabolic, neurologic, vascular and muscular components (22–25). Recently, L-arginine, as an alternative treatment which is an essential substance for the synthesis of nitric oxide (NO), might be benefit for diabetic erectile dysfunction (26). Previous study indicated that there was a synergistic effect of the combination therapy L-Arginine plus tadalafil and combination therapy was superior to monotherapies (27). More and more combined therapeutic schemes had obtained satisfactory outcomes in patients with complicated ED of specific etiology, such as PDE5is combined with VED in the management of postprostatectomy erectile dysfunction (pPED) (28). Despite widespread use of combination therapy in clinical research and practice of ED (29), no published data are available concerning the efficacy of intensity extracorporeal shock wave combined with vacuum erectile device for patients with diabetic ED. We introduced the concept of combination therapy into the study to explore a more effective and safe treatment strategy by combination therapy of vacuum device, shockwaves and on demand oral PDE5is, for initial non-response to PDE5is diabetic patients with moderate erectile dysfunction. In this study, we found that monotherapy with VED or Li-ESWT might be have certain effects (in MICD) on moderate vascular DMED (17.6%, 36.4%, respectively). More importantly, combination therapy VED and Li-ESWT showed more effective than monotherapy in MICD (66.7%), as well as synergistic benefits in the short term. The potential mechanisms may be related to the underlying rehabilitation effect of vacuum erectile device in the prevention of cavernosal fibrosis and presence of promotion of low-intensity shock wave in penile nervous, vascular, and muscular tissue regeneration and improvement of endothelial function (30–32).

According to an initial study by Price et al. (33), 75% (33/44) of diabetic men with impotence were able to have satisfactory intercourse by vacuum tumescence therapy, which was regarded

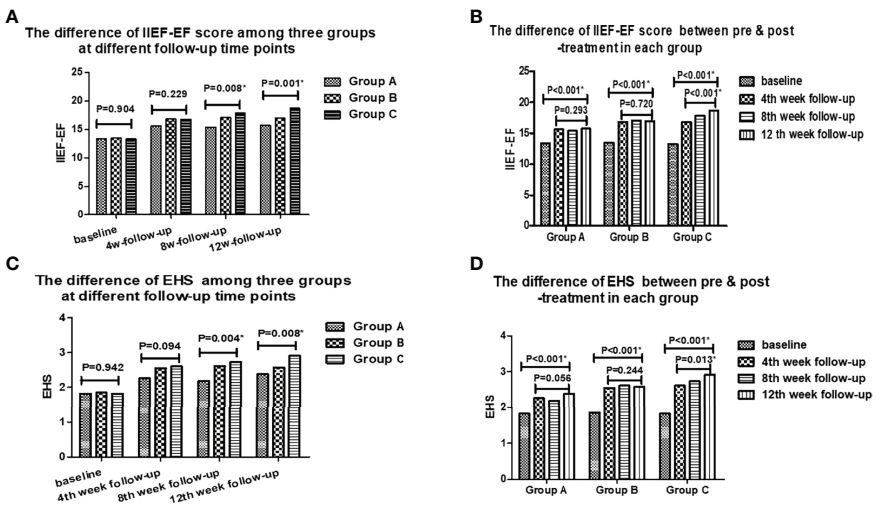


FIGURE 1 | The differences of IIEF-EF and EHS scores among three groups at different follow-up time points and between pre & post-treatment in each group.

as an effective and simple treatment which required little investigation. In the other previous study on the combined therapy VED and PDE5is for ED by Chen et al. (34), thirty five men with ED who were ineffective for PDE5is in 80 cases firstly preferring PDE5i medication were treated with PDE5is combined with VED, and 26 patients of them were satisfied, that is, the treatment satisfaction rate increased from 56.3% to 88.8%. Besides, Canguven's clinical research data showed that the mean IIEF-5 score in 69 men with ED caused by various reasons (including 16 patients with DMED) and poor responses to PDE5is increased significantly over baseline from 9.0 to 17.6 (P<0.001) after 4 weeks of combination therapy of VED and oral medication, and the results suggested that the combined therapy might be tried prior to initiating more invasive alternatives (35). Previous studies had indicated that vacuum constrictive devices (VCD) were usually reserved for patients who failed oral PDE5is, by improving hypoxia in corpus cavernosum, thereby inhibiting smooth muscle cell apoptosis and cavernous fibrosis (36, 37). In our study, VED was utilized for rehabilitative treatment without the use of tension rings, which was different from VCD with tension rings for the purpose of maintaining erection for successful sexual intercourse. However, based on our observations in this study, no more than 17.6% (yes%, MCID) of patients obtained certain curative effect during follow-up. It was our opinion that this relatively poor efficacy of vacuum therapy might be link with the major purpose of erectile tissue rehabilitation without the use of tension ring in the clinical trial. Our findings were kind of similar with the other study about VED by Raina (38), who assessed 109 patients with pPED and found that 17% of men had spontaneous erections sufficient for vaginal intercourse by the use of VED after 9 months, compared to 10% of men in the control group.

Li-ESWT, as an energy-based therapy technology, represents a new frontier of treatment geared towards reversing disease pathology rather than just treating symptoms (39). Li-ESWT might bring new hope to patients with multiple diabetic complications. Previous clinical trails showed that Li-ESWT had been tried to use for the management of diabetic complications such as diabetic foot ulcers and diabetic kidney disease (40, 41); and for the treatment of diabetic ED, and an increasing body of evidence demonstrated Li-ESWT was of satisfactory efficacy and fewer complications as a novel physical therapy of ED. Wang et al. reported that energy flux density (EFD) of 0.05mj/mm^2 of Li-ESWT therapy could turn 71% (27/38) of PDE5is non-responders to responders and could improve erection hard enough for vaginal penetration at 16th week follow-up (42). In the other study reported by Tsai et al. (43), 67.3% of patients (35/52) could achieve an erection hard enough for intercourse under PDE5is medication at the 1-month follow-up after treatment of Li-ESWT and 63.5% (33/52) of patients could maintain the erectile function at the 3-month follow-up. These studies suggested that Li-ESWT could be regard as a salvage therapy for ED patients who failed to respond to PDE5is and initial severity of ED was the only significant predictor of a successful response. Our results showed that the mean IIEF-EF score and EHS were significantly higher at follow-up than those at baseline in Group B (P<0.05), additionally, the proportion of cases reaching MCID (39.4%) in Group B was obvious higher than those (14.7%) in Group A at 8th week follow-up, but no significant differences were found at 12th week follow-up between two groups (17.6% vs. 36.4%, P=0.084). The proportion of MCID obtained in this study was lower than that reported in the literature, which might be related to the initial severity of DMED. Out findings indicated that Li-EWST monotherapy was possibly more effective than VED monotherapy in the early stage, but the superiority of Li-EWST monotherapy to VED is relatively limited in improving response to PDE5is for moderate diabetic ED in the longer term.

Fortunately, the results of our study showed that 66.7% (yes%, MCID) of subjects received combined therapy of VED, Li-EWST and PDE5is achieved relatively higher efficacy than those in group A or group B at 12th week follow-up, which implied that there was the gradual emergence of synergistic effect between VED and Li-ESWT in the early stage. Current experiments showed that the potential mechanism of Li-ESWT for ED involved in improving endothelial function, penile progenitior cell recruitment and activation, as well as inhibiting apoptosis and atrophy of the corpus cavernosum (44–46). Assaly et al. (47) found that smooth muscle/collagen ratio increased 2.5-fold in spontaneously hypertensive rats (SHRs) received Li-ESWT compared with sham, whereas neuronal nitric oxide synthase (nNOS) was unchanged. However, Jeong et al.'s report (48) showed that ESWT could not only increase the expression of nNOS, but also enhanced the expression of α smooth muscle actin (αSMA), vascular endothelial growth factor (VEGF), platelet endothelial cell adhesion molecule-1 (PECAM-1) and phosphorylated endothelial nitric oxide synthase (P-eNOS) in the corpus cavernosum of DM rats, which was implied to benefit the recovery of the muscle, nerve and blood vessels of erectile tissues. Furthermore, Lin et al. (49) found that VED therapy could preserve penile size effectively in rats with bilateral cavernous nerve crush (BCNC) injuries by increasing cavernous blood oxygen saturation (SO_2), and erection induced by VED was mainly due to the arterial blood inflow (62% arterial and 38% venous). Bosshardt et al.'s study (50) found that the average rigidity (monitored by Rigiscan) was >80% in 26 patients with ED after VED application and the increased penis volume was caused by 58% arterial and 42% venous inflow (calculated by blood gas analysis). In this study, combined therapy VED and Li-ESWT was more effective than either monotherpy. This finding suggested that regular VED physiotherapy could improve the blood supply of penile artery, which was similar to spontaneous nocturnal erection. In addition, sufficient penile length might improve their confidence in treatment, and provide good conditions in various place of penis for Li-ESWT positioning. Therefore, in addition to the subjects in Li-ESWT monotherapy, those patients in the other two groups received VED treatment during treatment and follow-up.

However, in the study, the patients with relatively severe and refractory DMED were selected, consequently, although the effectiveness of the combined group was acceptable, the overall effective rate of the subjects was low after treatment, and further treatment was insufficient after follow-up. Meanwhile, the small sample size and the short observation time limited the stronger persuasiveness of design concept of this study. An additional limitation is that the different type and exact dosage of PDE5is drugs and anti-diabetic drugs in different individuals during enrollment and follow-up, which might bring about the deflection in efficacy evaluation. The accurate diabetes time-course of individual patients was unavailable, which might also affect the results. Comparisons should be performed between different therapeutic regimen in our further studies, such as the combination therapy with LiESWT+ daily PDE5i. Moreover, the positive effects of the therapy on the penile vascularity should be evaluated by a Penile Doppler ultrasound, which could provide more objective efficacy indicators. Finally, as we known, the vascular damage of penile cavernous in non-diabetes patients was less than that in diabetes patients, therefore, this combined therapy would be more effective in patients with diabetes than in patients without diabetes. However, this problem needed to be explored by further studies with increasing sample size and type.

CONCLUSION

Our findings showed the combined therapy Li-ESWT and VED was more beneficial to shift turn PDE5is nonresponders to responders for moderate impotence men with DM than Li-ESWT or VED monotherapy due to their synergistic effect. Moreover, this study provided evidences that patients with DMED who failed after taking oral PDE5i drugs and receiving VED or Li-ESWT could attempt to opt for an alternative physicotherapy (Li-ESWT or VED) prior to more invasive alternatives. The long-term efficacy and safety of this treatment remained to be further investigated in well-characterized patients by more multi-center, randomized, controlled trials.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Nanjing Jiangning hospital ethics committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

RT, JC, JY, and QT designed the experiments. RT, DW, YL, LX, JJ, JW, SZ, CJ, JL, and QT contributed to clinical data collection and assessment. RT, JC, JX, JY, and QT analyzed the results. RT, JC, JY, and QT wrote the manuscript. All authors read and approved the final manuscript.

FUNDING

This work was supported by the key project of scientific research development fund of Kangda College of Nanjing Medical University in China (No. KD2019KYJJZD020); General project of Natural Science Foundation of Xinjiang Uygur Autonomous Region (2022D01A23).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.937958/full#supplementary-material

REFERENCES

1. Xu G, Liu B, Sun Y, Du Y, Snetselaar LG, Hu FB, et al. Prevalence of Diagnosed Type 1 and Type 2 Diabetes Among US Adults in 2016 and 2017: Population Based Study. *BMJ* (2018) 362:k1497. doi: 10.1136/bmj.k1497
2. Ma RCW. Epidemiology of Diabetes and Diabetic Complications in China. *Diabetologia* (2018) 61(6):1249–60. doi: 10.1007/s00125-018-4557-7
3. Whicher CA, O'Neill S, Holt RIG. Diabetes in the UK: 2019. *Diabetes Med* (2020) 37(2):242–7. doi: 10.1111/dme.14225
4. Stedman M, Whyte MB, Lunt M, Albanese M, Livingston M, Gadsby R, et al. The Treatment Rate of Erectile Dysfunction (ED) in Younger Men With Type 2 Diabetes Is Up to Four Times Higher Than the Equivalent non-Diabetes Population. *Int J Clin Pract* (2020) 74(9):e13538. doi: 10.1111/ijcp.13538
5. Zamorano-León JJ, Olivier C, de Las Heras N, Mateos-Cáceres PJ, Brime Menéndez R, Rodríguez-Sierra P, et al. Vardenafil Improves Penile Erection in Type 2 Diabetes Mellitus Patients With Erectile Dysfunction: Role of Tropomyosin. *J Sex Med* (2013) 10(12):3110–20. doi: 10.1111/jsm.12324
6. El Taieb M, Hegazy E, Ibrahim A. Daily Oral L-Arginine Plus Tadalafil in Diabetic Patients With Erectile Dysfunction: A Double-Blinded, Randomized, Controlled Clinical Trial. *J Sex Med* (2019) 16(9):1390–7. doi: 10.1016/j.jsxm.2019.06.009
7. Kim S, Cho MC, Cho SY, Chung H, Rajasekaran MR. Novel Emerging Therapies for Erectile Dysfunction. *World J Mens Health* (2021) 39(1):48–64. doi: 10.5534/wjmh.200007
8. Spivak L, Shultz T, Appel B, Verze P, Yagudaev D, Vinarov A. Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction in Diabetic Patients. *Sex Med Rev* (2019) 9(4):619–27. doi: 10.1016/j.sxmr.2019.06.007
9. Huang YP, Liu W, Liu YD, Zhang M, Xu SR, Lu MJ. Effect of Low-Intensity Extracorporeal Shockwave Therapy on Nocturnal Penile Tumescence and Rigidity and Penile Haemodynamics. *Andrologia* (2020) 52(10):e13745. doi: 10.1111/and.13745

10. Shendy WS, Elsoghier OM, El Semary MM, Ahmed AA, Ali AF, Saber-Khalaf M. Effect of Low-Intensity Extracorporeal Shock Wave Therapy on Diabetic Erectile Dysfunction: Randomised Control Trial. *Andrologia* (2021) 53(4): e13997. doi: 10.1111/and.13997
11. Kitrey ND, Gruenwald I, Appel B, Shechter A, Massarwa O, Vardi Y. Penile Low Intensity Shock Wave Treatment is Able to Shift PDE5i Nonresponders to Responders: A Double-Blind, Sham Controlled Study. *J Urol* (2016) 195 (5):1550–5. doi: 10.1016/j.juro.2015.12.049
12. Kitrey ND, Vardi Y, Appel B, Shechter A, Massarwi O, Abu-Ghanem Y, et al. Low Intensity Shock Wave Treatment for Erectile Dysfunction—How Long Does the Effect Last? *J Urol* (2018) 200:167–70. doi: 10.1016/j.juro.2018.02.070
13. Baas W, O'Connor B, Welliver C, Stahl PJ, Stember DS, Wilson SK, et al. Worldwide Trends in Penile Implantation Surgery: Data From Over 63,000 Implants. *Transl Androl Urol* (2020) 9(1):31–7. doi: 10.21037/tau.2019.09.26
14. Pahlajani G, Raina R, Jones S, Ali M, Zippe C. Vacuum Erection Devices Revisited: Its Emerging Role in the Treatment of Erectile Dysfunction and Early Penile Rehabilitation Following Prostate Cancer Therapy. *J Sex Med* (2012) 9(4):1182–9. doi: 10.1111/j.1743-6109.2010.01881.x
15. Wang R. Is There Still a Role for Vacuum Erection Devices in Contemporary Sexual Medicine? *J Sex Med* (2022) 19(5):682–5. doi: 10.1016/j.jsxm.2022.02.013
16. Kedia GT, Ückert S, Tsikas D, Becker AJ, Kuczyk MA, Bannowsky A. The Use of Vasoactive Drugs in the Treatment of Male Erectile Dysfunction: Current Concepts. *J Clin Med* (2020) 9(9):2987. doi: 10.3390/jcm9092987
17. Heaton JP, Lording D, Liu SN, Litonjua AD, Guangwei L, Kim SC, et al. Intracavernosal Alprostadil is Effective for the Treatment of Erectile Dysfunction in Diabetic Men. *Int J Impot Res* (2001) 13:317–21. doi: 10.1038/sj.ijir.3900760
18. Brison D, Seftel A, Sadeghi-Nejad H. The Resurgence of the Vacuum Erection Device (VED) for Treatment of Erectile Dysfunction. *J Sex Med* (2013) 10 (4):1124–35. doi: 10.1111/jsm.12046
19. Reinstatler L, Rodríguez D, Goddard B, Apoj M, Rezaee M, Gross M , et al. Postoperative Penile Prosthesis Pain: Is it Worse in Diabetic Patients? *Int J Impot Res* (2021) 33(3):286–90. doi: 10.1038/s41443-020-0284-y
20. McCullough AR, Barada JH, Fawzy A, Guay AT, Hatzichristou D. Achieving Treatment Optimization With Sildenafil Citrate (Viagra) in Patients With Erectile Dysfunction. *Urology* (2002) 60(2 Suppl 2):28–38. doi: 10.1016/S0090-4295(02)01688-6
21. Rosen RC, Allen KR, Ni X, Araujo AB. Minimal Clinically Important Differences in the Erectile Function Domain of the International Index of Erectile Function Scale. *Eur Urol* (2011) 60(5):1010–6. doi: 10.1016/j.eururo.2011.07.053
22. Hicks CW, Wang D, Windham BG, Selvin E. Association of Peripheral Neuropathy With Erectile Dysfunction in US Men. *Am J Med* (2021) 134 (2):282–4. doi: 10.1016/j.amjmed.2020.07.015
23. Yuan P, Ma D, Zhang Y, Gao X, Wang J, Li R, et al. Analysis of Cardiovascular Risks for Erectile Dysfunction in Chinese Patients With Type 2 Diabetes Mellitus Lacking Clinical Symptoms of Cardiovascular Diseases. *Transl Androl Urol* (2020) 9(6):2500–2509. doi: 10.21037/tau-20-999
24. Seppan P, Muhammed I, Mohammad ZIK, Sathyanathan SB. Pathobiology of Ischiocavernosus and Bulbospongiosus Muscles in Long-Term Diabetic Male Rats and Its Implication on Erectile Dysfunction. *Aging Male* (2020) 23 (5):979–90. doi: 10.1080/13685538.2019.1647160
25. Hassanin AM, Abdel-Hamid AZ. Cavernous Smooth Muscles: Innovative Potential Therapies Are Promising for an Unrevealed Clinical Diagnosis. *Int Urol Nephrol* (2020) 52(2):205–17. doi: 10.1007/s11255-019-02309-9
26. Wu G, Meininger CJ, McNeal CJ, Bazer FW, Rhoads JM. Role of L-Arginine in Nitric Oxide Synthesis and Health in Humans. *Adv Exp Med Biol* (2021) 1332:167–87. doi: 10.1007/978-3-030-74180-8_10
27. Gallo L, Pecoraro S, Sarnacchiaro P, Silvani M, Antonini G. The Daily Therapy With L-Arginine 2,500 Mg and Tadalafil 5 Mg in Combination and in Monotherapy for the Treatment of Erectile Dysfunction: A Prospective, Randomized Multicentre Study. *Sex Med* (2020) 8(2):178–85. doi: 10.1016/j.esxm.2020.02.003
28. Liu C, Lopez DS, Chen M, Wang R. Penile Rehabilitation Therapy Following Radical Prostatectomy: A Meta-Analysis. *J Sex Med* (2017) 14(12):1496–503. doi: 10.1016/j.jsxm.2017.09.020
29. Moncada I, Martinez-Salamanca J, Ruiz-Castañe E, Romero J. Combination Therapy for Erectile Dysfunction Involving a PDE5 Inhibitor and Alprostadil. *Int J Impot Res* (2018) 30(5):203–8. doi: 10.1038/s41443-018-0046-2
30. Yang XL, Yang Y, Fu FD, Wu CJ, Qin F, Yuan JH. Optimal Pressure in Penile Rehabilitation With a Vacuum Erection Device: Evidence Based on a Rat Model. *Asian J Androl* (2019) 21(5):516–21. doi: 10.4103/aja.aja_7_19
31. Li HX, Zhang ZC, Peng J. Low-Intensity Extracorporeal Shock Wave Therapy Promotes Recovery of Sciatic Nerve Injury and the Role of Mechanical Sensitive YAP/TAZ Signaling Pathway for Nerve Regeneration. *Chin Med J (Engl)* (2021) 134(22):2710–20. doi: 10.1097/CM9.0000000000001431
32. Fojecki GL, Tiessen S, Osther PJS. Effect of Linear Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction-12-Month Follow-Up of a Randomized, Double-Blinded, Sham-Controlled Study. *Sex Med* (2018) 6(1):1–7. doi: 10.1016/j.esxm.2017.09.002
33. Price DE, Cooksey G, Jehu D, Bentley S, Hearnshaw JR, Osborn DE. The Management of Impotence in Diabetic Men by Vacuum Tumescence Therapy. *Diabetes Med* (1991) 8(10):964–7. doi: 10.1111/j.1464-5491.1991.tb01538.x
34. Chen J, Sofer M, Kaver I, Matzkin H, Greenstein A. Concomitant Use of Sildenafil and a Vacuum Entrapment Device for the Treatment of Erectile Dysfunction. *J Urol* (2004) 171(1):292–5. doi: 10.1097/01.ju.0000098460.02560.fe
35. Canguven O, Bailen J, Fredriksson W, Bock D, Burnett AL. Combination of Vacuum Erection Device and PDE5 Inhibitors as Salvage Therapy in PDE5 Inhibitor Nonresponders With Erectile Dysfunction. *J Sex Med* (2009) 6 (9):2561–7. doi: 10.1111/j.1743-6109.2009.01364.x
36. Lima TFN, Bitran J, Frech FS, Ramasamy R. Prevalence of Post-Prostatectomy Erectile Dysfunction and a Review of the Recommended Therapeutic Modalities. *Int J Impot Res* (2021) 33(4):401–9. doi: 10.1038/s41443-020-00374-8
37. Ma M, Qin F, Wu C, Xiong W, Yu B, Wei S, et al. Optimal Vacuum Erectile Device Therapy Regimen for Penile Rehabilitation in a Bilateral Cavernous Nerve Crush Rat Model. *Andrology* (2021) 9(3):894–905. doi: 10.1111/andr.12968
38. Raina R, Agarwal A, Ausmundson S, Lakin M, Nandipati KC, Montague DK, et al. Early Use of Vacuum Constriction Device Following Radical Prostatectomy Facilitates Early Sexual Activity and Potentially Earlier Return of Erectile Function. *Int J Impot Res* (2006) 18(1):77–81. doi: 10.1038/sj.ijir.3901380
39. Pai R, Ory J, Delgado C, Ramasamy R. Energy-Based Therapies for Erectile Dysfunction: Current and Future Directions. *Urol Clin North Am* (2021) 48 (4):603–10. doi: 10.1016/j.ucl.2021.06.013
40. Chou WY, Wang CJ, Cheng JH, Chen JH, Chen CC, Kuo YR. Extended Extracorporeal Shockwave Therapy for Chronic Diabetic Foot Ulcers: A Case Series. *Wounds* (2019) 31(5):132–6.
41. Skov-Jeppesen SM, Yderstraede KB, Jensen BL, Bistrup C, Hanna M, Lund L. Low-Intensity Shockwave Therapy (LI-ESWT) in Diabetic Kidney Disease: Results From an Open-Label Interventional Clinical Trial. *Int J Nephrol Renovasc Dis* (2021) 14:255–66. doi: 10.2147/IJNRD.S315143
42. Wang J, Luo L, Zhao S, Liu Y, Zhu Z, Zhao Z. Low Intensity Extracorporeal Shockwave Therapy Shifts PDE5i Nonresponders to Responders. *Int Braz J Urol* (2020) 46(6):934–42. doi: 10.1590/s1677-5538.ibju.2019.0374
43. Tsai CC, Wang CJ, Lee YC, Kuo YT, Lin HH, Li CC, et al. Low-Intensity Extracorporeal Shockwave Therapy Can Improve Erectile Function in Patients Who Failed to Respond to Phosphodiesterase Type 5 Inhibitors. *Am J Mens Health* (2017) 11(6):1781–90. doi: 10.1177/1557988317721643
44. Zou ZJ, Liang JY, Liu ZH, Gao R, Lu YP. Low-Intensity Extracorporeal Shock Wave Therapy for Erectile Dysfunction After Radical Prostatectomy: A Review of Preclinical Studies. *Int J Impot Res* (2018) 30(1):1–7. doi: 10.1038/s41443-017-0002-6
45. Lin G, Reed-Maldonado AB, Wang B, Lee YC, Zhou J, Lu Z, et al. *In Situ* Activation of Penile Progenitor Cells With Low-Intensity Extracorporeal Shockwave Therapy. *J Sex Med* (2017) 14(4):493–501. doi: 10.1016/j.jsxm.2017.02.004
46. Lu Z, Lin G, Reed-Maldonado A, Wang C, Lee YC, Lue TF. Low-Intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-Analysis. *Eur Urol* (2017) 71(2):223–33. doi: 10.1016/j.eururo.2016.05.050

47. Assaly R, Giuliano F, Clement P, Laurin M, Favier M, Teo P, et al. Extracorporeal Shock Waves Therapy Delivered by Aries Improves Erectile Dysfunction in Spontaneously Hypertensive Rats Through Penile Tissue Remodeling and Neovascularization. *Sex Med* (2019) 7(4):441–450. doi: 10.1016/j.esxm.2019.08.006
48. Jeong HC, Bae WJ, Zhu GQ, Jeon SH, Choi SW, Kim SJ, et al. Synergistic Effects of Extracorporeal Shockwave Therapy and Modified Ojayeonjonghwan on Erectile Dysfunction in an Animal Model of Diabetes. *Investig Clin Urol* (2019) 60(4):285–294. doi: 10.4111/icu.2019.60.4.285
49. Lin HC, Yang WL, Zhang JL, Dai YT, Wang R. Penile Rehabilitation With a Vacuum Erectile Device in an Animal Model is Related to an Antihypoxic Mechanism: Blood Gas Evidence. *Asian J Androl* (2013) 15(3):387–90. doi: 10.1038/aja.2013.18
50. Bosshardt RJ, Farwerk R, Sikora R, Sohn M, Jakse G. Objective Measurement of the Effectiveness, Therapeutic Success and Dynamic Mechanisms of the Vacuum Device. *Br J Urol* (1995) 75(6):786–91. doi: 10.1111/j.1464-410X.1995.tb07392.x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Endocrinology

ORIGINAL RESEARCH
published: 12 July 2022
doi: 10.3389/fendo.2022.949762

Effect of Exercise Instructions With Ambulatory Accelerometer in Japanese Patients With Type 2 Diabetes: a Randomized Control Trial

Jin Matsushita[1], Hiroshi Okada[2,3], Yuki Okada[4], Takashi Sekiyama[1], Hideto Iida[1], Atsushi Shindo[1], Hiroaki Murata[5] and Michiaki Fukui[2]*

[1] Department of Rehabilitation, Matsushita Memorial Hospital, Moriguchi, Japan, [2] Department of Endocrinology and Metabolism, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [3] Department of Diabetes and Endocrinology, Matsushita Memorial Hospital, Moriguchi, Japan, [4] Department of Diabetes, Ikeda Hospital, Amagasaki, Japan, [5] Department of Orthopedic Surgery, Matsushita Memorial Hospital, Moriguchi, Japan

This study aimed to investigate the effects of physical therapists' exercise instructions in Japanese patients with type 2 diabetes. Thirty-six participants were recruited from the outpatient clinic at Matsushita Memorial Hospital, Osaka, Japan from June 2020 to September 2020 and were randomly assigned to either the non-intervention or intervention group. The intervention group received exercise instructions from physical therapists for 30 min at baseline (week 0) and at week 4 by referring to ambulatory accelerometer records. Laboratory parameters, physical activity, body composition, motor skill, and transtheoretical model were assessed in both the groups at baseline (week 0) and week 8. In week 8, patients in the intervention group had a statistically significant reduction in HbA1c levels compared with those in the non-intervention group (7.3% [6.8-%–7.9%] vs. 7.4% [7.3%–7.7%], P = 0.04). The number of steps per day (P = 0.001), energy expenditure (P = 0.01), lower extremity muscle strength (P = 0.002), and 6-min walk test results (P = 0.04) were significantly increased in the intervention group compared with those in the non-intervention group in week 8. The transtheoretical model varied between baseline (week 0) and week 8 only in the intervention group (P < 0.001). Thus, outpatient exercise instructions from physical therapists could improve glycemic control owing to physical activity by improving motor skills and changing the transtheoretical model in Japanese patients with type 2 diabetes.

Keywords: ambulatory accelerometer, diabetes mellitus, exercise therapy, physical therapist, transtheoretical model

OPEN ACCESS

Edited by:
Jun Wada,
Okayama University, Japan

Reviewed by:
Norikazu Maeda,
Osaka University Hospital, Japan
Nobuyuki Miyatake,
Kagawa University, Japan

***Correspondence:**
Hiroshi Okada
conti@koto.kpu-m.ac.jp

Specialty section:
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

Received: *21 May 2022*
Accepted: *20 June 2022*
Published: *12 July 2022*

Citation:
Matsushita J, Okada H, Okada Y, Sekiyama T, Iida H, Shindo A, Murata H and Fukui M (2022) Effect of Exercise Instructions With Ambulatory Accelerometer in Japanese Patients With Type 2 Diabetes: a Randomized Control Trial. Front. Endocrinol. 13:949762. doi: 10.3389/fendo.2022.949762

INTRODUCTION

Prevention of the onset and progression of diabetic complications is a major issue worldwide from the perspectives of extending healthy life expectancy and reducing medical expenditure. The pathophysiology of type 2 diabetes mainly involves a decrease in insulin secretion capacity and an increase in insulin resistance. In diabetes treatment, improvement in insulin resistance by dietary

therapy alone is limited, and it is important to combine it with exercise therapy (1). The combination of dietary and exercise therapy reduces the risk of diabetes by 30%–40% (2–4), and exercise therapy has attracted more attention in recent years since frailty and sarcopenia in older adults are becoming increasingly problematic. However, the rate of outpatient exercise therapy by physical therapists among patients with diabetes in Japan is low, and this issue needs to be addressed.

The low implementation rate of outpatient exercise therapy may be because of uncertainty about the effectiveness of exercise instructions from physical therapists. Previous studies showed the effect of supervised aerobic exercise in patients with type 2 diabetes in western countries (5). However, few studies have investigated the effects of supervised exercise in Japanese patients with type 2 diabetes. Moreover, the benefits of exercise might differ between the Japanese and western populations because of low body mass index (BMI) in Asian populations, which disrupts their insulin secretion capacity instead of building insulin resistance, a feature commonly observed in the Japanese population. Therefore, this randomized controlled study aimed to investigate the effects of exercise instructions by physical therapists in Japanese patients with type 2 diabetes.

MATERIALS AND METHODS

Ethics

The study was approved by the local ethics committee of Matsushita Memorial Hospital (approval number: 19033) and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Inclusion and Exclusion Criteria

Patients diagnosed with type 2 diabetes and who provided written consent were included in the study. Patients who did not provide written consent, those who were pregnant or breastfeeding, those whose HbA1c was 10% or higher, those receiving insulin therapy, those having contraindications to exercise therapy, and those who were deemed inappropriate by the investigator were excluded.

Study Design

Eligible trial participants were recruited from the outpatient clinic of Matsushita Memorial Hospital from June 2020 to September 2020 and were randomly assigned to either the non-intervention or intervention group by a third party using the envelope method. Primary care physicians were unaware of the group assignments. Laboratory parameters were measured at baseline (week 0) and visit 3 (week 8). The study design is illustrated in **Figure 1**. No medication changes were made during the study period.

Sample Size

The null hypothesis of this study is defined as follows: the effect of the intervention group is the same as the effect of the non-intervention group. The alternative hypothesis of this study is defined as follows: the effect of the intervention group is greater than the effect of the non-intervention group. The minimum sample size required to achieve a significance of 0.05 for a one-sided t-test with a statistical power of 80% was used. Previous studies showed that HbA1c decreases by approximately 0.6% in the intervention group compared with that in the non-intervention group (6, 7). A sample size of 13 patients in one group was estimated to be sufficient. With an estimated dropout rate of 15%, the planned number of participants (36 participants, 18 in each group) was considered to have sufficient statistical value.

Data Collection

Laboratory parameters were measured at baseline (week 0) and visit 3 (week 8). Serum total cholesterol and triglyceride concentrations were assessed using standard enzymatic methods. Hemoglobin A1c was assayed using high-performance liquid chromatography and expressed with the unit defined by the National Glycohemoglobin Standardization Program. Sitting blood pressure was measured after a 5-min rest at baseline (week 0) and visit 3 (week 8) in quiet space using an automatic device. Based on smoking habits, participants were classified as non-smokers and past or current smokers. A multifrequency impedance body composition analyzer (InBodyS10, Tokyo, Japan) was used to evaluate body composition at baseline (week 0) and visit 3 (week 8). InBodyS10 findings reportedly

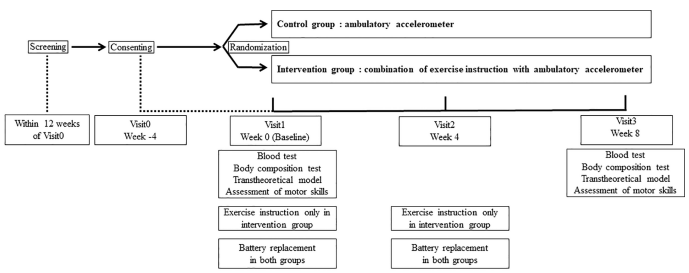


FIGURE 1 | The study design.

correlate well with dual-energy X-ray absorptiometry findings (8). Skeletal muscle mass index (kg/m^2), dividing appendicular muscle mass (kg) by height squared (m^2), was calculated. The transtheoretical model was devised and classified as precontemplation, contemplation, preparation, action, or maintenance and assessed by physical therapists at baseline (week 0) and visit 3 (week 8) (9).

Assessment of Physical Activity and Motor skills

Physical activity, including the number of steps per day and energy expenditure, was evaluated at visit -1 (week -4) to baseline (week 0) and visit 2 (week 4) to visit 3 (week 8) using the Active style Pro HJA-750C (OMRON Corporation, Kyoto, Japan). Energy expenditure was defined as metabolic equivalent (MET)-hours per week (10). Active style Pro HJA-750C can measure energy expenditure per 10 sec using tri-accelerometer. Previous study reported the strong relationships between measured energy expenditure from tri-accelerometer and indirect calorimetry (11). The validity and accuracy of the Active style Pro HJA-750C and mechanism of measurement of energy expenditure have been described in detail elsewhere (11, 12). Motor skills, including handgrip strength, lower extremity muscle strength, and 6-min walk test scores, were evaluated at baseline (week 0) and visit 3 (week 8). Grip strength and lower extremity muscle strength were assessed as the average of maximum values of two times each side. Lower extremity muscle strength (6) was assessed by measuring the maximal strength of the quadriceps femoris muscles using a hand-held dynamometer (μTasF-1; ANIMA Corporation, Tokyo, Japan) whose interclass correlation coefficients (1,1) was 0.87 to 0.92 (7). The 6-min walk test scores were based on the distance walked by patients in 6 min.

Intervention

The intervention group received exercise instructions from physical therapists for 30 min at baseline (week 0) and visit 2 (week 4) by referring to ambulatory accelerometer records. The physical therapist instructed the participants of the intervention group to walk for at least more than 150 min per week at moderate speed according to a guideline (13) and if possible, to walk more than 30 min per day. Both groups were provided ambulatory accelerometers (Active style Pro HJA-750C) during the observation period (week -4 to week 8) and were instructed to hold them when exercising or going out. The ambulatory accelerometer batteries were changed in both the groups at visit 2 (week 4).

Primary and Secondary Endpoints

The primary endpoint was defined as the change in HbA1c levels during the intervention period. The secondary endpoint was defined as the changes in BMI, systolic blood pressure, diastolic blood pressure, fasting blood glucose, lipid profile, number of steps per day, energy expenditure, body composition, motor skill, and transtheoretical model.

The amount of change was defined as follows:

amount of change = post-intervention measurements (week 8) – pre-intervention measurements (week 0).

Statistical Analyses

Participants enrolled in the study and assigned to the study treatment were defined as the largest analysis set (full analysis set [FAS]). The basic characteristics of the study participants were assessed for each group using FAS. To compare between the groups, Wilcoxon's rank sum test was applied for continuous variables and Fisher's exact test for categorical variables. Wilcoxon's signed-rank test was performed for within-group comparison of changes. Spearman's rank correlation coefficient test was performed to assess the association between the change in HbA1c and the change in number of steps per day, BMI, energy expenditure, appendicular muscle mass, body fat mass, skeletal muscle mass index, handgrip strength, lower-extremity muscle strength and 6-min walk test.

All continuous variables are presented as median ± interquartile range or absolute number. Differences were considered statistically significant at P values <0.05. Statistical analyses were performed using the JMP software, version 10 (SAS Institute, Cary, NC, USA).

RESULTS

Figure 2 shows the study flowchart. Thirty-six patients consented and were enrolled in this study. Participants who developed adverse events (n = 2; lumbago and cerebral infarction), did not visit a second time (visit 2) (n = 3), or had no ambulatory accelerometer data (n = 2) were excluded from the study. In the final analysis, 13 patients (non-intervention group) and 16 patients (intervention group) were included. The baseline characteristics of the study participants are presented in **Table 1**. The average HbA1c levels were 7.4% (7.3%–7.7%) and 7.3% (6.8%–7.9%) in the non-intervention and intervention groups, respectively, at baseline (week 0). We found no

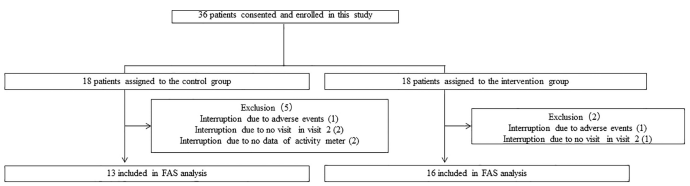


FIGURE 2 | Study flow diagram for the registration of participants.

TABLE 1 | Characteristics at baseline (week 0).

	Non-intervention group	Intervention group	*p*
Age (year)	61 (50.5–68)	62 (51.5–77)	0.46
Sex (male/female)	11/2	14/2	0.82
Body mass index (kg/m^2)	26.4 (22–31.1)	24.7 (22.5–28.7)	0.65
Duration of diabetes (year)	12 (2.5–18)	9 (2.3–14.8)	0.48
Systolic blood pressure (mmHg)	131 (125–1437)	129.5 (123–140.5)	0.88
Diastolic blood pressure (mmHg)	79 (72.5–82)	74 (69.3–85)	0.39
HbA_1c (%)	7.4 (7.3–7.7)	7.3 (6.8–7.9)	0.15
Fasting plasma glucose (mg/dl)	149 (134–166)	141 (120–147)	0.14
Total cholesterol (mg/dl)	180 (156.5–192)	162 (144–182.5)	0.23
High density cholesterol (mg/dl)	47 (37–53)	40 (37–45.5)	0.22
Triglyceride (mg/dl)	120 (94.5–256)	136 (99.5–207.5)	0.61
Antidiabetic treatment (diet/oral hypoglycemic agent)	1/12	1/15	0.88
Smoking (never/past or current)	5/8	7/9	0.77
Number of steps per day (step)	3649 (2627–6313)	3951 (2700–4941)	0.98
Energy expenditure (MET h × week)	21 (15.4–28)	19.6 (14.5–31.7)	0.88
Appendicular muscle mass (kg)	22.4 (19.3–27.1)	21.2 (19.4–24.9)	0.46
Body fat mass (kg)	21.9 (13.9–34.7)	19.7 (17.6–29.3)	0.91
Skeletal muscle mass index (kg/m^2)	7.8 (6.9–9.2)	7.5 (6.8–8.4)	0.31
Handgrip strength (kg)	37.9 (29.7–44.3)	32.1 (25.8–39.8)	0.39
Lower-extremity muscle strength (kgf/kg)	0.54 (0.42–0.66)	0.48 (0.36–0.53)	0.10
6-min walk test (m)	500 (454–544)	453 (405–510)	0.06
Transtheoretical model (precontemplation, contemplation, preparation, action or maintenance)	5/4/3/1	7/7/1/1	0.59

significant differences in any of the factors between the two groups at baseline (week 0).

Table 2 shows the changes in patient characteristics from baseline (week 0). BMI was similar between baseline (week 0) and week 8 in both the groups. A statistically significant treatment effect was found in glycemic control but not in blood pressure and lipid profile. Patients in the intervention group had a statistically significant reduction in HbA1c compared with that in those in the non-intervention group (P = 0.04). The number of steps per day (P = 0.001), energy expenditure (P = 0.01), lower extremity muscle strength (P = 0.002), and 6-min walk test results (P = 0.04) were significantly increased in the intervention group compared with those in the non-intervention group. The transtheoretical model was similar between baseline (week 0) and week 8 in the non-intervention group. However, the model varied between baseline (week 0) and week 8 in the intervention group (P < 0.001). The unadjusted regression analysis showed that the change in number of steps

TABLE 2 | Characteristics in week 8 and the change of characteristics from baseline.

	Week 8		Change from baseline		*p*
	Non-interventiongroup	Interventiongroup	Non-interventiongroup	Interventiongroup	
Body mass index (kg/m^2)	26.5 (22.1–30.5)	24.8 (22.6–28.5)	- 0.2 (-0.3–0.7)	-0.1 (-0.3–0.5)	0.97
Systolic blood pressure (mmHg)	126 (116.5–139)	128 (123.3–133.3)	-9 (-13–5.5)	-2 (-8.8–2.8)	0.74
Diastolic blood pressure (mmHg)	84 (72–91.5)	76.5 (66.3–79)	3 (0–7.5)	-2.5 (-12.5–5.8)	0.10
HbA_1c (%)	7.4 (7.1–8)	6.9 (6.6–7.3)	0 (-0.2–0.2)	-0.3 (-0.4–0)	0.04
Fasting plasma glucose (mg/dl)	151 (129.5–175)	136.5 (122.3–159.8)	39 (-74–60)	13.5 (-64.8–35.5)	0.23
Total cholesterol (mg/dl)	177 (156.5–190.5)	166.5 (156.8–185)	1 (-6–17.5)	3.5 (-6–14.8)	0.79
High density cholesterol (mg/dl)	44 (40.5–48.5)	43.5 (38.3–49.5)	0 (-3.5–3)	1.5 (0–2.8)	0.32
Triglyceride (mg/dl)	135 (92.5–222.5)	171 (84–203)	7 (-27.5–44.5)	-13 (-30.8–7.5)	0.35
Number of steps per day (step)	3246 (2579–6376)	8937 (6152–9814)	-559 (-1384–1743)	4054 (1742–6348)	0.001
Energy expenditure (MET h × week)	27.3 (15.4–41.3)	35.4 (29.1–50.8)	0.7 (-6.7–13.0)	17.5 (3.0–21)	0.01
Appendicular muscle mass (kg)	22.0 (19.4–26.9)	21.1 (18.6–23.6)	-0.2 (-0.7–0.6)	-0.3 (-0.8–0.1)	0.50
Body fat mass (kg)	22.4 (14.1–34.8)	20.2 (17.7–30.1)	0.1 (-0.8–1.2)	0.6 (-0.5–1.0)	0.71
Skeletal muscle mass index (kg/m^2)	7.8 (7.0–9.2)	7.4 (6.6–8.1)	-0.1 (-0.3–0.2)	-0.1 (-0.3–0)	0.52
Handgrip strength (kg)	36.8 (27.8–42.3)	31.9 (26–38.4)	-0.6 (-1.8–0.9)	-0.4 (-1.6–0.8)	0.95
Lower-extremity muscle strength (kgf/kg)	0.54 (0.4–0.65)	0.55 (0.42–0.63)	0 (-0.05–0.02)	0.06 (0.01–0.09)	0.002
6-min walk test (m)	495 (467–506)	490 (443–525)	9 (-35–26)	25 (11–44)	0.04
Transtheoretical model (precontemplation, contemplation, preparation, action or maintenance)	5/5/2/1	0/2/0/14*	–	–	–

**P<0.0001, vs baleline.*

per day was significantly associated with the change in HbA1c (r = -0.55, P = 0.03). The change in BMI, energy expenditure, appendicular muscle mass, body fat mass, skeletal muscle mass index, handgrip strength, lower-extremity muscle strength and 6-min walk test were not associated with the change in HbA1c.

DISCUSSION

In this study, we investigated the effect of exercise instructions from physical therapists using ambulatory accelerometers in Japanese patients with type 2 diabetes. Our major findings were as follows: glycemic control was better in the intervention group than in the non-intervention group, the intervention group had more improved motor skills than the non-intervention group, and the transtheoretical model varied in the intervention group but not in the non-intervention group between before and after intervention.

Walking is one of the most convenient and popular aerobic exercises for patients with type 2 diabetes. Recommendations for implementing exercise therapy include specific guidance on the type, duration, intensity, and frequency of exercise (14). A meta-analysis reported that at least 150 min of exercise per week is favorable for improved glycemic control (15). The Japanese diabetes treatment guideline also recommends aerobic exercise at moderate intensity for 150 min or more per week at least three times per week, with no more than 2 days of no exercise. In the current study, the number of steps per day and energy expenditure were sufficient to meet the guideline recommendations for the intervention group.

We showed that patients with supervised walking had significant reductions in HbA1c levels. However, this difference could not be entirely explained by participation in a supervised walking program alone. Behavioral changes and improved mobility owing to exercise instruction could also lead to increased and improved physical activity. In this study, the transtheoretical model varied between baseline (week 0) and week 8 only in the intervention group. Moreover, motor skills were greatly improved in the intervention group compared with those in the non-intervention group. When prescribing exercise therapy, instructions from a physical therapist with an ambulatory accelerometer as well as the loan of an ambulatory accelerometer might be effective. In other words, exercise therapy using only an ambulatory accelerometer may be less effective in self-care.

In this study, BMI was similar before and after the intervention, which is consistent findings of a previous study (16). A previous meta-analysis also reported that exercise could improve glycemic control, although no significant change in BMI was found for 18 weeks (16). There are some possible explanations for this finding. First, the intervention period of exercise could have been short, and the intensity of exercise could have been moderate. Second, the exercise intervention could have resulted in changes in food intake, with dietary intake possibly increasing in the intervention group. However, previous studies reported no significant differences in BMI between the exercise and diet group and the non-exercise and non-diet group (17, 18). Third, an increase in physical activity could have altered body composition. In other words, increased physical activity may reduce fat mass and increase muscle mass. In this study, fat mass and muscle mass were similar before and after the intervention, whereas motor performance differed significantly in the intervention group.

The finding that exercise can improve glycemic control without body weight reduction is important. Exercise can improve insulin resistance and chronic inflammation and reduce the accumulation of ectopic fat without body weight reduction (19–23). A previous report showed that a high-fat diet significantly increased intramyocellular lipids without body weight gain, resulting in worsening of insulin resistance in Japanese participants (24). In this regard, we suppose that increased and improved physical activity lead to improved insulin resistance owing to reduced ectopic fat accumulation, including intramyocellular lipids. Another explanation about improvement of glycemic control without body weight reduction is effect of exercise independent of insulin action. Insulin action causes glucose uptake *via* glucose transporter type 4. There is also a pathway for glucose uptake independent of exercise-induced insulin action. Intracellular adenosine monophosphate-activated protein kinase is activated by exercise, and this activation promotes glucose transporter type 4 translocation independent of insulin action (25).

This study had few limitations. The dietary intake may have affected our results. Unfortunately, there are no data on dietary intake. The number of 13 and 16 in each group was finally analyzed in this study. This study did not include intention to treat analysis because several people have dropped out. Our study population comprised Japanese people whose BMI was lower than that of the western population. Therefore, it is unclear whether our findings can be generalized to other ethnic groups.

In conclusion, outpatient exercise instructions from a physical therapist increased physical activity by improving motor performance and transtheoretical model. Outpatient exercise instructions by physical therapists with an ambulatory accelerometer can improve glycemic control in Japanese patients with type 2 diabetes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethics committee of Matsushita Memorial Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All persons who fulfill the authorship criteria are listed as authors, and all authors certify that they have participated in this work sufficiently to take public responsibility for its content. JM and HO researched the data and wrote the manuscript. AS and HM contributed to the discussion. HO, JM, YO, TS, and HI researched the data and contributed to the conception and discussion. MF reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by Japanese Society of Hospital General Medicine.

ACKNOWLEDGMENTS

We thank Editage (Tokyo, JAPAN) for the assistance in English language editing. We thank Hiroki Isono (HITO hospital, Shikoku chuo, Japan) for his advice in this manuscript.

REFERENCES

1. Tamura Y, Tanaka Y, Sato F, Choi JB, Watada H, Niwa M, et al. Effects of Diet and Exercise on Muscle and Liver Intracellular Lipid Contents and Insulin Sensitivity in Type 2 Diabetic Patients. *J Clin Endocrinol Metab* (2005) 90 (6):3191–6. doi: 10.1210/jc.2004-1959
2. Lindström J, Peltonen M, Eriksson JG, Ilanne-Parikka P, Aunola S, Keinänen-Kiukaanniemi S, et al. Finnish Diabetes Prevention Study (DPS). Improved Lifestyle and Decreased Diabetes Risk Over 13 Years: Long-Term Follow-Up of the Randomised Finnish Diabetes Prevention Study (DPS). *Diabetologia* (2013) 56(2):284–93. doi: 10.1007/s00125-012-2752-5
3. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, et al. 10-Year Follow-Up of Diabetes Incidence and Weight Loss in the Diabetes Prevention Program Outcomes Study. *Lancet* (2009) 374(9702):1677–86. doi: 10.1016/S0140-6736(09)61457-4
4. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, et al. The Long-Term Effect of Lifestyle Interventions to Prevent Diabetes in the China Da Qing Diabetes Prevention Study: A 20-Year Follow-Up Study. *Lancet* (2008) 371 (9626):1783–9. doi: 10.1016/S0140-6736(08)60766-7
5. Qiu S, Cai X, Schumann U, Velders M, Sun Z, Steinacker JM. Impact of Walking on Glycemic Control and Other Cardiovascular Risk Factors in Type 2 Diabetes: A Meta-Analysis. *PLoS One* (2014) 9(10):e109767. doi: 10.1371/journal.pone.0109767
6. Almeida GPL, Albano TR, Melo AKP. Hand-Held Dynamometer Identifies Asymmetries in Torque of the Quadriceps Muscle After Anterior Cruciate Ligament Reconstruction. *Knee Surg Sports Traumatol Arthrosc* (2019) 27 (8):2494–501. doi: 10.1007/s00167-018-5245-3
7. Aoyama M, Ohnishi Y, Utsunomiya H, Kanezaki S, Takeuchi H, Watanuki M, et al. A Prospective, Randomized, Controlled Trial Comparing Conservative Treatment With Trunk Stabilization Exercise to Standard Hip Muscle Exercise for Treating Femoroacetabular Impingement: A Pilot Study. *Clin J Sport Med* (2019) 29(4):267–75. doi: 10.1097/JSM.0000000000000516
8. Kim M, Shinkai S, Murayama H, Mori S. Comparison of Segmental Multifrequency Bioelectrical Impedance Analysis With Dual-Energy X-Ray Absorptiometry for the Assessment of Body Composition in a Community-Dwelling Older Population. *Geriatr Gerontol Int* (2015) 15(8):1013–22. doi: 10.1111/ggi.12384
9. Prochaska JO, Velicer WF. The Transtheoretical Model of Health Behavior Change. *Am J Health Promot* (1997) 12(1):38–48. doi: 10.4278/0890-1171-12.1.38
10. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of Physical Activities: An Update of Activity Codes and MET Intensities. *Med Sci Sports Exerc* (2000) 32(9 Suppl):S498–504. doi: 10.1097/00005768-200009001-00009
11. Ohkawara K, Oshima Y, Hikihara Y, Ishikawa-Takata K, Tabata I, Tanaka S. Real-Time Estimation of Daily Physical Activity Intensity by a Triaxial Accelerometer and a Gravity-Removal Classification Algorithm. *Br J Nutr* (2011) 105(11):1681–91. doi: 10.1017/S0007114510005441
12. Oshima Y, Kawaguchi K, Tanaka S, Ohkawara K, Hikihara Y, Ishikawa-Takata K, et al. Classifying Household and Locomotive Activities Using a Triaxial Accelerometer. *Gait Posture* (2010) 31(3):370–4. doi: 10.1016/j.gaitpost.2010.01.005
13. American Diabetes Association. 4. Lifestyle Management: Standards of Medical Care in Diabetes-2018. *Diabetes Care* (2018) 41(Suppl 1):S38–50. doi: 10.2337/dc18-S004
14. Löllgen H. Bedeutung Und Evidenz Der Körperlichen Aktivität Zur Prävention Und Therapie Von Erkrankungen [Importance and Evidence of Regular Physical Activity for Prevention and Treatment of Diseases]. *Dtsch Med Wochenschr* (2013) 138(44):2253–9. doi: 10.1055/s-0033-1349606
15. Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ, et al. Physical Activity Advice Only or Structured Exercise Training and Association With HbA1c Levels in Type 2 Diabetes: A Systematic Review and Meta-Analysis. *JAMA* (2011) 305(17):1790–9. doi: 10.1001/jama.2011.576
16. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of Exercise on Glycemic Control and Body Mass in Type 2 Diabetes Mellitus: A Meta-Analysis of Controlled Clinical Trials. *JAMA* (2001) 286(10):1218–27. doi: 10.1001/jama.286.10.1218
17. Agurs-Collins TD, Kumanyika SK, Ten Have TR, Adams-Campbell LL. A Randomized Controlled Trial of Weight Reduction and Exercise for Diabetes Management in Older African-American Subjects. *Diabetes Care* (1997) 20 (10):1503–11. doi: 10.2337/diacare.20.10.1503
18. Vanninen E, Uusitupa M, Siitonen O, Laitinen J, Länsimies E. Habitual Physical Activity, Aerobic Capacity and Metabolic Control in Patients With Newly-Diagnosed Type 2 (non-Insulin-Dependent) Diabetes Mellitus: Effect of 1-Year Diet and Exercise Intervention. *Diabetologia* (1992) 35(4):340–6. doi: 10.1007/BF00401201
19. Thomas DE, Elliott EJ, Naughton GA. Exercise for Type 2 Diabetes Mellitus. *Cochrane Database Syst Rev* (2006) 2006(3):CD002968. doi: 10.1002/14651858.CD002968.pub2
20. Sabag A, Way KL, Keating SE, Sultana RN, O'Connor HT, Baker MK, et al. Exercise and Ectopic Fat in Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Diabetes Metab* (2017) 43(3):195–210. doi: 10.1016/j.diabet.2016.12.006
21. Way KL, Hackett DA, Baker MK, Johnson NA. The Effect of Regular Exercise on Insulin Sensitivity in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Diabetes Metab J* (2016) 40(4):253–71. doi: 10.4093/dmj.2016.40.4.253
22. Hayashino Y, Jackson JL, Hirata T, Fukumori N, Nakamura F, Fukuhara S, et al. Effects of Exercise on C-Reactive Protein, Inflammatory Cytokine and Adipokine in Patients With Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. *Metabolism* (2014) 63(3):431–40. doi: 10.1016/j.metabol.2013.08.018
23. Melo LC, Dativo-Medeiros J, Menezes-Silva CE, Barbosa FT, de Sousa-Rodrigues CF, Rabelo LA. Physical Exercise on Inflammatory Markers in Type 2 Diabetes Patients: A Systematic Review of Randomized Controlled Trials. *Oxid Med Cell Longev* (2017) 2017:8523728. doi: 10.1155/2017/8523728
24. Sakurai Y, Tamura Y, Takeno K, Kumashiro N, Sato F, Kakehi S, et al. Determinants of Intramyocellular Lipid Accumulation After Dietary Fat Loading in non-Obese Men. *J Diabetes Investig* (2011) 2(4):310–7. doi: 10.1111/j.2040-1124.2010.00091.x
25. Hayashi T, Wojtaszewski JF, Goodyear LJ. Exercise Regulation of Glucose Transport in Skeletal Muscle. *Am J Physiol* (1997) 273(6):E1039–51. doi: 10.1152/ajpendo.1997.273.6.E1039

Conflict of Interest: HO received personal fees from MSD K.K., Mitsubishi Tanabe Pharma Corporation, Sumitomo Dainippon Pharma Co., Ltd., Novo Nordisk Pharma Ltd., Daiichi Sankyo Co., Ltd, Eli Lilly Japan K.K, Kyowa Hakko Kirin Company Ltd, Ltd, Kowa Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd. and Sanofi K.K. MF received grants from Ono Pharma Co. Ltd., Oishi Kenko inc., Yamada Bee Farm, Astellas Pharma Inc., Mitsubishi Tanabe Pharma Corp., Nippon Boehringer Ingelheim Co. Ltd., MSD K.K., Kissei Pharma Co. Ltd., Daiichi Sankyo Co. Ltd., Sanwa Kagagu Kenkyusho Co., Ltd., Sanofi K.K., Kyowa Kirin Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Terumo Corp., Tejin Pharma Ltd., Novo Nordisk Pharma Ltd., Eli Lilly, Japan, K.K., Taisho Pharma Co., Ltd., Abbott Japan Co. Ltd., Nippon Chemiphar Co., Ltd., Kowa Pharma Co. Ltd. and Johnson & Johnson K.K. Medical Co. and received personal fees from Abbott Japan Co. Ltd., Kissei Pharma Co., Ltd., Sumitomo Dainippon Pharma Co. Ltd., Mitsubishi Tanabe Pharma Corp., Daiichi Sankyo Co. Ltd., Sanofi K.K., Astellas Pharma Inc., MSD K.K., Kyowa Kirin Co. Ltd., Taisho Pharma Co., Ltd., Kowa Pharma Co. Ltd., Mochida Pharma Co. Ltd., Novo Nordisk Pharma Ltd., Ono Pharma Co. Ltd., Sanwa Kagaku Kenkyusho Co. Ltd., Eli Lilly Japan K.K., Bayer Yakuhin, Ltd., AstraZeneca K.K., Nippon Boehringer Ingelheim Co., Ltd., Teijin Pharma Ltd., Medtronic Japan Co. Ltd., Arkray Inc. and Nipro Corp. outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 22 July 2022
DOI 10.3389/fendo.2022.924451

OPEN ACCESS

EDITED BY
Edward Zimbudzi,
Monash Health, Australia

REVIEWED BY
Parisa Hosseini Koukamari,
Shahid Beheshti University of Medical Sciences, Iran
Habib Ojaghi,
Ardabil University of Medical Sciences, Iran
Elahe Mohammadi,
Khalkhal University of Medical Sciences, Iran
Atefeh Ashabi,
Semnan University of Medical Sciences, Iran
Habibeh Matin,
Iran University of Medical Sciences, Iran

*CORRESPONDENCE
Aghil Habibi Soola
habibiarums@gmail.com

SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 20 April 2022
ACCEPTED 27 June 2022
PUBLISHED 22 July 2022

CITATION
Moghaddam HR, Sobhi E and Soola AH (2022) Determinants of quality of life among elderly patients with type 2 diabetes in northwest of iran: based on problem areas in diabetes.
Front. Endocrinol. 13:924451.
doi: 10.3389/fendo.2022.924451

Determinants of quality of life among elderly patients with type 2 diabetes in northwest of iran: based on problem areas in diabetes

Hamed Rezakhani Moghaddam[1], Eslam Sobhi[2] and Aghil Habibi Soola[3]*

[1]Department of Public Health, Khalkhal University of Medical Sciences, Khalkhal, Iran, [2]Students Research Committee School of Nursing and Midwifery, Ardabil University of Medical Sciences, Ardabil, Iran, [3]Department of Nursing, School of Nursing and Midwifery, Ardabil University of Medical Sciences, Ardabil, Iran

Background: Diabetes is a metabolic disease characterized by chronic hyperglycemia, leading to damage to various organs of the patients and a reduction of their life expectancy and quality of life (QOL). The aim of this study was to explore the determinants of the QOL based on the Problem Areas in Diabetes (PAID).

Methods: This cross-sectional study was carried out in an Iranian diabetic clinic in Ardabil. The PAID, the short form health survey (SF-12), and the sociodemographic questionnaire were all employed. Using the census sample method, 266 elderly people with type 2 diabetes from the lone diabetic clinic at Ardabil took part in this study. One-way ANOVA, t-test, one-sample Kolmogorov–Smirnov test, and multiple regression were used to analyze the data.

Results: Data analysis showed that there was a statistically negative significant relationship between the QOL dimensions and the triple domains of PAID ($p < 0.01$). In the final model of the predictors of the QOL, treatment barriers, psychological distress related to diabetes management, the type of treatment, age, and the duration of diabetes were statistically significant predictors of the QOL dimensions ($p>0.05$).

Conclusion: Individual characteristics and factors connected to health services should be prioritized in any intervention program aimed at improving the QOL of elderly patients with diabetes. Psychological distress should be considered in addition to regular physician visits.

KEYWORDS

quality of life, elderly, psychological distress, diabetes mellitus, self-management

Introduction

Nowadays, factors like increasing life expectancy and declining fertility rates have led to an increase in the number of elderly population worldwide in a way that the aging of the population of the world has been introduced as one of the major public health challenges in recent years (1). Entering the elderhood, the probability of developing chronic diseases is increased significantly. Recent studies show that approximately 8% of the elderly have at least one chronic disease that makes them at risk for disability and death (2). Nearly 40% of the elderly living in the community also experience some kinds of limitations due to chronic diseases like diabetes (3, 4). One of the most debilitating diseases common among elderly is diabetes, which imposes enormous costs to the governments throughout the world (5).

Diabetes is a global health concern that affects approximately 382 million people throughout the world, and it is estimated to affect up to 592 million people by 2035 (6). According to the latest statistics reported by the World Health Organization (WHO), approximately 8 million Iranians (10.3%) have diabetes (7). The research of diabetes-related factors in Iranian elderly persons is crucial since diabetes affects approximately 22% of Iran's elderly population (8). Many factors such as diet, blood glucose monitoring, medications, and physical activity may help patients to achieve the optimal blood sugar control (9). Diabetes is a metabolic disease characterized by chronic hyperglycemia, leading to damage to various organs of the patients and and a reduction of their life expectancy and QOL (10, 11).

The WHO has provided the comprehensive definition for QOL: "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (The WHOQOL Group, 1995). As defined by the WHO, it is affected in a complex way by one's "physical and psychological health, level of independence, social relationships as well as his relationship to salient features of the environment" (12–14).

Various studies have identified various characteristics of the QOL. Physical, psychological, individual self-efficacy, and spiritual aspects and social participation are among these dimensions (15). Diabetes, in general, produces poor physical, social, and psychological health, which leads to restrictions in physical functioning and mental health, lowering the QOL among the elderly (16, 17). Several studies have shown that the QOL in "elderly people with diabetes" decreases compared to the non-diabetics (18, 19). Because of the difficulty of dietary restriction and the requirement to maintain self-management behavior, the QOL of patients with diabetes is significantly impacted (20). As the world's diabetic and aging populations have grown in recent years, the need for health promotion planning to improve all aspects of life (physical, mental, social, and so on) in this group of individuals has become apparent (21, 22).

Psychological health has already been found to be effective in predicting general wellbeing, such as physical health and the QOL. The study by Nedeljkovic et al. found that the psychological status can be used to guide therapies for improving the QOL in elderly patients with diabetes, as well as strategies for maintaining health-promoting behaviors (23). Depression has been highlighted as a key component in lowering the QOL of patients with diabetes in a study by Gomez et al. (24).

Diabetic-related stress evaluation and discussion can be a useful treatment technique for addressing barriers to these patients' therapeutic goals (25). One of the health domains of patients with diabetes affected by the disease is their psychological health, which, if neglected, may result in poor self-care behaviors (26). In addition, several studies have shown that poor glycemic control is associated with many problems such as depression and anxiety (27, 28).

Despite these studies, it has been shown that many aspects of the elderly's personality and psychological challenges remain unknown, and many of their psychological and physical problems remain unaddressed, despite improvements in medical science and the establishment of specialized trends in geriatrics (29). Problem areas in diabetes on predicting the QOL among elderly patients with diabetes, especially in developing countries, have not been well surveyed.

This study was conducted to examine the determinants of the QOL among elderly patients with diabetes based on problem areas in diabetes. Identifying the QOL influential factors in such studies may be useful in designing interventional programs aiming at improving the QOL according to problem areas in diabetes. Therefore, our objectives in the current study were as follows: (a) to determine the predictors of QOL based on the problem areas in diabetes and (b) to measure the QOL of the elderly patients with diabetes.

Method

Design and sample

From July to December 2021, a cross-sectional study was conducted on a census sample of 266 elderly patients with type 2 diabetes in the only diabetes clinic in Ardabil, a mountainous city in northwestern Iran. During the study, a total of 312 "elderly patients with diabetes" were referred to the clinic. According to the inclusion criteria and their willingness to participate in the study, 266 patients participated in the study. Data were collected in a private room in the clinic. The respondents were explained about the purpose of the study, and all of them signed an informed consent form. Those subjects

who gave consent to participate in the study were interviewed to complete the questionnaires. The participants were included if they were 60 years of age or older, diagnosed with type 2 diabetes by a specialist, with no cognitive and perception impairments, with no chronic diseases affecting the QOL (severe heart disease, stroke, severe neurological disorders, and end-stage renal disease), and required drug treatment due to their diabetes.

Measures

The Problem Areas in Diabetes questionnaire (PAID) is a standard questionnaire with 20 items that measures the negative emotions related to diabetes (e.g., fear, anger, and frustration) commonly experienced by patients with diabetes. The answer to the items is based on a five-point Likert-type scale ranged from 0 to 4 (0 = not a problem, 1= minor problem, 2= moderate problem, 3= somewhat-serious problem, 4 = serious problem). Scores ranged from 0 to 80; a higher score indicates more perceived problems. The original questionnaire assesses four domains of problem areas in diabetes: 1.emotional distress, 2. treatment barriers, 3. problems related to food, and 4. the lack of social support. In different studies conducted in several countries, the number of subcategories has been changed (30, 31). The Iranian version of PAID was validated by Arzaghi et al. (32), which resulted in three domains: "psychological distress in relation to diabetes management," "depression-related problems," and "treatment barriers". The internal consistency and test–retest reliability of the Iranian version of PAID was high (Cronbach's alpha 0.94 and 0.88, respectively). In the present study, this version of PAID was used. The examples of questions were as follows: "Feeling scared when you think about living with diabetes?" (depression-related problems), "Feeling burned out by the constant effort needed to manage diabetes?" (psychological distress related to diabetes management), and "Feeling unsatisfied with your diabetes physician?" (Treatment barriers).

The Persian version of Short Form Health Survey (SF-12) was used to measure the QOL among the participants in the present study. The SF-12 includes 12 items grouped into 2 scales and 8 subscales: the physical component summary (PCS) scale includes 4 subscales (general health, physical functioning, physical role limitation, and bodily pain), and the mental component summary (MCS) scale also includes 4 subscales (mental role limitation, vitality, social functioning, and mental health). The scores in each area are scored to be in a range from 0 to 100. A higher score shows better QOL. The validity and reliability of this instrument was also confirmed in a previous study in Iran (33).

The demographic characteristics included age, gender, educational status (illiterate/literate), marital status (married/single), living status (living alone/living with a partner/living with family members), economic status (economically dependent to others/economically independent), the duration of diabetes, and the type of treatment (oral treatment/insulin therapy).

Statistical analysis

In order to summarize and organize the data, the measures of central tendency and variability were used. The normality of data distribution was tested by the one-sample Kolmogorov–Smirnov test. The differences in the psychological wellbeing construct by demographic variables were analyzed using one-way ANOVA or the t-test. Multiple regression was performed to investigate the relationships between the sociodemographic variables and problem areas in diabetes and the QOL as the dependent variable to find a set of the best predictors. All the scores of the QOL are standardized in a range of 0 to 100 so that the worst possible score is 0 and the best possible score is 100. The correlation of study variables (scales of SF-12 and PAID domains) was tested using Pearson's correlation coefficient test. The level of significance was considered to be 0.05 at prior. The Statistical Package for Social Sciences (SPSS) v. 22 for Windows (SPSS Inc., Chicago, IL, USA) was used to conduct all statistical analyses.

Ethical considerations

Written informed consent was obtained from all the respondents prior to data collection. This research was approved by the Medical Ethics Committee of Ardabil University of Medical Sciences (approval number: IR.ARUMS.REC.1399.097). The study adhered to the tenets of the Declaration of Helsinki.

Result

The information on 266 elderly patients with type 2 diabetes was included in data analysis. More than half of the respondents (57.5%) were women, and 67.3% were married. The mean age of participants was 69.48 (SD = 7.4) years with the range of 60–90 years. In addition, the mean duration of diabetes was 10.6 ± 6.3 years and the number of chronic diseases was 0.67 ± 0.47. Less than half of the elderly were living their own house with their wife (45.9%), and 65.4% had an economically independent income. More than half (64.6%) of them were illiterate, and 65.4% received oral treatment. As shown in Table 1, statistically significant differences were found in the QOL of the patients by

TABLE 1 Demographic characteristics of elderly patients with type 2diabetes (n=266).

Variables		Mean ± SD	N (%)	P-value
Age		69.48 ± 7.4		r=-0.289 p=**0.000**
Gender	Male	54.9 ± 25.3	113(42.5)	t=3.62 p=**0.000**
	Female	44.2 ± 22.5	153 (57.5)	
Duration of diabetes (yrs.)		10.6 ± 6.3		r=-0.183 p=**0.003**
Number of Chronic Diseases		0.67 ± 0.47		r=-0.09 p=0.13
Marital Status	Married	51.7 ± 24	179 (67.3)	t=2.94 p=**0.004**
	Widowed and divorced	42.5 ± 23.7	87 (32.7)	
Educational Status	Illiterate	43.72 ± 23.3	172 (64.6)	t=4.75 p=**0.000**
	Literate	57.98 ± 23.4	94 (35.4)	
Economic status	Independent	52.6 ± 24.7	174 (65.4)	t=3.67 p=**0.000**
	Dependent	41.4 ± 21.7	92 (34.6)	
Living status	Alone	45.7 ± 21.4	27 (10.0)	F=3.42 p=**0.034**
	With wife	52.9 ± 24.2	122 (45.9)	
	With family	45 ± 24.3	117 (44.1)	
Kind of treatment	Oral treatment	52.2 ± 24.1	174 (65.4)	F=5.34 p=**0.005**
	Insulin therapy	42.6 ± 23.6	75 (28.1)	
	Oral and insulin therapy	40.1 ± 22.1	17 (6.5)	

The bold values related to significant relationship (p<0.01).

age, gender, the duration of diabetes, marital status, educational status, economic status, living status, and the type of treatment (p<0.05).

The participants' "quality of life" score averaged 48.76 ± 24.30 (min: 1.67—max: 90.83 and range: 0–100). The average "PAID" score was 32.12 ± 11.93 (min: 2—max: 60 and range: 0–80) (Table 2).

According to the results, there was a negative relationship between the physical component summary (PCS) of the patients and the triple domains of PAID (p < 0.01). Statistical analysis also showed that there was a negative relationship between the mental component summary (MCS) of the patients and the triple domains of PAID (p < 0.001) (Table 3).

The results obtained from the multiple regression model to predict the PCS and MCS of QOL based on problem areas in diabetes and the demographic variables are shown in Table 4. The results showed that the variables of age (β=0.31, p<0.001), the duration of diabetes (β=-0.12, p=0.026), the type of treatment (β=0.12, p=0.023), psychological distress (β=-0.13, p=0.031), and treatment barriers (β=-0.16, p=0.014) were significant predictors of the PCS of QOL, and age (β=0.22, p<0.001), the type of treatment (β=0.11, p=0.044), psychological

TABLE 2 Descriptive statistics of study variables in elderly patients with type 2 diabetes (n = 266).

Variable	Mean ± SD	Min	Max	Range
Quality of life	**48.76 ± 24.30**	**1.67**	**90.83**	**0–100**
PCS[1]	41.32 ± 31.24	0.00	95.83	0–100
MCS[2]	56.65 ± 20.84	3.33	90.00	0–100
PAID[3]	**32.12 ± 11.93**	**2.00**	**60.00**	**0–80**
Psychological distress related to diabetes management	10.47 ± 3.39	2.00	17.00	0–20
Depression-related problems	10.95 ± 4.56	2.00	22.00	0–24
Treatment barriers	11.97 ± 5.29	2.00	26.00	0–36

[1]Physical component summary.
[2]Mental component summary.
[3]Problem Areas in Diabetes.
Bold values means related to the total values of study variables.

TABLE 3 Correlation of study variables in elderly patients with type 2 diabetes (n = 266).

Variable	Quality of life			
PAID	PCS		MCS	
	r	p-value	r	p-value
Psychological distress related to diabetes management	-0.195	**0.001**	-0.293	**0.000**
Depression-related problems	-0.174	**0.004**	-0.261	**0.000**
Treatment barriers	-0.258	**0.000**	-0.297	**0.000**

The bold values related to significant relationship (p<0.01).

distress (β=-0.22, p=0.001), and treatment barriers (β=-0.22, p=0.001) were signifcant predictors of the MCS of QOL among elderly patients with type 2 diabetes (Table 4).

Discussion

The present study revealed that treatment barriers, psychological distress related to diabetes management, the type of treatment, and age were statistically significant predictors of QOL dimensions.

The age of the elderly was one of the most important determinants of the QOL in this study. This finding is in line with the results of the majority of similar studies in this field. In the investigations of Jing et al. (34), age had a significant relationship with the dimensions of the QOL; thus, as people aged older, their QOL decreased. Given that aging affects all major physiological systems, including anatomical and functional systems, and reduces scores in all elements of the elderly's QOL, this seems to be an obvious finding. Senez et al. (35) and Mokhtari et al. (36) investigations support these findings, demonstrating a significant inverse relationship between the average QOL in all domains and the number of comorbidities.

The findings of this study showed that the domains of problem areas in diabetes are favorable predictors of the QOL, with the exception of depression-related problems. Psychological distress related to diabetes management is very common, according to studies conducted in thirteen countries, and has a major impact on diabetes patients' QOL (37). Findings on the investigations of Eriksson (38) and Khalil Karami (39) also indicated that psychological distress is associated with poor QOL in patients with diabetes. To explain these findings, it may be claimed that when the elderly suffers from diseases like diabetes that are accompanied by psychological issues, they experience worry in the face of the sickness and a sense of powerlessness in personal and social relationships, lowering their QOL.

According to the current study, patients with highly perceived treatment barriers had a lower chance of having a good QOL. The results of various studies show that those with highly perceived obstacles have a higher risk of poor QOL (40, 41),

TABLE 4 Linear regression model of the factors associated with quality- of-life (QOL) domains in elderly patients with type 2 diabetes.

Variable	Quality of life among elderly patients with type 2 diabetes							
	PCS (Physical Component Summary)				MCS (Mental Component Summary)			
	SE	Beta	t	Sig	SE	Beta	t	Sig
Age	0.24	0.31	5.31	**0.000**	0.17	0.22	3.65	**0.000**
Gender	4.46	0.13	1.92	0.055	3.16	0.08	1.13	0.259
Duration of diabetes	0.26	-0.12	2.23	**0.026**	0.18	-0.07	1.29	0.196
Number of chronic diseases	3.69	0.05	0.97	0.332	2.62	0.10	1.76	0.080
Marital status	4.05	0.02	0.37	0.711	2.87	0.05	0.85	0.393
Education status	4.47	0.96	1.39	0.164	3.17	0.003	0.04	0.965
Economic status	4.09	-0.05	0.94	0.346	2.90	0.05	0.05	0.417
Living status	2.63	0.07	1.34	0.179	1.86	0.07	1.25	0.212
Kind of treatment	2.78	0.12	2.28	**0.023**	1.97	0.11	2.02	**0.044**
Psychological distress	0.56	-0.13	2.16	**0.031**	0.40	-0.22	-3.50	**0.001**
Depression-related problems	0.31	-0.04	0.68	0.492	0.32	-0.08	-1.16	0.244
Treatment barriers	0.39	-0.16	2.48	**0.014**	0.27	-0.22	-3.25	**0.001**

The bold values related to significant relationship (p<0.01).

which is consistent with the findings of this study. Diabetic caregivers should seek psychological and family counseling to help them overcome the obstacles and challenges of diabetes care as treatment barriers signal problems with regular care plans and access to doctors.

The physical dimension of patients' QOL declined with increasing diabetes duration in the current study, and this finding has been confirmed in other studies (42, 43). Patients who have been sick for a longer period of time face higher medical costs, lost wages owing to illness, and treatment problems. These elements have a direct impact on patients' QOL.

The multiple regression analyses revealed that oral treatment was a good prediction for the QOL. Insulin users experienced fewer issues and a higher QOL in a study conducted in Brazil (44). This could be owing to injection pain, a higher risk of hypoglycemic consequences, or issues with insulin delivery. It should be mentioned that the Sadeghieh study found no link between patients' QOL and the type of medication they were taking (45). This could be owing to the varied statistical population of the study.

Limitations

The current study had a number of limitations. First, the cross-sectional nature of the present study precluded the examination of causality. Second, the results of this study can be generalized only to similar samples and not beyond. Finally, utilizing self-reported questionnaires in surveys may lead to respondents' underestimation or overestimation of their health-related QOL, in turn, may affect the study findings.

The current study cannot be extended to all elderly patients with diabetes because it was conducted among "elderly patients with diabetes" referred to the Imam Hospital Diabetes Clinic in Ardabil (such as patients who are receiving care at home). Because many patients with diabetes are cared for in other locations such as rural areas, the study's lack of access to their individual and socioeconomic characteristics was another limitation. Given that the present study only looks at the QOL of elderly patients with diabetes, it is advised that future studies look at the QOL of other patients with diabetes, depending on problem areas in diabetes.

Conclusion

Individual characteristics and factors connected to health services have the largest impact on the QOL, according to the findings of this study; thus, it is expected that treatments related to these factors will improve the QOL of the elderly with type 2 diabetes. Our recommendation is that, in addition to regular physician appointments, these patients' unpleasant feelings associated to diabetes be evaluated.

Implications

The most effective clinical method in evaluating the QOL problems of diabetic elderly people is to pay attention to the psychological anguish produced by diabetes and to identify it quickly. The outcomes of this study will aid officials in developing and implementing scientifically sound policies to improve the QOL of "elderly peaple with diabetes." Psychological distress and treatment barriers must be highlighted in interventions.

Strengths of study

This study supports the validity, reliability, and responsiveness of the problem areas in PAID and the SF-12 in modeling health outcomes for health practitioners and the health institution management of type 2 diabetics.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ardabil University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HM: The concept of study/design, helping to collect data, analysis, and preparig a manuscript. ES with a detailed review of the proposal and article design. A-HS Study design, important reviews for important intellectual content, data analysis, monitoring, and final review.

Acknowledgments

We appreciate the Deputy Vice-chancellor for Research and Technology of Ardabil University of Medical Sciences, for their valuable support. We acknowledge Dr. Manouchehr Iranparvar, Associate Professor of Endocrinology & Metabolism,

Department of Internal Medicine, School of Medicine, and Imam Khomeini Hospital for his help in conducting the research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer HO declared a shared affiliation with the author(s) ES, AS to the handling editor at the time of review.

The reviewer EM declared a shared affiliation with the author(s) HM to the handling editor at the time of review.

Publisher's Note

References

1. Islam A, Tahir MZ. Health sector reform in south Asia: new challenges and constraints. *Health policy* (2002) 60(2):151–69. doi: 10.1016/S0168-8510(01)00211-1

2. Zanjiran S, Borjali A, Kraskian A. Effect of group logotherapy education on quality of life and general health in women of sanatorium. *Razi J Med Sci* (2015) 21(127):39–51.

3. Jain S, Kaware AC, Doibale MK, Shaikh S, Radhey BK, Mathurkar MP. Morbidity pattern among geriatric population in urban field practice area of district of maharashtra: a cross sectional study. *Int J Community Med Public Health* (2017) 3(2):523–9. doi: 10.18203/2394-6040.ijcmph20160444

4. Maresova P, Javanmardi E, Barakovic S, Barakovic Husic J, Tomsone S, Krejcar O, et al. Consequences of chronic diseases and other limitations associated with old age–a scoping review. *BMC Public Health* (2019) 19(1):1–7. doi: 10.1186/s12889-019-7762-5

5. Bellary S, Kyrou I, Brown JE, Bailey CJ. Type 2 diabetes mellitus in older adults: clinical considerations and management. *Nat Rev Endocrinology* (2021) 17(9):534–48. doi: 10.1038/s41574-021-00512-2

6. Habibi A, Nikpour S, Seiedoshohadaei M, Haghani HA. Quality of life and status of physical functioning among elderly people in west region of Tehran: a cross-sectional survey. *Iran J Nursing* (2008) 21(53):29–39.

7. World Health Organisation. *Diabetes country profiles 2016*. Available at: https://cdn.who.int/media/docs/default-source/country-profiles/diabetes/irn_en.pdf?sfvrsn=5d4dafb7_38&download=true.

8. Mirzaei M, Rahmaninan M, Mirzaei M, Nadjarzadeh A. Epidemiology of diabetes mellitus, pre- diabetes, undiagnosed and uncontrolled diabetes in central Iran: results from yazd health study. *BMC Public Health* (2020) 20(1):1–9. doi: 10.1186/s12889-020-8267-y

9. Habibi Soola A, Davari M, Rezakhani Moghaddam H. Determining the predictors of self-management behaviors in patients with type 2 diabetes: An application of socio-ecological approach. *Front Public Health* (2022) 10:820238. doi: 10.3389/fpubh.2022.820238

10. Khanna A, Bush AL, Swint JM, Peskin MF, Street RL, Naik AD. Hemoglobin a 1c improvements and better diabetes-specific quality of life among participants completing diabetes self-management programs: A nested cohort study. *Health Qual Life outcomes* (2012) 10(1):48. doi: 10.1186/1477-7525-10-48

11. Alshayban D, Joseph R. Health-related quality of life among patients with type 2 diabetes mellitus in Eastern province, Saudi Arabia: A cross-sectional study. *PLoS One* (2020) 15(1):e0227573. doi: 10.1371/journal.pone.0227573

12. de Oliveira LD, Souza EC, Rodrigues RA, Fett CA, Piva AB. The effects of physical activity on anxiety, depression, and quality of life in elderly people living in the community. *Trends Psychiatry psychotherapy* (2019) 41:36–42. doi: 10.1590/2237-6089-2017-0129

13. Bech P. *Rating scales for psychopathology, health status and quality of life: A compendium on documentation in accordance with the DSM-III-R and WHO systems*. Berlin: Springer Science & Business Media (2012).

14. Şahin DS, Özer Ö, Yanardağ MZ. Perceived social support, quality of life and satisfaction with life in elderly people. *Educ Gerontology* (2019) 45(1):69–77. doi: 10.1080/03601277.2019.1585065

15. Zabihi Maddah Z, Aghajani Mersa H. Dimensions of quality of life of the elderly by reviewing previous research. *Soc Welfare Quarterly* (2020) 19(75):123–81.

16. Azizpour I, Mehri S, Moghaddam HR, Mirzaei A, Soola AH. The impact of psychological factors on bereavement among frontline nurses fighting covid-19. *Int J Afr Nurs Sci* (2021) 15:100341. doi: 10.1016/j.ijans.2021.100341

17. Knowles SR, Apputhurai P, O'Brien CL, Ski CF, Thompson DR, Castle DJ. Exploring the relationships between illness perceptions, self-efficacy, coping strategies, psychological distress and quality of life in a cohort of adults with diabetes mellitus. *Psychology Health Med* (2020) 25(2):214–28. doi: 10.1080/13548506.2019.1695865

18. Jin Y, Ding L, Wang Q, He L, Nie M, Song X, et al. Factors affecting the quality of life of elderly diabetic patients: survey in north and south wanjiang river regions. *Nan fang yi ke da xue xue bao= J South Med University* (2014) 34(2):283–5.

19. Taha RM. Geriatric conditions and quality of life among older adults with diabetes. *Egyptian J Geriatrics Gerontology* (2021) 8(2):14–9. doi: 10.21608/ejgg.2021.204173

20. Davari M, Moghaddam HR, Soola AH. Identifying the predictors of self-management behaviors in patients with diabetes based on ecological approach: A systematic review. *Curr Diabetes Rev* (2021) 17(6):71–83. doi: 10.2174/1573399816666201026161009

21. Dal Canto E, Ceriello A, Rydén L, Ferrini M, Hansen TB, Schnell O, et al. Diabetes as a cardiovascular risk factor: an overview of global trends of macro and micro vascular complications. *Eur J Prev Cardiol* (2019) 26(2_suppl):25–32. doi: 10.1177/2047487319878371

22. Kim DJ, Cho SJ. Psychological state and self-esteem of elderly living alone in relation to socio-demographic characteristics. *Advanced Sci Technology* (2015) 119:28–32. doi: 10.14257/astl.2015.119.07

23. Nedeljkovic UD, Krstic NM, Varagic-Markovic SL, Putnik SM. Quality of life and functional capacity one year after coronary artery bypass graft surgery. *Acta Chirurgica Iugoslavica* (2011) 58(3):81–6. doi: 10.2298/ACI1103081N

24. Gomez-Pimienta E, González-Castro TB, Fresan A, Juárez-Rojop IE, Martínez-López MC, Barjau-Madrigal HA, et al. Decreased quality of life in individuals with type 2 diabetes mellitus is associated with emotional distress. *Int J Environ Res Public Health* (2019) 16(15):2652. doi: 10.3390/ijerph16152652

25. Graue M, Haugstvedt A, Wentzel-Larsen T, Iversen MM, Karlsen B, Rokne B. Diabetes-related emotional distress in adults: reliability and validity of the Norwegian versions of the problem areas in diabetes scale (PAID) and the diabetes distress scale (DDS). *Int J Nurs Stud* (2012) 49(2):174–82. doi: 10.1016/j.ijnurstu.2011.08.007

26. Kalra S, Jena BN, Yeravdekar R. Emotional and psychological needs of people with diabetes. *Indian J Endocrinol Metab* (2018) 22(5):696. doi: 10.4103/ijem.IJEM_579_17

27. Kampling H, Mittag O, Herpertz S, Baumeister H, Kulzer B, Petrak F. Can trajectories of glycemic control be predicted by depression, anxiety, or diabetes-related distress in a prospective cohort of adults with newly diagnosed type 1 diabetes? results of a five-year follow-up from the German multicenter diabetes cohort study (GMDC-study). *Diabetes Res Clin Practice* (2018) 141:106–17. doi: 10.1016/j.diabres.2018.04.017

28. Gois C, Duarte TA, Paulino S, Raposo JF, Carmo I, Barbosa A. Depressive symptoms are associated with poor glycemic control among women with type 2 diabetes mellitus. *BMC Res notes* (2018) 11(1):38. doi: 10.1186/s13104-018-3141-z

29. Nasseh H, Arzaghi M, Ghasemzade R, Rahimi Foroushani A, Kamali M, Arastoo AA. Status of problem areas in diabeticin kahrizak nursing home in Tehran. *Iranian Journl Diabetes Lipid Disord* (2012) 11(5):449–54.

30. Fenwick EK, Rees G, Holmes-Truscott E, Browne JL, Pouwer F, Speight J. What is the best measure for assessing diabetes distress? a comparison of the problem areas in diabetes and diabetes distress scale: results from diabetes MILES–Australia. *J Health Psychol* (2018) 23(5):667–80. doi: 10.1177/1359105316642006

31. Tinsley LJ, Commissariat PV, Volkening L, Anderson B, Katz M, Laffel LM. Establishing a clinically meaningful cut-point for the PAID-PR (Problem areas in diabetes-parent revised) survey. *Diabetes* 2018 67(Supplement_1). doi: 10.2337/db18-1395-P

32. Arzaghi SM, Mahjouri MY, Heshmat R, Khashayar P, Larijani B. Psychometric properties of the Iranian version of the problem areas in diabetes scale (IR-PAID-20). *J Diabetes Metab Disord* (2011) 10:16.

33. Montazeri A, Vahdaninia M, Mousavi SJ, Omidvari S. The Iranian version of 12-item short form health survey (SF-12): factor structure, internal consistency and construct validity. *BMC Public Health* (2009) 9(1):341. doi: 10.1186/1471-2458-9-341

34. Jing X, Chen J, Dong Y, Han D, Zhao H, Wang X, et al. Related factors of quality of life of type 2 diabetes patients: a systematic review and meta-analysis. *Health Qual Life outcomes* (2018) 16(1):1–4. doi: 10.1186/s12955-018-1021-9

35. Senez B, Felicioli P, Moreau A, Le Goaziou MF. Quality of life assessment of type 2 diabetic patients in general medicine. *Presse medicale (Paris France: 1983)* (2004) 33(3):161–6. doi: 10.1016/S0755-4982(04)98513-2

36. Mokhtari Z, Gheshlagh RG, Kurdi A. Health-related quality of life in Iranian patients with type 2 diabetes: An updated meta-analysis. *Diabetes Metab Syndrome: Clin Res Rev* (2019) 13(1):402–7. doi: 10.1016/j.dsx.2018.10.007

37. Peyrot M, Rubin RR, Lauritzen T, Snoek FJ, Matthews DR, Skovlund SE. Psychosocial problems and barriers to improved diabetes management: results of the cross-national diabetes attitudes, wishes and needs (DAWN) study. *Diabetic Med* (2005) 22(10):1379–85. doi: 10.1111/j.1464-5491.2005.01644.x

38. Eriksson AK, Gustavsson JP, Hildin A, Granath F, Ekbom A, Ostenson CG. Personality traits and abnormal glucose regulation in middle-aged Swedish men and women. *Diabetes Res Clin Pract* (2012) 95(1):145–52. doi: 10.1016/j.diabres.2011.10.003

39. Karami K, Karimi J, Sepahvand T. The role of neurosis and mindfulness in predicting the quality of life of diabetes patients in delfan. *J Sabzevar Univ Med Sci* (2019) 26(5):568–74.

40. Mashitani T, Hayashino Y, Okamura S, Kitatani M, Furuya M, Iburi T, et al. Diabetes treatment-related quality of life is associated with levels of self-care activities in insulin injection among Japanese patients with type 2 diabetes: Diabetes distress and care registry at tenri (DDCRT 8). *Acta diabetologica* (2015) 52(4):639–47. doi: 10.1007/s00592-015-0725-0

41. O'Shea MP, Teeling M, Bennett K. Comorbidity, health-related quality of life and self-care in type 2 diabetes: a cross-sectional study in an outpatient population. *Irish J Med Sci (1971-)* (2015) 184(3):623–30. doi: 10.1007/s11845-014-1190-4

42. Eljedi A, Mikolajczyk RT, Kraemer A, Laaser U. Health-related quality of life in diabetic patients and controls without diabetes in refugee camps in the Gaza strip: a cross-sectional study. *BMC Public Health* (2006) 6(1):268. doi: 10.1186/1471-2458-6-268

43. Lou P, Qin Y, Zhang P, Chen P, Zhang L, Chang G, et al. Association of sleep quality and quality of life in type 2 diabetes mellitus: a cross-sectional study in China. *Diabetes Res Clin practice* (2015) 107(1):69–76. doi: 10.1016/j.diabres.2014.09.060

44. Gross CC, Scain SF, Scheffel R, Gross JL, Hutz CS. Brazilian Version of the problem areas in diabetes scale (B-PAID): validation and identification of individuals at high risk for emotional distress. *Diabetes Res Clin practice* (2007) 76(3):455–9. doi: 10.1016/j.diabres.2006.09.022

45. Sadeghieh Ahari S, Arshi S, Iranparvar M, Amani F, Siahpoosh H. The effect of complications of type ii diabetes on patients' quality of life. *J Ardabil Univ Med Sci* (2009) 8(4):394–402.

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 08 September 2022
DOI 10.3389/fendo.2022.943750

OPEN ACCESS

EDITED BY
Hiroshi Okada,
Matsushita Memorial Hospital, Japan

REVIEWED BY
Giulia Ferrannini,
Karolinska Institutet (KI), Sweden
Ching Feng Weng,
Xiamen Medical College, China

*CORRESPONDENCE
Li Yan
yanli@mail.sysu.edu.cn
Guixia Wang
gwang168@jlu.edu.cn

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 14 May 2022
ACCEPTED 19 August 2022
PUBLISHED 08 September 2022

CITATION
Sun K, Xiao X, You L, Hong X, Lin D, Liu Y, Huang C, Wang G, Li F, Sun C, Chen C, Lu J, Qi Y, Wang C, Li Y, Xu M, Ren M, Yang C, Wang G and Yan L (2022) Development and validation of a nomogram for assessing risk of isolated high 2-hour plasma glucose.
Front. Endocrinol. 13:943750.
doi: 10.3389/fendo.2022.943750

Development and validation of a nomogram for assessing risk of isolated high 2-hour plasma glucose

Kan Sun[1†], Xianchao Xiao[2†], Lili You[1†], Xiaosi Hong[1], Diaozhu Lin[1], Yujia Liu[2], Chulin Huang[1], Gang Wang[2], Feng Li[1], Chenglin Sun[2], Chaogang Chen[3], Jiahui Lu[3], Yiqin Qi[1], Chuan Wang[1], Yan Li[1], Mingtong Xu[1], Meng Ren[1], Chuan Yang[1], Guixia Wang[2*] and Li Yan[1*]

[1]Department of Endocrinology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, [2]Department of Endocrinology, The First Hospital of Jilin University, Changchun, China, [3]Department of Clinical Nutrition, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

A tool was constructed to assess need of an oral glucose tolerance test (OGTT) in patients whose fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) are normal. Data was collected from the longitudinal REACTION study conducted from June to November 2011 (14,686 subjects, aged ≥ 40 y). In people without a prior history of diabetes, isolated high 2-hour plasma glucose was defined as 2-hour plasma glucose ≥ 11.1 mmol/L, FPG < 7.0 mmol/L, and HbA1c < 6.5%. A predictive nomogram for high 2-hour plasma glucose was developed *via* stepwise logistic regression. Discrimination and calibration of the nomogram were evaluated by the area under the receiver operating characteristic curve (AUC) and Hosmer-Lemeshow test; performance was externally validated in Northeast China. Parameters in the model included gender, age, drinking status, marriage status, history of hypertension and hyperlipidemia, waist-to-hip ratio, FPG, and HbA1c. All variables were noninvasive, except FPG and HbA1c. The AUC of the nomogram for isolated high 2-hour plasma glucose was 0.759 (0.727-0.791) in the development dataset. The AUCs of the internal and externally validation datasets were 0.781 (0.712-0.833) and 0.803 (0.778-0.829), respectively. Application of the nomogram during the validation study showed good calibration, and the decision curve analysis indicated that the nomogram was clinically useful. This practical nomogram model may be a reliable screening tool to detect isolated high 2-hour plasma glucose for individualized assessment in patients with normal FPG and HbA1c. It should simplify clinical practice, and help clinicians in decision-making.

KEYWORDS

diabetes mellitus, hyperglycemia, 2h OGTT, nomogram model, risk assessment model

Introduction

Diabetes mellitus (DM) is a metabolic disorder that impairs biological function. The etiological factors are both genetic and environmental. In 2017, it was estimated that 9.7% of the United States population had DM (1). In the same year, the prevalence of DM in China was 12.8% (2). The high prevalence of DM and its related disability and mortality has made it a critical health problem worldwide (3–5). Delays in the diagnosis and treatment of DM lead to a greater incidence of associated mortality. An improved method for identifying hyperglycemia could significantly benefit the population at risk (6–8).

A diagnosis of DM is currently based on plasma glucose criteria: fasting plasma glucose (FPG); the 2-hour oral glucose tolerance test (2-h OGTT); or hemoglobin A1c (HbA1c) (9). Each is considered standard, but measuring FPG and HbA1c levels is more convenient than administering the 2-h OGTT. The latter requires two blood samples, and is time-consuming and cumbersome for both the primary care physician and the patients. Especially when both the FPG and HbA1c levels are normal, compliance with the 2-h OGTT may be neglected (10). A simple and convenient tool is urgently needed, that is appropriately sensitive and specific, to assess the risk of OGTT ≥ 11.1 mmol/L at 2 hours (i.e., isolated high 2-hour plasma glucose), in populations with FPG and HbA1c levels that are within normal range.

There have been several reports of assessment models that identify risk of DM, with areas under the receiver-operating characteristic curve (AUC) of 0.60 to 0.80. The majority of these models outperformed their validation datasets in their original population (11–13). A nomogram model designed to assess risk factors for DM based on 8999 patients in Korea showed an AUC of ~0.80 (14). In 2013, Zhou et al. (12) developed the new Chinese Diabetes Risk Score for detecting DM in a Chinese population, and the AUC for undiagnosed type 2 diabetes was 0.748. Most mathematical models designed for assessing risk of DM have not included 2-h OGTT, and their accuracy has been low.

The 2-h OGTT has been the mainstay for diagnosing DM for decades, and is the gold standard recognized by the American Diabetes Association (9). Two-hour OGTT detects diabetes most efficiently and provides metabolically relevant information. Furthermore, ~40% of subjects who later develop DM are within the normal glucose tolerance at OGTT. These subjects constitute a large reservoir of future DM cases (15). Yet, there is no nomogram to depict an individual's probability of DM based on isolated high 2-hour plasma glucose.

The present study initially developed and validated a convenient predictive nomogram for patients with FPG and HbA1c levels within normal range, who require a 2-h OGTT. This approach should improve our ability to identify individuals who are at high risk of isolated high 2-hour plasma glucose, and facilitate a more personalized approach to their care.

Methods

Participants

From June to November of 2011, a study known as REACTION (i.e., Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal) was performed in China. REACTION was a multi-institutional large prospective cohort study. REACTION was conducted in 25 localities across the country, divided by geographic location (Northeast, North, East, South Central, Northwest, and Southwest China). Participants in the research had to be at least 40 years old and were identified using local registration data. The results of this research have already been published (16, 17). The study procedure followed the principles of the Helsinki Declaration II and was approved by the Ethics Committee of Ruijin Hospital (IRB number: [2011] Ethics Record No (14).

To construct the assessment model, data for the development and internal validation populations were collected in Guangzhou, South China (Figure 1), which was cross-sectional data and one of the parts of the REACTION study. During the recruitment process, 10,104 residents aged 40 and above were requested to participate by examination notifications or home visits, and 9916 (98.1%) signed the consent form and consented to take part in the survey.

For the external validation of the assessment model, data for the external validation population was collected from Changchun, Northeast China (Figure 1), which was cross-sectional data and another parts of REACTION study. Of the 10,080 residents aged at least 40 years, 9598 (95.2%) signed the consent form and completed the survey.

Participants in the initial development and validation populations were excluded for the following reasons: history of DM or lack of information regarding history of DM; lack of FPG or HbA1c data; FPG ≥ 7.0 mmol/L or HbA1c ≥ 6.5%; or missing 2-hour OGTT data.

Finally, 7841 and 6845 individuals were included in the development and validation groups, from Guangzhou and Changchun, respectively (Figure 1). The missing-at-random assumption was used for missing data, and multiple imputations were done using the multivariate imputation by chained equations (MICE) approach with 5 imputed datasets and 10 iterations (18–20).

Clinical and biochemical measurements

A standardized data form was created to retrieve all relevant information on lifestyle factors, medical histories, socio demographics, and family histories. Information collected by trained medical personal included the following: gender; age; family history of DM (yes or no); marriage status (married or

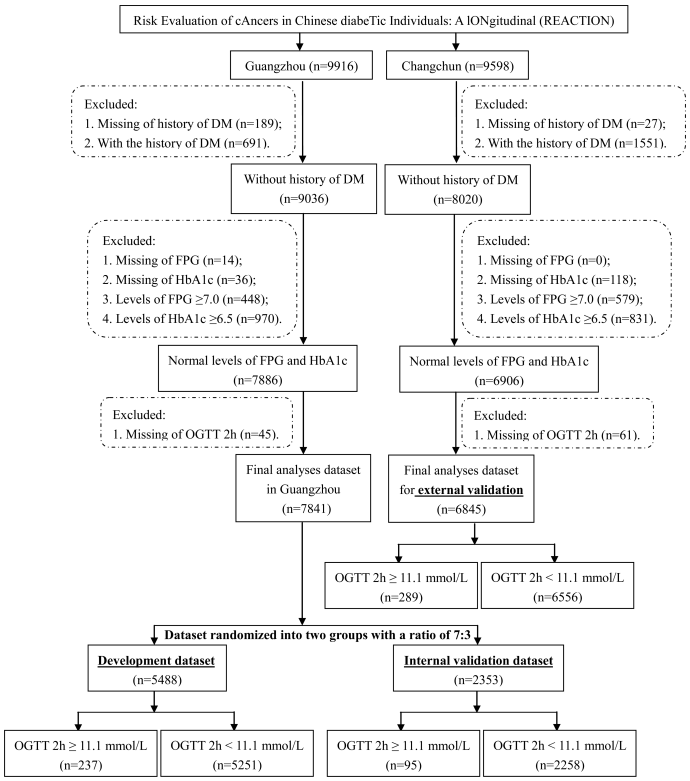


FIGURE 1
Flow chart of the selection of the research participants.

cohabitating, unmarried, and others); history of hypertension (yes or no); and hyperlipidemia (yes or no). Never, current (smoking or drinking frequently over the preceding 6 months), or ever were the categories for smoking and drinking behaviors (prior to the previous 6 months only). By adding questions on the frequency and duration of walking and moderate or vigorous activities, a condensed version of the International Physical Activity Questionnaire (IPAQ) was utilized to evaluate physical activity during leisure time (21). For evaluating overall physical activity, separate metabolic equivalent hours per week (MET-h/week) calculations were made.

All subjects had their anthropometric measures taken using conventional methods by well-trained assessors. With individuals clothed in light indoor clothing and no shoes, body weight and standing height were measured to the closest 0.1 cm and 0.1 kg, respectively. The Body Mass Index (BMI) was computed by dividing the weight in kilograms by the height in meters squared (kg/m^2). At the end of a mild expiration, participants' waist circumference (WC) was measured at the umbilical level to the closest 0.1 cm while standing. A plastic flexible tape was used to measure the hipline above the great trochanters to the closest 0.1 cm. The waist-to-hip ratio (WHR) was computed by subtracting the WC from the hipline. After the participants had been sitting and resting peacefully for more than 5 minutes with feet on the ground and back supported, blood pressure measurements were taken three times consecutively by the same observer using an automated electronic instrument (OMRON, Omron, China). For the analysis, each subject's mean systolic and diastolic blood pressures (SBP and DBP) were employed.

Participants were requested to fast for at least 10 hours before the baseline survey, and venous blood samples were obtained for laboratory tests by competent nurses. Blood samples were centrifuged at 2500g for 15 minutes to extract serum or plasma within 2 hours of collection and kept at –80°C at the Shanghai Institute of Endocrine and Metabolic Disease's Central Laboratory (certified by the College of American Pathologists). For both the Guangzhou and Changchun datasets, HbA1c was measured using high-performance liquid chromatography (Bio-Rad, Hercules, CA, USA) at the Central Laboratory.

Individuals were required to attend a clinical facility where a health care professional can obtain venous blood samples at times 0 and 2 h after an oral 75-g anhydrous glucose challenge. For the Guangzhou dataset, measurements of FPG and 2-h plasma glucose were performed using an autoanalyzer

(Beckman CX-7 Biochemical Auto-analyzer, Brea, CA) in the Central Laboratory of Sun Yat-sen Memorial Hospital. For the Changchun dataset, these measurements were conducted with a Bayer ADVIA2400 (Leverkusen, Germany) in the Central Laboratory of First Hospital of Jilin University.

Development of an individualized assessment model

Using a simple random sample procedure, the 7841 subjects registered in Guangzhou were separated into development model (n = 5488) and internal validation (n = 2353) datasets in a 7:3 ratio. Recognition models for undiagnosed isolated high 2-hour plasma glucose were developed using data from the training set. The assessment model was created using a multivariable binary logistic regression model and the backward stepwise selection approach.

Gender, age, drinking status, married status, history of hypertension, history of hyperlipidemia, SBP, DBP, BMI, WC and WHR were all included as noninvasive clinical variables in multivariable logistic regression analysis. The likelihood ratio test using Akaike's information criteria was used to do backward stepwise selection (AIC). The final model was chosen based on its lowest AIC.

The noninvasive model included the following factors: gender, age, drinking status, marriage status, history hypertension, history of hyperlipidemia, SBP and WHR. The FPG and HbA1c results were added to the noninvasive model and considered for final construction of the nomogram. For a quantitative tool to assess the individual probability of isolated high 2-hour plasma glucose, a nomogram was established for further application using the rms package in RStudio software version 3.6.1.

The nomogram's validation and calibration

The internal and external validation populations (Guangzhou, n = 2353 and Changchun, n = 6845, respectively) were used to validate the nomogram model from the development population. The accuracy of the models was assessed using a receiver operating characteristic (ROC) curve analysis. The concordance index was used to measure the model's effectiveness in assessing isolated high 2-hour plasma glucose (C-index). The calibration of the nomogram was assessed using a calibration plot and the Hosmer-Lemeshow test. Using rmda in RStudio Version 3.6.1, decision curve analysis was used to evaluate the net benefit of the nomogram models at various threshold probabilities in the datasets.

Statistical methods

Except for skewed variables, which are given as median, continuous variables are shown as mean standard deviation (interquartile range, IQR). In both the Guangzhou and Changchun datasets, an independent samples t-test or a Kruskal-Wallis H test was employed to analyze the differences between subjects with and without isolated high 2-hour plasma glucose. Numbers are used to express categorical variables (percent). The differences based on isolated high 2-hour plasma glucose were compared using Chi-squared testing. The impact of clinical and biochemical measures on the prevalence of isolated high 2-hour plasma glucose was determined using logistic regression, and the results were displayed with odds ratios (ORs) and 95 percent confidence intervals (95% CIs). Model 1 included noninvasive clinical factors selected after backward stepwise regression with AIC in multivariate logistic regression. Model 2 further included FPG and HbA1c based on Model 1.

RStudio program was used for statistical analysis (version 3.6.1). All statistical tests were two-sided, with a significance level of 0.05.

Results

Clinical characteristics

After excluding participants with FPG ≥ 7.0 mmol/L or HbA1c ≥ 6.5%, the prevalence of isolated high 2-hour plasma glucose was 4.11% in Guangzhou and 4.22% in Changchun, and the two datasets were similar (Table 1; P = 1.000). Participants with isolated high 2-hour plasma glucose were significantly older; had greater BMI and WC; and higher FPG, HbA1c, and blood pressure; compared with those without isolated high 2-hour plasma glucose. In both regions (Guangzhou and Changchun), the participants with isolated high 2-hour plasma glucose were significantly more likely to have a history of hyperlipidemia, hypertension and metabolic syndrome.

Associations between isolated high 2-hour plasma glucose and the selected biochemical measurements were confirmed by the logistic regression analyses (Table 2). Participants with the following were more likely to show high 2-hour plasma glucose: drinking (OR: 1.04, 95% CI: 0.79-1.35); non-married (OR: 1.15, 95% CI: 0.92-1.42); and with a history of hypertension (OR: 1.48, 95% CI: 1.06-2.06). Moreover, the following were significantly associated with an increased prevalence of isolated high 2-hour plasma glucose: SBP (OR: 1.01, 95% CI: 1.00-1.02); FPG (OR: 2.72, 95% CI: 2.16-3.43); and HbA1c (OR: 3.43, 95% CI: 2.21-5.39).

TABLE 1 Characteristics of participants in the Guangzhou and Changchun datasets in China; without and with isolated high 2-hour plasma glucose.

	Guangzhou			Changchun		
	No	Yes*	*P*	No	Yes*	*P*
Subjects, n	7509	332		6556	289	
Age, y	55.16 ± 7.64	58.62 ± 9.89	<0.001	56.85 ± 9.77	61.36 ± 10.17	<0.001
Male	2099 (27.95)	109 (32.83)	0.0613	2070 (31.57)	118 (40.83)	0.001
Family history of DM	1140 (15.19)	59 (17.78)	0.228	754 (11.50)	33 (11.42)	1.000
Current smoking	745 (9.92)	40 (12.05)	0.416	908 (13.85)	45 (15.57)	0.703
Current drinking	246 (3.28)	22 (6.63)	0.003	557 (8.50)	38 (13.15)	0.018
Married or cohabitating	6801 (90.57)	283 (85.24)	0.005	6051 (92.30)	267 (92.39)	0.709
Hypertension history	997 (13.28)	86 (25.90)	<0.001	1051 (16.03)	90 (31.14)	<0.001
Hyperlipidemia history	461 (6.14)	41 (12.35)	<0.001	422 (6.44)	34 (11.76)	<0.001
SBP, mmHg	124.11 ± 15.27	131.40 ± 16.56	<0.001	138.43 ± 21.53	148.85 ± 21.87	<0.001
DBP, mmHg	74.77 ± 9.51	77.16 ± 9.79	<0.001	79.95 ± 11.94	82.91 ± 11.77	<0.001
Height, cm	158.39 ± 7.40	157.74 ± 7.07	0.103	161.43 ± 7.58	161.01 ± 7.67	0.366
Weight, kg	58.56 ± 9.11	59.00 ± 9.25	0.395	64.69 ± 10.78	66.35 ± 11.31	0.015
BMI, kg/m^2	23.29 ± 2.96	23.68 ± 3.19	0.033	24.76 ± 3.29	25.53 ± 3.59	<0.001
WC, cm	80.59 ± 8.72	82.49 ± 9.46	<0.001	83.01 ± 9.26	86.17 ± 8.23	<0.001
Hipline, cm	93.60 ± 6.50	93.57 ± 6.98	0.933	96.91 ± 6.92	98.47 ± 6.73	<0.001
WHR	0.86 ± 0.06	0.88 ± 0.06	<0.001	0.86 ± 0.06	0.87 ± 0.05	<0.001
FPG, mmol/L	5.13 ± 0.57	5.78 ± 0.65	<0.001	5.47 ± 0.53	5.98 ± 0.56	<0.001
HbA1c,%	5.79 ± 0.35	5.97 ± 0.32	<0.001	5.67 ± 0.38	5.94 ± 0.35	<0.001
Physical activity (MET-h/week)	21.0[10.5, 45.0]	21.0[9.0, 43.0]	0.185	21.0[0.0, 42.0]	20.0[0.0, 31.5]	0.371
Prevalence of metabolic syndrome (%)	1120 (16.25)	101 (30.42)	<0.001	1731 (26.40)	152 (52.60)	<0.001
Prevalence of hypertension (%)	1843 (24.54)	146 (43.98)	<0.001	3122 (47.62)	198 (68.51)	<0.001
Prevalence of dyslipidemia (%)	5392 (71.81)	269 (81.02)	<0.001	4225 (64.44)	217 (75.09)	<0.001

*Without (no) and with (yes) isolated high 2-hour plasma glucose. Guangzhou and Changchun datasets are n = 7841 and n = 6845, respectively. Data are reported as n (%) for categorical variables and mean ± SD or median (interquartile ranges) for skewed variables. The P-value is derived from the univariable association analyses between each of the characteristics and isolated high 2-hour plasma glucose.

Development and validation of a predictive model for 2-h OGTT glucose ≥ 11.1 mmol/L

The best noninvasive model (model 1) generated after backward stepwise regression with AIC in multivariate logistic regression suggested that the following might be factors that influence the incidence of isolated high 2-hour plasma glucose: gender, age, drinking status, marriage status, history of hypertension, history of hyperlipidemia, SBP, and WHR. After adding FPG and HbA1c to the noninvasive model to generate the nomogram, the C-index was larger (Table 2). The final model for individualized assessment with the incorporated risk factors was depicted as a nomogram (Figure 2).

In the development, interval validation, and external validation datasets, a ROC curve was created to test the risk variables' capacity to identify the incidence of isolated high 2-hour plasma glucose (Figure 3). The AUCs of the ROC were 0.759 (95 percent CI: 0.727-0.791), 0.781 (95 percent CI: 0.712-0.833), and 0.803 (95 percent CI: 0.778-0.829) in the development, internal validation, and external validation datasets, respectively.

In the internal and external validation datasets, the calibration curve of the evaluating nomogram for the prevalence of isolated high 2-hour plasma glucose demonstrated good agreement (Figure 4). The Development datasets (Guangzhou) (P = 0.600), and external validation datasets (Changchun) (P = 0.825) produced nonsignificant P-values for the Hosmer-Lemeshow test, confirming satisfactory nomogram model calibration.

Clinical use

The nomogram's clinical usefulness was examined using a decision curve analysis (Figure 5). The standard net benefit utilizing the models was represented on the y-axis, and the threshold probability for isolated high 2-hour plasma glucose was plotted on the x-axis. The decision curve revealed that the nomogram model was more effective for determining the prevalence of isolated high 2-hour plasma glucose. than either the treat-all-participant scheme or the treat-none scheme when the threshold probability was between 0.2 and 0.7. In both the

TABLE 2 Risk of factors for isolated high 2-hour plasma glucose in the development dataset [1].

	Model 1			Model 2		
	β	OR (95% CI)	*P*	β	OR (95% CI)	*P*
Intercept	-10.178	—	<0.001	-20.543	—	<0.001
Age	0.029	1.03 (1.01, 1.05)	<0.001	0.020	1.02 (1.00, 1.04)	0.020
Female	0.051	1.05 (0.78, 1.44)	0.745	0.049	1.05 (0.77, 1.44)	0.757
Drinking status	0.056	1.06 (0.81, 1.36)	0.669	0.041	1.04 (0.79, 1.35)	0.762
Marriage status	0.134	1.15 (0.92, 1.41)	0.203	0.139	1.15 (0.92, 1.42)	0.209
Hypertension history	0.410	1.51 (1.08, 2.07)	0.013	0.395	1.48 (1.06, 2.06)	0.019
Hyperlipidemia history	0.331	1.39 (0.90, 2.07)	0.117	0.271	1.31 (0.84, 1.97)	0.210
SBP	0.018	1.02 (1.01, 1.03)	<0.001	0.012	1.01 (1.00, 1.02)	0.011
WHR[2]	0.032	1.03 (1.01, 1.05)	0.004	0.020	1.02 (1.00, 1.04)	0.072
Physical activity (MET-h/week)	-0.002	1.00 (0.99, 1.00)	0.240	-0.003	1.00 (0.99, 1.00)	0.114
FPG	NA	NA	NA	1.001	2.72 (2.16, 3.43)	<0.001
HbA1c	NA	NA	NA	1.232	3.43 (2.21, 5.39)	<0.001
C-index datasets						
Development		0.676 (0.641-0.711)			0.759 (0.727-0.791)	
Internal validation		0.664 (0.602-0.726)			0.773 (0.712-0.833)	
External validation		0.686 (0.655-0.716)			0.803 (0.778-0.829)	

[1]β is the regression coefficient. Participant without (with) isolated high 2-hour plasma glucose was defined as 0 (1).
[2]Increasing for 0.01 units. NA, Not Available.

development and validation datasets, the net effect was positive within this range.

Discussion

In this study, a nomogram model was developed and validated for assessing the risk of isolated high 2-hour plasma glucose. The analysis was based on 2 large cross-sectional datasets from Guangzhou (South China) and Changchun (North China). The model incorporates 10 indices: gender, age, drinking status, marriage status, history of hypertension, history of hyperlipidemia, SBP, WHR, FPG, and HbA1c. Good discrimination was demonstrated in both the development and validation sets of subjects. The performance of the nomogram model is adequate for detecting isolated high 2-hour plasma glucose in the Chinese population.

Relying on the 2-h OGTT for the prevention and diagnosis of DM has several advantages. It can establish whether a subject has impaired glucose tolerance or undiagnosed type 2

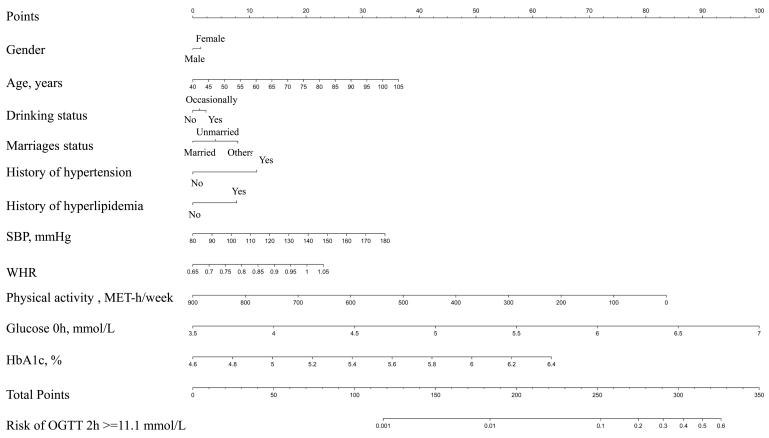


FIGURE 2
Nomogram for participants with isolated high 2-hour plasma glucose.

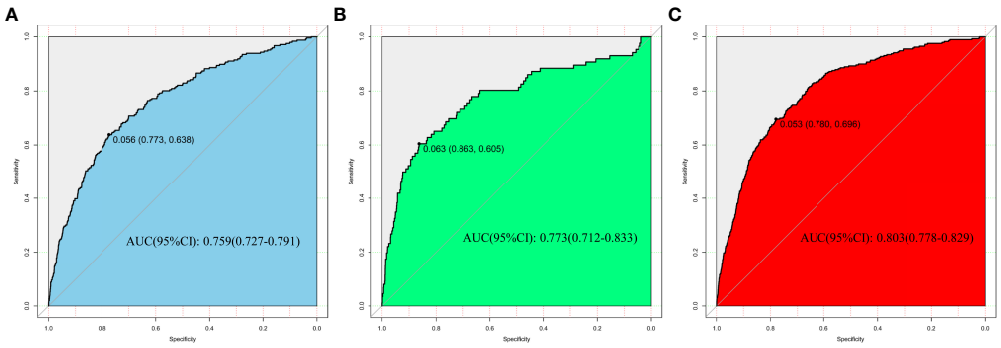


FIGURE 3
Nomogram performance for assessing the rate of isolated high 2-hour plasma glucose. **(A)** Development dataset. **(B)** Internal validation dataset. **(C)** External validation dataset.

diabetes, predicts the risk of heart disease more effectively than FPG, and possibly diagnoses more patients with diabetes (15, 22, 23). Besides, due to the lack of standardized detection methods and the detection results are susceptible to many factors, such as detection methods, anemia and abnormal hemoglobin diseases, red blood cell conversion speed, age and so on, the use of HbA1c alone as the diagnostic as a diagnostic criterion for diabetes has a low predictive value (24). However, the American Diabetes Association suggests abandoning the 2-h OGTT because it is time consuming, poorly reproducible, and not well accepted by patients (25). Furthermore, the 2-h OGTT is often accompanied by adverse reactions such as nausea and vomiting (26). Thus, if subjects who do not need 2-h OGTT could be identified, this would save medical resources and reduce the rate of adverse reactions. In this study, we developed and validated a nomogram model for assessing the risk of high 2-hour plasma glucose. The nomogram is valuable for distinguishing subjects who need a 2-h OGTT, and thereby improves the management of patients.

The development dataset was obtained from Guangzhou from South China. Through univariate analysis and subsequent multivariable analysis, the following independent factors were identified: gender, age, drinking status, marriage status, history of hypertension, history of hyperlipidemia, SBP, WHR, FPG and HbA1c.

To minimize over-fitting and assess generalizability, the nomogram must be validated. Calibration plots demonstrated the best agreement between prediction and actual observation in the current investigation, ensuring the repeatability and dependability of the constructed nomogram. The model also suited the datasets, which included patients from both the south (internal validation) and north (external validation) of China. This supports the widespread usage of this nomogram, independent of area, lifestyle, or health-care inequities. To our best knowledge, this is the first nomogram for identifying participants who are risk of isolated high 2-hour plasma glucose. It is based on a large database from South and North China. Using an easy scoring system, both physicians and

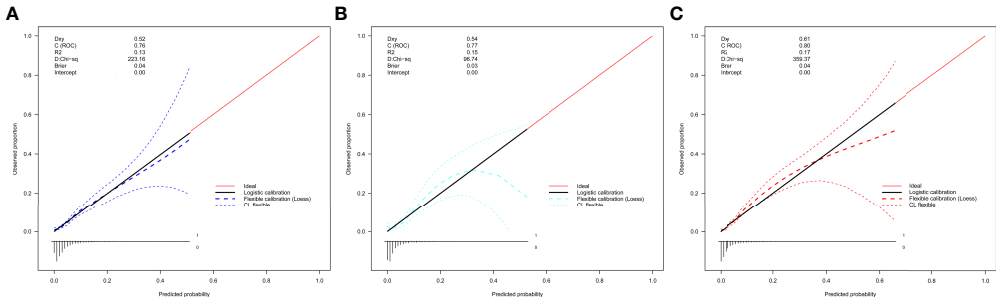


FIGURE 4
Calibration curves of the nomogram for rates of isolated high 2-hour plasma glucose in the validation datasets. **(A)** Development datasets (Guangzhou). **(B)** Internal validation datasets (Guangzhou). **(C)** External validation datasets (Changchun). The curves represent calibration of each model in terms of agreement between the assessed risk and observed outcomes of isolated.

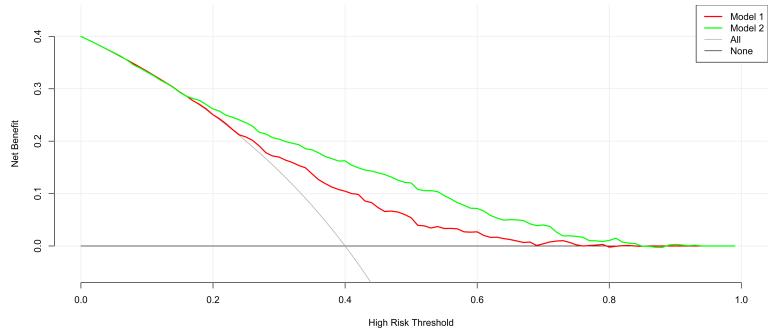


FIGURE 5
Decision curve analysis for the nomogram model in the development and internal and external validation datasets.

patients can determine if a 2-h OGTT is necessary, even when both the FPG and HbA1c levels have not reached the criteria for a diagnosis of DM. Identifying subgroups of participants at varied risk of isolated high 2-hour plasma glucose can benefit the selection of care options. Determining which subjects require additional 2-h OGTT for the diagnosis of DM remains controversial. This scoring system should help physicians address such issues.

Because the nomogram based only on noninvasive factors may predict high 2-hour plasma glucose, it has wide application for individuals in various medical settings, including those with limited resources. The semi-lab model is more appropriate for individuals who are under the care of community doctors, and is also useful for epidemiologic studies for isolated high 2-hour plasma glucose screening.

Limitations

There are several drawbacks to this study. First, the research population was mostly female, owing to the fact that we only invited residents above the age of 40, and women make up the majority of the population in this age range. Second, because the nomogram model only included Chinese individuals, it may not be typical of other ethnic groups, particularly those in foreign nations. The model's strength, to some part, stems from the fact that it was built using data from a large national representative sample in South China and verified using data from an external population in North China. Data that have been included in other published nomogram models concerning daily consumption of vegetables, fruits, or berries (27) and use of steroids (28) were not available in our study questionnaire. It is not clear to what extent these missing variables will affect the need to assess risk of isolated high 2-hour plasma glucose. In addition, although using a semi-lab nomogram model to screen isolated high 2-hour plasma glucose may reduce the number of individuals who undergo testing, the lack of testing might miss people with DM. The choice of cutoff value with its related sensitivity and specificity should depend on the purpose of the semi-lab nomogram model. Besides, this study only explored the diagnostic threshold of diabetes, failing to provide the diagnostic critical value of impaired glucose tolerance, which requires further research. Last but not least, incomplete data compilation may influence the interpretation of the result of this study. Therefore, other important characteristics and lifestyle information, such as regional dietary habits and economic income, should also be considered to strengthen the findings of the study.

Conclusion

In summary, we initially established and validated a novel nomogram based on two large databases for assessing patients with risk of isolated high 2-hour plasma glucose. With this model, clinicians may more precisely identify those individuals who are in need of a 2-h OGTT test for diagnosis of DM, when both FPG and HbA1c levels are normal. This nomogram should optimize screening of DM in these patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Sun Yat-sen Memorial Hospital affiliated with Sun Yat-sen University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceiving ideas and experiment design: KS, LYa and GuW. Actual experimentation: XX, LYo, XH, DL, YL, CH, FL, CS, CC, JL, YQ, CW, YaL, MX, MR, CY. Manuscript writing: KS, XX, and LYo. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants from: 1) National Key Research and Development Project of China (2016YFC0901204); 2) The National Science Foundation of China (81970696); 3) The Natural Science Foundation of China (82000784); 4) Sun Yat-sen Clinical Research Cultivating Program (SYS-Q-201801); 5) Sun Yat-sen University Clinical Research 5010 Program (2018021); 6) Medical Science and Technology Research Fund Project of Guangdong Province (A2019391); 7) Science and Technology Planning Project of Guangdong Province, China (2014A020212069); 8) Guang Dong Clinical Research Center for Metabolic Diseases (2020B1111170009); 9) Natural Science Foundation of Guangdong Province, China (2022A1515012111); 10) Guangzhou Basic Research Program [Basic and Applied Basic Research Project] (202102080101).

Acknowledgments

We are indebted to the participants in the present study for their outstanding support and to our colleagues for their valuable assistance. The authors acknowledge Guang Ning (RuiJin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China) for valuable advice regarding data collection.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Xu G, Liu B, Sun Y, Du Y, Snetselaar LG, Hu FB, et al. Prevalence of diagnosed type 1 and type 2 diabetes among us adults in 2016 and 2017: Population based study. *Bmj* (2018) 362:k1497. doi: 10.1136/bmj.k1497

2. Li Y, Teng D, Shi X, Qin G, Qin Y, Quan H, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American diabetes association: National cross sectional study. *BMJ* (2020) 369:m997. doi: 10.1136/bmj.m997

3. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the global burden of disease study 2016. *Lancet (London England)* (2017) 390(10100):1211–59. doi: 10.1016/s0140-6736(17)32154-2

4. Schwarzenberg SJ, Thomas W, Olsen TW, Grover T, Walk D, Milla C, et al. Microvascular complications in cystic fibrosis-related diabetes. *Diabetes Care* (2007) 30(5):1056–61. doi: 10.2337/dc06-1576

5. Huang ES, Brown SE, Ewigman BG, Foley EC, Meltzer DO. Patient perceptions of quality of life with diabetes-related complications and treatments. *Diabetes Care* (2007) 30(10):2478–83. doi: 10.2337/dc07-049

6. Raghavan S, Vassy JL, Ho YL, Song RJ, Gagnon DR, Cho K, et al. Diabetes mellitus-related all-cause and cardiovascular mortality in a national cohort of adults. *J Am Heart Assoc* (2019) 8(4):e011295. doi: 10.1161/jaha.118.011295

7. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassaï B, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: Meta-analysis of randomised controlled trials. *Bmj* (2011) 343:d4169. doi: 10.1136/bmj.d4169

8. Hippisley-Cox J, Coupland C. Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality: Cohort study in primary care. *Bmj* (2016) 354:i3477. doi: 10.1136/bmj.i3477

9. American Diabetes Association. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2019. *Diabetes Care* (2019) 42(Suppl 1): S13–s28. doi: 10.2337/dc19-S002

10. Sacks DB. A1c versus glucose testing: A comparison. *Diabetes Care* (2011) 34(2):518–23. doi: 10.2337/dc10-1546

11. Kim JS, Ko SH, Baeg MK, Han KD. A simple screening score to predict diabetes in cancer patients: A Korean nationwide population-based cohort study. *Medicine* (2019) 98(51):e18354. doi: 10.1097/md.0000000000018354

12. Zhou X, Qiao Q, Ji L, Ning F, Yang W, Weng J, et al. Nonlaboratory-based risk assessment algorithm for undiagnosed type 2 diabetes developed on a nation-wide diabetes survey. *Diabetes Care* (2013) 36(12):3944–52. doi: 10.2337/dc13-0593

13. Wong CK, Siu SC, Wan EY, Jiao FF, Yu EY, Fung CS, et al. Simple non-laboratory- and laboratory-based risk assessment algorithms and nomogram for detecting undiagnosed diabetes mellitus. *J Diabetes* (2016) 8(3):414–21. doi: 10.1111/1753-0407.12310

14. Chung SM, Park JC, Moon JS, Lee JY. Novel nomogram for screening the risk of developing diabetes in a Korean population. *Diabetes Res Clin Pract* (2018) 142:286–93. doi: 10.1016/j.diabres.2018.05.036

15. Bartoli E, Fra GP, Carnevale Schianca GP. He oral glucose tolerance test (Ogtt) revisited. *Eur J Internal Med* (2011) 22(1):8–12. doi: 10.1016/j.ejim.2010.07.008

16. Bi Y, Lu J, Wang W, Mu Y, Zhao J, Liu C, et al. Cohort profile: Risk evaluation of cancers in Chinese diabetic individuals: A longitudinal (Reaction) study. *J Diabetes* (2014) 6(2):147–57. doi: 10.1111/1753-0407.12108

17. Ning G. Risk evaluation of cancers in Chinese diabetic individuals: A longitudinal (Reaction) study. *J Diabetes* (2012) 4(2):172–3. doi: 10.1111/j.1753-0407.2012.00182.x

18. Pedersen AB, Mikkelsen EM, Cronin-Fenton D, Kristensen NR, Pham TM, Pedersen L, et al. Missing data and multiple imputation in clinical epidemiological research. *Clin Epidemiol* (2017) 9:157–66. doi: 10.2147/clep.s129785

19. Croy CD, Novins DK. Methods for addressing missing data in psychiatric and developmental research. *J Am Acad Child Adolesc Psychiatry* (2005) 44 (12):1230–40. doi: 10.1097/01.chi.0000181044.06337.6f

20. de Lusignan S, Dorward J, Correa A, Jones N, Akinyemi O, Amirthalingam G, et al. Isk factors for sars-Cov-2 among patients in the Oxford royal college of general practitioners research and surveillance centre primary care network: A cross-sectional study. *Lancet Infect Dis* (2020) 20(9):1034–42. doi: 10.1016/s1473-3099(20)30371-6

21. Tomioka K, Iwamoto J, Saeki K, Okamoto N. Reliability and validity of the international physical activity questionnaire (Ipaq) in elderly adults: The fujiwara-kyo study. *J Epidemiol* (2011) 21(6):459–65. doi: 10.2188/jea.je20110003

22. Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Sundvall J, et al. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and Hba1c: A report from euroaspire iv–a survey from the European society of cardiology. *Eur Heart J* (2015) 36(19):1171–7. doi: 10.1093/eurheartj/ehv008

23. Ferrannini G, De Bacquer D, De Backer G, Kotseva K, Mellbin L, Wood D, et al. Screening for glucose perturbations and risk factor management in dysglycemic patients with coronary artery disease-a persistent challenge in need of substantial improvement: A report from esc eorp euroaspire V. *Diabetes Care* (2020) 43(4):726–33. doi: 10.2337/dc19-2165

24. Welsh KJ, Kirkman MS, Sacks DB. Role of glycated proteins in the diagnosis and management of diabetes: Research gaps and future directions. *Diabetes Care* (2016) 39(8):1299–306. doi: 10.2337/dc15-2727

25. ngelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, et al. Comparison of fasting and 2-hour glucose and Hba1c levels for diagnosing diabetes. diagnostic criteria and performance revisited. *Diabetes Care* (1997) 20 (5):785–91. doi: 10.2337/diacare.20.5.785

26. Schwartz JG, Phillips WT, Aghebat-Khairy B. Revision of the oral glucose tolerance test: A pilot study. *Clin Chem* (1990) 36(1):125–8. doi: 10.1093/clinchem/36.1.125

27. Rolka DB, Narayan KM, Thompson TJ, Goldman D, Lindenmayer J, Alich K, et al. Performance of recommended screening tests for undiagnosed diabetes and dysglycemia. *Diabetes Care* (2001) 24(11):1899–903. doi: 10.2337/diacare.24.11.1899

28. Griffin SJ, Little PS, Hales CN, Kinmonth AL, Wareham NJ. Diabetes risk score: Towards earlier detection of type 2 diabetes in general practice. *Diabetes/metabolism Res Rev* (2000) 16(3):164–71. doi: 10.1002/1520-7560(200005/06)16:3<164::aid-dmrr103>3.0.co;2-r

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 29 September 2022
DOI 10.3389/fendo.2022.1013162

OPEN ACCESS

EDITED BY
Hiroshi Okada,
Matsushita Memorial Hospital, Japan

REVIEWED BY
Youngju Jee,
Kyungnam University, South Korea
Na Rae Bae,
Konyang Cyber University, South Korea

*CORRESPONDENCE
Haewon Byeon
bhwpuma@naver.com

SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 06 August 2022
ACCEPTED 16 September 2022
PUBLISHED 29 September 2022

CITATION
Byeon H (2022) Exploring the risk factors of impaired fasting glucose in middle-aged population living in South Korean communities by using categorical boosting machine. *Front. Endocrinol.* 13:1013162. doi: 10.3389/fendo.2022.1013162

Exploring the risk factors of impaired fasting glucose in middle-aged population living in South Korean communities by using categorical boosting machine

Haewon Byeon[1,2]*

[1]Department of Digital Anti-aging Healthcare (BK21), Graduate School of Inje University, Gimhae, South Korea, [2]Department of Medical Big Data, College of AI Convergence, Inje University, Gimhae, South Korea

Objective: This epidemiological study (1) identified factors associated with impaired fasting glucose using 3,019 subjects (≥30 years old and <60 years old) without diabetes mellitus from national survey data and (2) developed a nomogram that could predict groups vulnerable to impaired fasting glucose by using machine learning.

Methods: This study analyzed 3,019 adults between 30 and 65 years old who completed blood tests, physical measurements, blood pressure measurements, and health surveys. Impaired fasting glucose, a dependent variable, was classified into normal blood glucose (glycated hemoglobin<5.7% and fasting blood glucose ≤ 100mg/dl) and impaired fasting glucose (glycated hemoglobin is 5.7-6.4% and fasting blood glucose is 100-125mg/dl). Explanatory variables included socio-demographic factors, health habit factors, anthropometric factors, dietary habit factors, and cardiovascular disease risk factors. This study developed a model for predicting impaired fasting glucose by using logistic nomogram and categorical boosting (CatBoost).

Results: In this study, the top eight variables with a high impact on CatBoost model output were age, high cholesterol, WHtR, BMI, drinking more than one shot per month for the past year, marital status, hypertension, and smoking.

Conclusion: It is necessary to improve lifestyle and continuously monitor subjects at the primary medical care level so that we can detect non-diabetics vulnerable to impaired fasting glucose living in the community at an early stage and manage their blood glucose.

KEYWORDS

impaired fasting glucose, risk factor, CatBoost, machine learning, middle-aged population

Introduction

The number of diabetic patients is increasing rapidly worldwide. The International Diabetes Federation predicted that if the current rate of increase would continue, the number of people with diabetes will increase from 425 million at present to approximately 700 million in 2045 (1). It is also estimated that diabetes prevalence will rapidly increase in South Korea as well and the number of people with diabetes will exceed 6 million around 2050 (2). As the prevalence of diabetes has skyrocketed explosively in Asia as well as North and South America in recent years, it has become an important issue in health science.

Diabetes mellitus is a disease that maintains a high blood glucose level for a long period (3–5). It is known to cause various complications such as diabetic retinopathy and kidney disease because it leads to disorders in microvessels such as the retina or kidneys (3–5). It is also reported that 1 million people die each year worldwide from diabetes mellitus and its complications (3, 6). Therefore, the prevention and continuous management of diabetes mellitus have emerged as important health issues after middle age (3, 6). Diabetes mellitus can be divided into type 1 diabetes mellitus and type 2 diabetes mellitus (7, 8). Type 1 diabetes mellitus occurs because the beta cells of the pancreas are destroyed by the immune system and are unable to secrete insulin (7, 8). Type 2 diabetes mellitus is caused by relatively increased insulin resistance due to various causal factors such as health habits, even though insulin-secreting function remains partially (7, 8). In South Korea, 97% of diabetic patients are diagnosed with type 2 diabetes mellitus. The known key causal factors of type 2 diabetes mellitus are aging, obesity, dietary habits (e.g., excessive intake of simple sugar, high calorie, and high-fat food), and living habits (e.g., insufficient exercise and curtailed sleep) in addition to family medical history (9–14).

Although the prevalence of diabetes mellitus has steadily increased over the past 20 years, it is difficult to detect diabetes mellitus early because there are almost no subjective symptoms unless the blood glucose level is too high (15). Ramachandran (2014) (16) reported that many diabetic patients who were diagnosed with diabetes mellitus at a health medical examination already had vascular complications. In particular, when fasting blood glucose is between 100 and 125mg/dL, which is an intermediate level between normal and diabetes, or when glycated hemoglobin is between 5.7 and 6.4%, it is diagnosed with impaired fasting glucose (17). Since people satisfying these criteria are more likely to develop diabetes in the future, it is defined as prediabetes (17).

Diabetes Fact Sheets in Korea (2021) (15) reported that as of 2021, one in seven (13.8%) adults (≥30 years old) suffered from diabetes mellitus and one in four (26.9%) adults were prediabetes. However, 35% of patients who were diagnosed with diabetes mellitus between 2016 and 2018 did not have a subjective symptom (15). Therefore, to prevent diabetes, it requires to detect impaired fasting glucose, the pre-diabetes stage, as soon as possible, regulate diet (e.g., proper eating habits), improve lifestyle habits (e.g., exercise and weight control), and monitor the progress to diabetes by conducting a blood glucose test regularly (18). This epidemiological study (1) identified factors associated with impaired fasting glucose using 3,019 subjects (≥30 years old and <60 years old) without diabetes mellitus from national survey data and (2) developed a nomogram that could predict groups vulnerable to impaired fasting glucose by using machine learning.

Methods and materials

Subjects

This study used secondary data based on the raw data of the 2020 Korea National Health and Nutrition Examination Survey (KNHANES), a national statistic (No. 117002), supervised by the Ministry of Health and Welfare and the Korea Centers for Disease Control and Prevention. The KNHANES was approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention (No. 2018-01-03-2C-A). Moreover, de-identification measures were applied to some variables such as health insurance types for protecting personal information. The population of the KNHANES was the people living in South Korea. It chose study subjects (samples) from the Population and Housing Census (complete enumeration survey) data by using the stratified cluster sampling method and the systematic sampling method. The 2020 KNHANES targeted 9,949 people in 192 sampling districts across the country. However, the health and examination survey completed only 7,359 people (participation rate=74.0%) in 180 sampling districts due to the suspension of the investigation caused by the COVID-19 pandemic. The health survey of the KNHANES was conducted by face-to-face interviews and self-reporting after a surveyor visited the target household. The examination consists of blood pressure measurement, physical measurement, and blood test. During the survey period, medical workers (e.g., doctors and nurses) conducted a 1:1 examination and health survey by visiting the survey area using a mobile examination vehicle. This study excluded pregnant women at the time of the survey and those who were already diagnosed with diabetes. This study analyzed 3,019 adults between 30 and 65 years old who completed blood tests, physical measurements, blood pressure measurements, and health surveys.

Measurement and definition of variables

Impaired fasting glucose, a dependent variable, was classified into normal blood glucose (glycated hemoglobin<5.7% and

fasting blood glucose ≤ 100mg/dl) and impaired fasting glucose (glycated hemoglobin is 5.7-6.4% and fasting blood glucose is 100-125mg/dl) based on the Clinical Practice Guidelines of the Korean Diabetes Association (2021) (19) according to the diagnosis of medical personnel. For the sample container, NaF, SST, and EDTA tubes were used for a blood glucose test, a general blood chemistry test, and a hematology test, respectively. They were processed in accordance with the specimen storage and separation regulations. Fasting blood glucose, HbA1c, insulin, triglycerides, and total cholesterol were measured with the separated plasma and serum. This study measured fasting blood glucose with Pureauto S GLU (Hexokinase UV method), triglyceride with Pureauto S TG-N (enzyme method), and total cholesterol with Pureauto SCHO-N (Daiichi Pure Chemicals Corporation, Tokyo, Japan) by using Hitachi 7600-210 (Hitachi high-technologies Co., Tokyo, Japan), an automated analyzer for blood tests.

Explanatory variables included socio-demographic factors, health habit factors, anthropometric factors, dietary habit factors, and cardiovascular disease risk factors, referring to previous studies (9–14). Socio-demographic factors included gender (male or female), marital status (living with a spouse, separated/divorced/bereaved, or single), age (30-39, 40-49, or 50-64), living area (urban or rural), and monthly mean household income (<2 million KRW, 2-4 million KRW, or >4 million KRW). Health habit factors included drinking more than one shot per month for the past year (yes or no), smoking (non-smoker, former smoker, or smoker), subjective stress level (almost none, moderate, or high), mean length of moderate level physical activities during leisure activities per day (activities that make a person slightly short of breath or the heart slightly faster, such as jogging or strength training: none, 10 minutes≤ and <1 hour, or 1 hour≤), mean daily sitting time (≤4 hours, 5 hours ≤ and ≤ 7 hours, or 8 hours≤), number of days of walking for more than 10 minutes per day in the past week (none, 1-2 days, 3-4 days, 5-6 days, or every day), and weekly mean sleeping hours per day (≤5 hours, 6-7 hours, or 8 hours≤). Anthropometric factors included body mass index (BMI: underweight (<18.5kg/m2), normal weight (18.5-23kg/m2), pre-obesity class (23-25kg/m2), class 1 obesity (25-30kg/m2), or class 2 obesity or higher (>30kg/m2)) and waist-to-height ratio (WHtR: <0.5 or 0.5≤ (Zeng et al. (2014) (20)). Dietary habit factors included the mean number of days of having breakfast per week for the past year (5-7 days per week, 3-4 days per week, 1-2 days per week, or rarely) and the mean frequency of eating out including delivery for the past year (<1 per day or 1 per day≤). For cardiovascular disease risk factors, this study referred to systolic blood pressure and total cholesterol, the criteria announced by the American Heart Association (21) used to calculate cardiovascular disease risk, and triglyceride and diastolic blood pressure, which were factors related to the risk of cardiovascular disease in Kim & Ryu (2018) (22). The cardiovascular disease risk factors of this study included high cholesterol prevalence (total cholesterol≥240mg/dL: yes or no), high triglyceride prevalence (triglyceride content≥200mg/dL: yes or no), hypertension prevalence ((1) normal blood pressure: systolic blood pressure < 120mmHg and diastolic blood pressure < 80mmHg, (2) pre-hypertension: systolic blood pressure is between 120 and 140mmHg and diastolic blood pressure is 80-90mmHg, and (3) hypertension: systolic blood pressure > 120mmHg and diastolic blood pressure > 80mmHg). Blood pressure was measured on the right upper arm using a mercury sphygmomanometer (Wall Unit 33, Baumanometer, America) after the subject rested for five minutes under the supervision of the nurse in charge (23).

Variable selection

CatBoost (category boosting) is an algorithm developed by Yandex Technologies and is known to be useful for processing categorical variables (24). Previously developed gradient boosting techniques such as XGBoost and LightGBM have two shortfalls. First, as the learning of boosting progresses, the distribution of data is changed. As a result, prediction shift that leads to overfitting problems or inaccurate predictions occurs. Second, it takes a lot of time to process categorical variables. For example, when XGBoost and LightGBM newly create binary variables, the amount of statistics increases, and, as a result, computation time and memory consumption increase. CatBoost constructs a model using ordered boosting to overcome these limitations. Existing boosting models (e.g., XGBoost and LightGBM) build models by calculating residuals for all training data. However, CatBoost calculates residuals by using only a portion of the training data, as shown in Equation (1), and builds a model based on them. Afterward, the residual of the data reuses the value predicted by this model.

$$\begin{aligned} &input: \{(X_k,\ Y_k)\}_{k=1}^{n} \text{ ordered according to } \sigma, \\ &\qquad\qquad\qquad\qquad\qquad\qquad \text{the number of trees } I; \\ &\sigma \leftarrow \text{random permutation of } [1, n]; \\ &M_i \leftarrow 0 \text{ for } i = 1,\ \cdots,\ n; \\ &\text{for } t \leftarrow 1 \text{ to } I \text{ do} \\ &\text{for } i \leftarrow 1 \text{ to } n \text{ do} \\ &r_i \leftarrow y_i - M_{\sigma(i)-1}(X_i); \\ &\text{for } i \leftarrow 1 \text{ to } n \text{ do} \end{aligned} \tag{1}$$

$$\Delta M \leftarrow LearnModel\left[\left(X_i, r_j\right) \ : \sigma(j) \leq i\right]$$

$$M_i \leftarrow M_i + \Delta M$$

return M_n

CatBoost is easier to use than other gradient boosting algorithms because it optimizes hyperparameters by using an internal algorithm without a special hyperparameter optimization process, its advantage. For CatBoost, this study set the number of trees to 100, the Lambda of regularization to 3, the learning rate to 0.300, and the limit depth of individual trees to 6. The CatBoost algorithm calculates feature importance by using a mean decrease in impurity to select important variables for predicting impaired fasting glucose. This study developed a nomogram for predicting groups vulnerable to impaired fasting glucose by selecting the eight variables with the highest feature importance for interpreting risk probabilities efficiently.

Development a nomogram for predicting impaired fasting glucose

This study developed a model for predicting impaired fasting glucose by using logistic regression analysis to identify the independent relevance of variables related to impaired fasting glucose in people without diabetes residing in the local community by entering the top variables with high feature importance found in CatBoost. The regression model presented a 95% confidence interval (CI) and adjusted odds ratio (aOR), which adjusted for all confounding factors. A nomogram was developed based on the developed predictive model (final model) for impaired fasting glucose so that medical personnel could easily interpret the prediction result (prediction probability). The nomogram was composed of four components: a point line, a risk factor line, a probability line, and a total point line. Please refer to Byeon (2022) (25) for a detailed description of the function and composition of the nomogram. The predictive performance of the nomogram for predicting impaired fasting glucose in non-diabetics was evaluated using F1-score, the area under the curve (AUC), precision, recall, general accuracy, and calibration plots. The final model was validated using 10-fold cross-validation. All analyses were performed using Python version 3.9.12 (https://www.python.org).

Results

General characteristics of subjects according to impaired fasting glucose

Table 1 presents the results of the chi-square test, which analyzed the differences in general characteristics between groups according to the prevalence of impaired fasting glucose. Among 3,019 subjects, 879 subjects (29.1%) had impaired fasting glucose. The results of the chi-square test showed that the two groups were significantly different in marital status, age, mean monthly household income, drinking experience for the past year, subjective stress, the mean number of days of walking per week, weekly mean sleeping hours per day, BMI, WHtR, mean number of days of having breakfast per week for the past year, mean frequency of eating out including delivery for the past year, high cholesterol, high triglycerides, and hypertension ($p<0.05$).

Predictors for impaired fasting glucose in non-diabetes living in local communities in South Korea

Figure 1 shows the calculated feature importance of factors related to impaired fasting glucose in people without diabetes using CatBoost. The results of this study revealed that age, high cholesterol, WHtR, BMI, drinking more than one shot per month for the past year, marital status, hypertension, and smoking were the top eight variables based on feature importance.

Table 2 shows the results of the logistic regression analysis for predicting impaired fasting glucose in South Korean non-diabetics using the top eight variables with high importance obtained from CatBoost. The analysis results of the adjusted model confirmed that separated/divorced/bereaved from their spouse (AOR=1.79, 95% CI: 1.26, 2.55), age (40-49 years old: AOR=1.59, 50-64 years old:AOR=4.09), no drinking experience for the past year (AOR=1.47, 95% CI: 1.21, 1.77), smoker (AOR=1.36, 95% CI: 1.06, 1.74), class 2 obesity or higher base on BMI (AOR=3.80, 95% CI: 1.80, 8.01), WHtR≥0.5 (AOR=1.37, 95% CI: 1.04, 1.81), high cholesterol (AOR=2.03, 95% CI: 1.66, 2.49) hypertension (pre-hypertension:AOR=1.34, hypertension: AOR=1.31) were the independent influencing factors of impaired fasting glucose ($p<0.05$).

Development and validation of the nomogram for predicting groups vulnerable to impaired fasting glucose in South Korean non-diabetics

Figure 2 presents the nomogram for predicting impaired fasting glucose in South Korean non-diabetics. The nomogram predicted that those who lived with a spouse, were class 2 obesity or higher based on BMI (>30kg/m2), had hypertension and high cholesterol, did not drink in the past one year, were smoking, and were between 50 and 64 years old had an 87% chance to have impaired fasting glucose (a high-risk group).

The predictive performance of the developed impaired fasting glucose prediction nomogram was validated by using

TABLE 1 General characteristics of subjects according to the prevalence of impaired fasting glucose (n, %).

Variables	Impaired fasting glucose		p
	No (n = 2,140)	Yes (n = 879)	
Gender			0.149
Male	898 (69.5)	394 (30.5)	
Female	1,242 (71.9)	485 (28.1)	
Marital Status			<0.001
Living with a spouse	1,614 (69.2)	719 (30.8)	
Separated/divorced/bereaved	190 (65.7)	99 (34.3)	
Single	333 (84.5)	61 (15.5)	
Age			<0.001
30-39	647 (87.9)	89 (12.1)	
40-49	706 (78.8)	190 (21.2)	
50-64	787 (56.7)	600(43.3)	
Living area			0.758
Urban	1,763 (71.0)	720 (29.0)	
Rural	377 (70.3)	159 (29.7)	
Monthly mean household income			0.029
<2 million KRW	267 (66.4)	135 (33.6)	
2-4 million KRW	506 (69.2)	225 (30.8)	
>4 million KRW	1,364 (72.4)	519 (27.6)	
Drinking experience for the past year			<0.001
No	833 (66.2)	425 (33.8)	
Yes	1,298 (74.3)	449 (25.7)	
Smoking			0.392
Non-smoker	1,268 (71.6)	504 (28.4)	
Former smoker	486 (71.2)	197 (28.8)	
Smoker	377 (68.5)	173 (31.5)	
Subjective stress			0.008
Almost none	206 (64.6)	113 (35.4)	
Moderate	1,239 (70.6)	515 (29.4)	
High	686 (73.7)	245 (26.3)	
Mean length of moderate level physical activities per day			0.157
None	1,419 (69.7)	618 (30.3)	
<1 hour	379 (73.9)	134 (26.1)	
1 hour≤	228 (71.7)	90 (28.3)	
Mean daily sitting time			0.056
≤4 hours	334 (69.6)	146 (30.4)	
5-7 hours	518 (67.7)	247 (32.3)	
8 hours≤	1,171 (72.4)	447 (27.6)	
Mean number of days of walking per week			0.028
None	360 (68.3)	167 (31.7)	
1-2 days	408 (75.1)	135 (24.9)	
3-4 days	392 (68.3)	182 (31.7)	
5-6 days	363 (73.3)	132 (26.7)	
7 days (every day)	503 (69.0)	226 (31.0)	
Weekly mean sleeping hours per day			0.006
≤5 hours	310 (64.9)	168 (35.1)	
6-7 hours	1,224 (71.6)	485 (28.4)	
8 hours≤	604 (72.8)	226 (27.2)	

(Continued)

TABLE 1 Continued

Variables	Impaired fasting glucose		p
	No (n = 2,140)	Yes (n = 879)	
BMI			<0.001
Underweight	91 (85.8)	15 (14.2)	
Normal weight	866 (79.2)	228 (20.8)	
Pre-obesity class	489 (70.6)	203 (29.4)	
Class 1 obesity	588 (62.9)	347 (37.1)	
Class 2 obesity or higher	89 (52.4)	81 (47.6)	
WHtR			<0.001
<0.5	1,103 (81.6)	249 (18.4)	
0.5≤	1,018 (62.0)	625 (38.0)	
Mean number of days of having breakfast per week for the past year			<0.001
5-7 days per week	825 (67.5)	398 (32.5)	
3-4 days per week	176 (71.8)	69 (28.2)	
1-2 days per week	258 (77.9)	73 (22.1)	
Rarely	402 (77.3)	118 (22.7)	
Mean frequency of eating out including delivery for the past year			0.009
1 per day≤	446 (75.9)	142 (24.1)	
<1 per day	1,215 (70.2)	516 (29.8)	
High cholesterol			<0.001
No	1,748 (76.1)	548 (23.9)	
Yes	345 (52.8)	308 (47.2)	
High triglyceride			<0.001
No	1,486 (72.4)	567 (27.6)	
Yes	232 (62.0)	142 (38.0)	
Hypertension			<0.001
Normal	1,120 (79.6)	287 (20.4)	
Pre-hypertension	570 (67.9)	269 (32.1)	
Hypertension	416 (57.5)	307 (42.5)	

general accuracy (Figure 3), AUC (Figure 4), precision, recall, F1-score (2(precision*recall)/precision+recall), and calibration plot (Figure 5). A calibration plot (Figure 5) and the chi-square test showed that the predicted and observed probabilities of the impaired fasting glucose group and the normal blood glucose group were not significantly different ($p<0.05$). The results of 10-fold cross validation revealed that the general accuracy, AUC, precision, recall, and F1-score of the nomogram for predicting impaired fasting glucose in non-diabetics were 0.73, 0.75, 0.71, 0.73, and F1-score, respectively.

Discussion

This study identified factors related to impaired fasting glucose in non-diabetics according to the diagnostic criteria for impaired fasting glucose suggested by the Korean Diabetes Association by using epidemiological data representing the South Korean population. It was confirmed that age, high cholesterol, WHtR, BMI, drinking more than one shot per month for the past year, marital status, hypertension, and smoking were factors independently related to impaired fasting glucose. Many previous studies (26–31) also reported that age, high cholesterol, hypertension, abdominal obesity, smoking experience (past and current smoking), and drinking were risk factors for pre-diabetes, which agreed with the results of this study. Socio-demographic factors such as age and marital status were identified as major risk factors for impaired fasting glucose in previous studies (32–34). Kwon & Na (2017) (32) reported that the risk of pre-diabetes also significantly increased as the age of subjects increased. Moreover, Cornelis et al. (2014) (34) revealed that men living with their spouses had a 16% higher risk of type 2 diabetes than men who did not live with a spouse. Socio-demographic factors such as marital status could increase the risk of diabetes by ultimately mediating non-lifestyle habits or obesity due to their impacts on dietary habits and other factors.

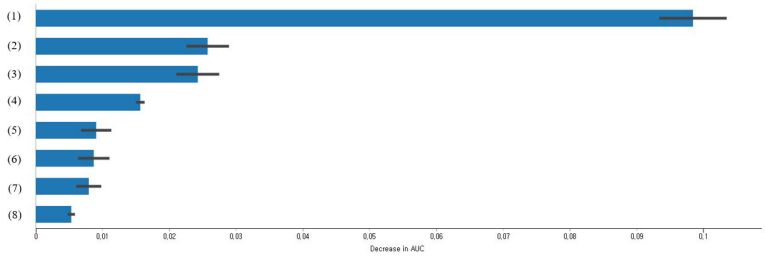


FIGURE 1
Feature importance of impaired fasting glucose predictors in non-diabetics based on CatBoost (only the top eight variables are presented); (1) Age (1 = 30-39 years old, 2 = 40-49 years old, or 3 = 50-64 years old); (2) High cholesterol (0 = no or 1 = yes); (3) WHtR (1 = <0.5 or 2 = 0.5≤); (4) BMI (1 = underweight, 2 = normal weight, 3 = pre-obesity class, 4 = class 1 obesity, or 5 = class 2 obesity or higher); (5) Drinking more than one shot per month for the past year (0 = no or 1 = yes); (6) Marital status (1 = living with a spouse, 2 = separated/divorced/bereaved, or 3 = single); (7) Hypertension (1 = normal, 2 = pre-hypertension, or 3 = hypertension); and (8) Smoking (1 = non-smoker, 2 = former smoker, or 3 = smoker).

TABLE 2 Predictors for impaired fasting glucose in non-diabetics living in local communities in South Korea: aOR and 95% CI.

Variables	aOR	95% CI	p
Marital Status			
Living with a spouse (ref)	1	1	
Separated/divorced/bereaved	1.79	1.26, 2.55	0.001
Single	1.47	0.94, 2.30	0.084
Age			
30-39(ref)	1	1	
40-49	1.59	1.17, 2.16	0.003
50-64	4.09	3.04, 5.49	<0.001
Drinking experience for the past year			
No	1.47	1.21, 1.77	<0.001
Yes (ref)	1	1	
Smoking			
Non-smoker (ref)	1	1	
Former smoker	0.97	0.77, 1.22	0.818
Smoker	1.36	1.06, 1.74	0.015
BMI			
Underweight (ref)	1	1	
Normal weight	1.10	0.59. 2.06	0.743
Pre-obesity class	1.22	0.63, 2.35	0.538
Class 1 obesity	1.69	0.86, 3.30	0.123
Class 2 obesity or higher	3.80	1.80, 8.01	<0.001
WHtR			
<0.5 (ref)	1	1	
0.5≤	1.37	1.04, 1.81	0.023
High cholesterol			
No (ref)	1	1	
Yes	2.03	1.66, 2.49	<0.001
Hypertension			
Normal (ref)	1	1	
Pre-hypertension	1.34	1.07, 1.67	0.008
Hypertension	1.31	1.03, 1.66	0.024

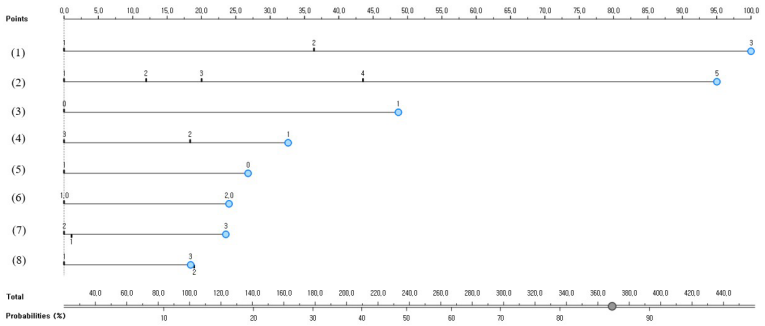


FIGURE 2
A nomogram for predicting impaired fasting glucose predictors in South Korean non-diabetics; (1) Age (1 = 30-39 years old, 2 = 40-49 years old, or 3 = 50-64 years old); (2) BMI (1 = underweight, 2 = normal weight, 3 = pre-obesity class, 4 = class 1 obesity, or 5 = class 2 obesity or higher); (3) High cholesterol (0 = no or 1 = yes); (4) Marital status (1 = living with a spouse, 2 = separated/divorced/bereaved, or 3 = single); (5) Drinking more than one shot per month for the past year (0 = no or 1 = yes); (6) WHtR (1 = <0.5 or 2 = 0.5≤); (7) Smoking (1 = non-smoker, 2 = former smoker, or 3 = smoker); and (8) Hypertension (1 = normal, 2 = pre-hypertension, or 3 = hypertension).

The results of this study showed that the risk of impaired fasting glucose increased when body fat distribution scales (e.g., WHtR and BMI) were higher, which were similar to the results of previous studies (35–38). Previous studies (35, 37, 39, 40) reported that obesity was a major cause of pre-diabetes and diabetes and obese adults had a high risk of pre-diabetes (35, 39, 40). Halpern & Mancini (2005) (41) revealed that 80% of patients with type 2 diabetes were obese.

In particular, it is noteworthy that many previous studies reported WHtR, a criterion for judging abdominal obesity, as a major factor influencing fasting blood glucose, which agreed with the results of this study (38, 42). Mi et al. (2013) (38) compared the odds ratio of type 2 diabetes with BMI, waist circumferences, WHtR, visceral fat index, and body fat index using 8,121 adults living in the local community and confirmed WHtR as the most effective screening index for type 2 diabetes. It is believed that it is because the risk of hyperinsulinemia increases when abdominal obesity is higher (43). Obesity excessively accumulates body fat in the abdomen, which increases the activity of hormone-sensitive fat enzymes in the

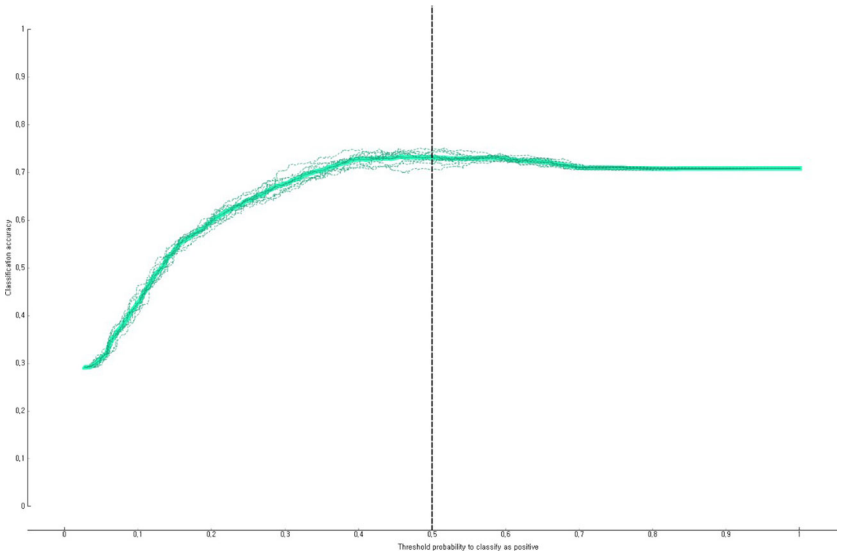


FIGURE 3
Accuracy of the nomogram for predicting impaired fasting glucose in South Korean non-diabetics.

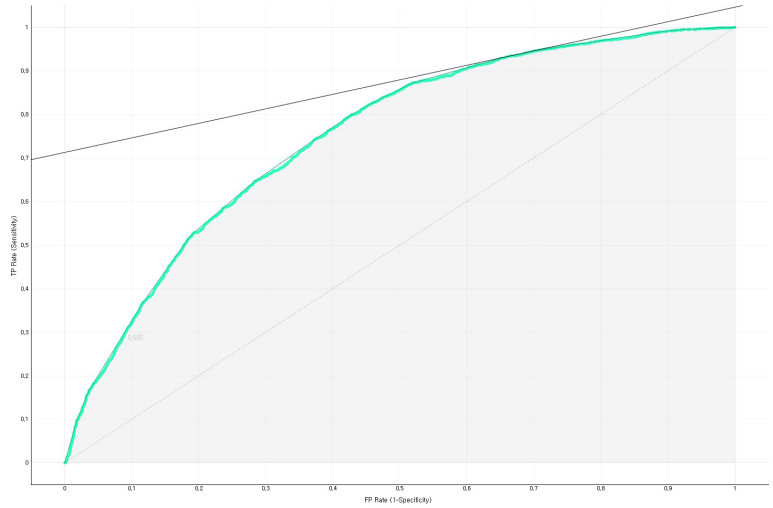


FIGURE 4
AUC of the nomogram for predicting impaired fasting glucose in South Korean non-diabetics.

adipose tissue and lipolysis (44). As a result, the concentration of free fatty acids increases (44). The increased free fatty acid lowers muscle glycogen synthesis by inhibiting the uptake and utilization of glucose in the muscle and liver (44). Furthermore, it worsens insulin resistance by affecting the insulin receptor in the muscle and liver (44). Consequently, adults with abdominal obesity are more likely to progress to impaired fasting glucose.

This study confirmed that hypertension and high cholesterol were also major risk factors for impaired fasting glucose. Emdin et al. (2015) (45) evaluated the relationship between blood pressure and the risk of type 2 diabetes using meta-analysis and reported that blood pressure and blood glucose were closely related ((1) when systolic blood pressure increased by 20mmHg increased, the risk of type 2 diabetes increased by 58% and (2) when diastolic blood pressure increased by 10mmHg, the risk of type 2 diabetes increased by 52%). In addition, Meikle et al. (2013) (46) also confirmed a significant positive correlation between total cholesterol concentration and type 2 diabetes. However, it is still limited to predicting impaired fasting glucose

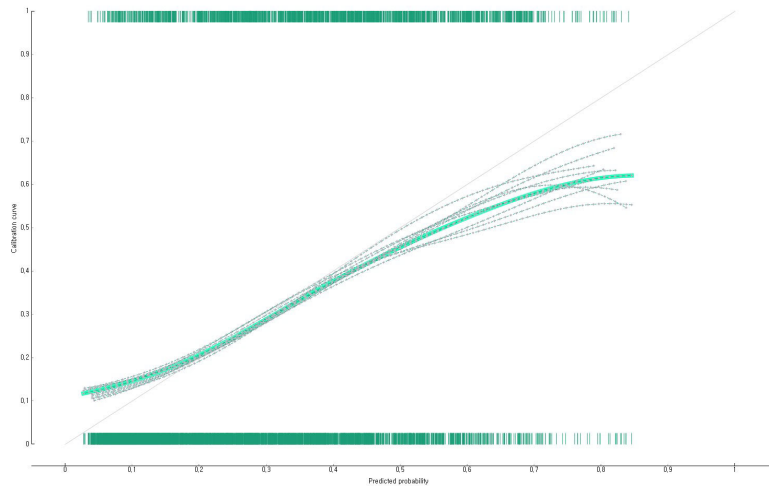


FIGURE 5
Calibration plot of the nomogram for predicting impaired fasting glucose in South Korean non-diabetics.

early while reflecting the actual characteristics of the local community population, which have diverse risk factors at the same time because there most of the previous studies that discovered the risk factors of impaired fasting glucose used regression analysis. To predict groups vulnerable to impaired fasting glucose early, it is necessary to conduct studies for identifying multiple risk factors for impaired fasting glucose based on real-world data.

Another finding of this study's nomogram was that it predicted that those who lived with a spouse, were class 2 obesity or higher based on BMI (>30kg/m2), had hypertension and high cholesterol, did not drink in the past one year, were smoking, and were between 50 and 64 years old had an 87% chance to have impaired fasting glucose, which was very high. In South Korea, adults with impaired fasting glucose also receive a blood test (fasting glucose test) once a year using the National Health Screening Program, just like those with normal blood sugar. However, there is a limit to sensitively identifying the group vulnerable to diabetes just by using one fasting blood glucose test per year in the National Health Screening Program. To more sensitively identify groups vulnerable to diabetes through the National Health Screening Program in the future, it is needed to perform additional screening tests such as the oral glucose tolerance test or the glycated hemoglobin test for the group vulnerable to impaired fasting glucose found in this study. It is also necessary to improve the system so that groups vulnerable to impaired fasting glucose can receive a glycated hemoglobin test every 3 months through the National Health Screening Program. Since there are only a few previous studies that analyzed multiple health risk factors for impaired fasting glucose, additional epidemiological studies are required to analyze multiple health risk factors for impaired fasting glucose while considering various factors. It is also necessary to actively publicize and educate the risk of high blood glucose and measures to prevent diabetes for the group vulnerable to impaired fasting glucose.

This study has several limitations. First, since this epidemiological study analyzed cross-sectional data, it could not reveal a clear causal relationship. Additional prospective cohort studies are required to understand the causal relationship between the group vulnerable to impaired fasting glucose and impaired fasting glucose. Second, there may be potential factors of impaired fasting glucose not included in this study. The source data of this study did not investigate the nutrient intake ratio according to the frequency of food intake and family medical history. Future studies are needed to develop models to predict groups vulnerable to impaired fasting glucose while considering various potential variables highly related to fasting blood glucose, such as genetic data, nutrient intake ratio, and family medical history.

Conclusions

This epidemiological study confirmed that age, high cholesterol, WHtR, BMI, drinking more than one shot per month for the past year, marital status, hypertension, and smoking were independently related to the impaired fasting glucose of non-diabetics. It is necessary to improve lifestyle and continuously monitor subjects at the primary medical care level so that we can detect non-diabetics vulnerable to impaired fasting glucose living in the community at an early stage and manage their blood glucose. Furthermore, it is needed to prepare a system that can actively implement additional screening tests such as an oral glucose tolerance test and a glycated hemoglobin test for groups vulnerable to impaired fasting glucose for preventing diabetes and detecting diabetes early at the community level. Additional longitudinal studies are required to confirm the causality between impaired fasting glucose and high-risk factors related to impaired fasting glucose identified in this study.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Korea Disease Control and Prevention Agency (protocol code 2018-01-03-2C-A and date: 2020.05.01). The patients/participants provided their written informed consent to participate in this study.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Funding

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2018R1D1A1B07041091, 2021S1A5A8062526) and 2022 Development of Open-Lab based on 4P in the Southeast Zone.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1013162/full#supplementary-material

References

1. International Diabetes Federation. *IDF diabetes atlas. 8th edn*. (Brussels, Belgium: International Diabetes Federation) (2017).

2. Park JH. Factor influencing influenza vaccination among Korean adults diabetic patients. *J Korea Academia Ind Cooperation Soc* (2018) 19:447–54. doi: 10.5762/KAIS.2018.19.6447

3. Zhang L, Qiao Q, Tuomilehto J, Hammar N, Alberti KG, Eliasson M, et al. Blood lipid levels in relation to glucose status in European men and women without a prior history of diabetes: the DECODE study. *Diabetes Res Clin Prac* (2008) 82(3):364–77. WHO (2016) Global Report on Diabetes. doi: 10.1016/j.diabres.2008.08.022

4. Choby B. Diabetes update: Prevention and management of diabetes complications. *Fp Essentials* (2017) 456:36–40.

5. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: A review of current evidence. *Diabetologia* (2019) 62:3–16. doi: 10.1007/s00125-018-4711-2

6. Lim JH, Oh CS. Medical care utilization status and quality of life in diabetes mellitus patients. *J Digital Convergence* (2013) . 11:609–18. doi: 10.14400/JDPM.2013.11.10609

7. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* (2018) 14:88–98. doi: 10.1038/nrendo.2017.151

8. Tao Z, Shi A, Zhao J. Epidemiological perspectives of diabetes. *Cell Biochem Biophysics* (2015) 73:181–85. doi: 10.1007/s12013-015-0598-4

9. Arslanian SA. Type 2 diabetes mellitus in children: Pathophysiology and risk factors. *J Pediatr Endocrinol Metab* (2000) 13:1385–394. doi: 10.1515/jpem-2000-s612

10. Verma S, Hussain ME. Obesity and diabetes: An update. *Diabetes Metab Syndrome: Clin Res Rev* (2017) 11:73–9. doi: 10.1016/j.dsx.2016.06.017

11. Wilmot E, Idris I. Early onset type 2 diabetes: risk factors, clinical impact and management. *Ther Adv Chronic Dis* (2014) 5:234–44. doi: 10.1177/2040622314548679

12. Cosansu G, Celik S, Özcan S, Olgun N, Yıldırım N, Demir HG. Determining type 2 diabetes risk factors for the adults: A community based study from Turkey. *Primary Care Diabetes* (2018) 12:409–15. doi: 10.1016/j.pcd.2018.05.001

13. Wang L, Li X, Wang Z, Bancks MP, Carnethon MR, Greenland P, et al. Trends in prevalence of diabetes and control of risk factors in diabetes among US adults, 1999-2018. *JAMA* (2021) 326:704–16. doi: 10.1001/jama.2021.9883

14. Zhang H, Ni J, Yu C, Wu Y, Li J, Liu J, et al. Sex-based differences in diabetes prevalence and risk factors: A population-based cross-sectional study among low-income adults in China. *Front Endocrinol* (2019) 10:658. doi: 10.3389/fendo.2019.00658

15. Jung CH, Son JW, Kang S, Kim WJ, Kim HS, Kim HS, et al. Diabetes fact sheets in Korea, 2020: An appraisal of current status. *Diabetes Metab J* (2021) 45:1–10. doi: 10.4093/dmj.2020.0254

16. Ramachandran A. Know the signs and symptoms of diabetes. *Indian J Med Res* (2014) 140:579–81.

17. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: A high-risk state for diabetes development. *Lancet* (2012) 379:2279–290. doi: 10.1016/S0140-6736(12)60283-9

18. Khetan AK, Rajagopalan S. Prediabetes. *Can J Cardiol* (2018) 34:615–23. doi: 10.1016/j.cjca.2017.12.030

19. Hur KY, Moon MK, Park JS, Kim SK, Lee SH, Yun JS, et al. Clinical practice guidelines for diabetes mellitus in Korea. *Diabetes Metab J* (2021) 45:461–81. doi: 10.4093/dmj.2021.0156

20. Zeng Q, He Y, Dong S, Zhao X, Chen Z, Song Z, et al. Optimal cut-off values of BMI, waist circumference and waist: Height ratio for defining obesity in Chinese adults. *Br J Nutr* (2014) 112:1735–744. doi: 10.1017/S0007114514002657

21. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: The framingham heart study. *Circulation* (2008) 117:743–53. doi: 10.1161/CIRCULATIONAHA.107.699579

22. Kim HS, Ryu SY. Relevance of serum vitamin d and indices related to cardiovascular disease among Korean adults. *J Korea Academia-Industrial* (2018) 19:365–74. doi: 10.5762/KAIS.2018.19.6.365

23. Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III). *JAMA* (2001) 285:2486–497. doi: 10.1001/jama.285.19.2486

24. Hancock JT, Khoshgoftaar TM. CatBoost for big data: An interdisciplinary review. *J Big Data* (2020) 7:1–45. doi: 10.1186/s40537-020-00369-8

25. Byeon H. Factors influencing the utilization of diabetes complication tests under the COVID-19 pandemic: Machine learning approach. *Front Endocrinol* (2022) 13:. doi: 10.3389/fendo

26. Sangrós FJ, Torrecilla J, Giraldez-Garcia C, Carrillo L, Mancera J, Mur T, et al. Association of general and abdominal obesity with hypertension, dyslipidemia and prediabetes in the PREDAPS study. *Rev Española Cardiología (English Edition)* (2018) 71:170–77. doi: 10.1016/j.rec.2017.04.035

27. Bucheli JR, Manshad A, Ehrhart MD, Camacho J, Burge MR. Association of passive and active smoking with pre-diabetes risk in a predominantly Hispanic population. *J Investig Med* (2017) 65:328–32. doi: 10.1136/jim-2016-000246

28. Heianza Y, Arase Y, Saito K, Tsuji H, Fujihara K, Hsieh SD, et al. Role of alcohol drinking pattern in type 2 diabetes in Japanese men: The toranomon hospital health management center study 11 (TOPICS 11). *Am J Clin Nutr* (2013) 97:561–68. doi: 10.3945/ajcn.112.043364

29. Maddatu J, Anderson-Baucum E, Evans-Molina C. Smoking and the risk of type 2 diabetes. *Transl Res* (2017) 184:101–07. doi: 10.1016/j.trsl.2017.02.004

30. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, et al. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. *Eur J Epidemiol* (2013) 28:169–80. doi: 10.1007/s10654-013-9771-5

31. Brož J, Malinovská J, Nunes MA, Kučera K, Rožeková K, Žejglicová K, et al. Prevalence of diabetes and prediabetes and its risk factors in adults aged 25–64 in the Czech republic: A cross-sectional study. *Diabetes Res Clin Pract* (2020) 170:108470. doi: 10.1016/j.diabres.2020.108470

32. Kwon S, Na Y. The distribution and characteristics of abnormal findings regarding fasting plasma glucose and HbA1c-based on adults except for known diabetes. *Korean Soc Clin Lab Sci* (2017) 49:239–47. doi: 10.15324/kjcls.2017.49.3.239

33. Mansour MAAL. The prevalence and risk factors of type 2 diabetes mellitus (DMT2) in a semi-urban Saudi population. *Int J Environ Res Public Health* (2020) 17:1. doi: 10.3390/IJERPH17010007

34. Cornelis MC, Chiuve SE, Glymour MM, Chang SC, Tchetgen EJT, Liang L, et al. Bachelors, divorcees, and widowers: Does marriage protect men from type 2 diabetes? *PloS One* (2014) 9:9. doi: 10.1371/journal.pone.0106720

35. Wang H, Qiu Q, Tan LL, Liu T, Deng XQ, Chen YM, et al. Prevalence and determinants of diabetes and impaired fasting glucose among urban community-

dwelling adults in guangzhou, China. *Diabetes Metab* (2009) 35:378–84. doi: 10.1016/j.diabet.2009.03.006

36. Akter S, Rahman MM, Abe SK, Sultana P. Prevalence of diabetes and prediabetes and their risk factors among Bangladeshi adults: A nationwide survey. *Bull World Health Organ* (2014) 92:204–13A. doi: 10.2471/BLT.13.128371

37. Choi O, Cho S. Changes in prevalence of obesity according to gender in Korea adults: Using a population-based Korea national health check-up database, 2011–2013. *Korean Public Health Res* (2018) 44:87–97. doi: 10.22900/kphr.2018.44.4.008

38. Mi SQ, Yin P, Hu N, Li JH, Chen XR, Chen B, et al. BMI, WC, WHtR, VFI and BFI: which indictor is the most efficient screening index on type 2 diabetes in Chinese community population. *BioMed Environ Sci* (2013) 26:485–91. doi: 10.3967/0895-3988.2013.06.009

39. Chen CM, Yeh MC. The prevalence and determinants of impaired fasting glucose in the population of Taiwan. *BMC Public Health* (2013) 13:11–23. doi: 10.1186/1471-2458-13-1123

40. Bullard KM, Saydah SH, Imperatore G, Cowie CC, Gregg EW, Geiss LS, et al. Secular changes in U.S. prediabetes prevalence defined by hemoglobin A1c and fasting plasma glucose: National health and nutrition examination surveys, 1999-2010. *Diabetes Care* (2013) 36:2286–293. doi: 10.2337/dc12-2563

41. Halpern A, Mancini MC. Diabesity: Are weight loss medications effective? *Treat Endocrinol* (2005) 4:65–74. doi: 10.2165/00024677-200504020-00001

42. Veghari G, Sedaghat M, Joshaghani H, Banihashem S, Moharloei P, Angizeh A, et al. The association of fasting blood glucose(FBG) and waist circumference in northern adults in Iran: A population based study. *J Diabetes Metab Disord* (2014) 13:2. doi: 10.1186/2251-6581-13-2

43. Castro AVB, Kolka CM, Kim SP, Bergman RN. Obesity, insulin resistance and comorbidities? Mechanisms of association. *Arq Bras Endocrinol Metabol* (2014) 58:600–09. doi: 10.1590/0004-2730000003223

44. Roden M, Price TB, Perseghin G, Petersen KF, Rothman DL, Cline GW, et al. Mechanism of free fatty acid-induced insulin resistance in humans. *J Clin Investig* (1996) 97:2859–865. doi: 10.1172/JCI118742

45. Emdin CA, Anderson SG, Woodward M, Rahimi K. Usual blood pressure and risk of new-onset diabetes: Evidence from 4.1 million adults and a meta-analysis of prospective studies. *J Am Coll Cardiol* (2015) 66:1552–562. doi: 10.1016/j.jacc.2015.07.059

46. Meikle PJ, Wong G, Barlow CK, Weir JM, Greeve MA, MacIntosh GL, et al. Plasma lipid profiling shows similar associations with prediabetes and type 2 diabetes. *PloS One* (2013) 8:9. doi: 10.1371/journal.pone.0074341

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 11 October 2022
DOI 10.3389/fendo.2022.999715

OPEN ACCESS

EDITED BY
Edward Zimbudzi,
Monash Health, Australia

REVIEWED BY
Leanne Brown,
James Cook University, Australia
Rui Rui Wang,
Shanghai University of Traditional Chinese Medicinei, China
Xu Zhang,
Center for Biologics Evaluation, Canada

*CORRESPONDENCE
Wei Zhao
zhaow@jiangnan.edu.cn
Feng Zhang
fengzhang@jiangnan.edu.cn

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 21 July 2022
ACCEPTED 23 September 2022
PUBLISHED 11 October 2022

CITATION
Feng Y, Zhu J, Wang Q, Cao H, He F, Guan Y, Li D, Yan J, Yang J, Xia Y, Dong M, Hu F, Cao M, Wang J, Ding X, Feng Y, Zou H, Han Y, Sun S, Zhang J, Tang A, Jiang M, Deng Y, Gao J, Jia Y, Zhao W and Zhang F (2022) White common bean extract remodels the gut microbiota and ameliorates type 2 diabetes and its complications: A randomized double-blinded placebo-controlled trial.
Front. Endocrinol. 13:999715.
doi: 10.3389/fendo.2022.999715

White common bean extract remodels the gut microbiota and ameliorates type 2 diabetes and its complications: A randomized double-blinded placebo-controlled trial

Yuwei Feng[1,2,3†], Jie Zhu[2,4†], Qinyue Wang[1,2†], Hong Cao[1,2,5†], Fang He[6,7], Yin Guan[8], Dan Li[1,2], Jiai Yan[1,2], Ju Yang[1,2], Yanping Xia[1,2], Meihua Dong[9], Feng Hu[10], Min Cao[11], Jian Wang[12], Xiaoying Ding[13], Yufei Feng[14], Hong Zou[15], Ying Han[15], Su Sun[16], Jin Zhang[16], Aijuan Tang[16], Minhong Jiang[17], Yu Deng[17], Jianfen Gao[18], Yanxin Jia[18], Wei Zhao[6*] and Feng Zhang[1,2,3*]

[1]Department of Nutrition, Affiliated Hospital of Jiangnan University, Wuxi, China, [2]Clinical Evaluation Center for Functional Food, Affiliated Hospital of Jiangnan University, Wuxi, China, [3]Wuxi School of Medicine Jiangnan University, Wuxi, China, [4]Department of Infection Control, Affiliated Hospital of Jiangnan University, Wuxi, China, [5]Department of Endocrinology, Affiliated Hospital of Jiangnan University, Wuxi, China, [6]State Key Laboratory of Food Science and Technology, School of Food Science and Technology, Jiangnan University, Wuxi, China, [7]School of Public Health (Shenzhen), Sun Yat-sen University, Guangzhou, China, [8]Yinglongqiao Community Health Service Center, Health Commision of Liangxi District, Wuxi, China, [9]Department of Health Promotion, Wuxi Center for Disease Control and Prevention, Wuxi, China, [10]Department of Functional Examination, Affiliated Hospital of Jiangnan University, Wuxi, China, [11]Special Ward, Affiliated Hospital of Jiangnan University, Wuxi, China, [12]Department of Urology, Affiliated Hospital of Jiangnan University, Wuxi, China, [13]Department of Endocrinology and Metabolism, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [14]Mashan Community Healthcare Center, Health Commision of Binhu District, Wuxi, China, [15]Guangrui and Tongjiang Community Healthcare Center, Health Commision of Liangxi District, Wuxi, China, [16]Beidajie Community Healthcare Center, Health Commision of Liangxi District, Wuxi, China, [17]Yangming Community Healthcare Center, Health Commision of Liangxi District, Wuxi, Jiangsu, China, [18]Shanbei Community Healthcare Center, Health Commision of Liangxi District, Wuxi, China

Objective: Excessive carbohydrate intake is a high risk factor for increased morbidity of type 2 diabetes (T2D). A novel regimen for the dietary care of diabetes that consists of a highly active α-amylase inhibitor derived from white common bean extract (WCBE) and sufficient carbohydrates intake was applied to attenuate T2D and its complications. Furthermore, the role of gut microbiota in this remission was also investigated.

Methods: We conducted a 4-month randomized double-blinded placebo-controlled trial. During the intense intervention period, ninety subjects were randomly assigned to the control group (Group C) and WCBE group (Group W). Subjects in Group C were supplemented with 1.5 g of maltodextrin as a

placebo. Subjects in Group W took 1.5 g of WCBE half an hour before a meal. Fifty-five participants continued the maintenance intervention receiving the previous dietary intervention whereas less frequent follow-up. The variation in biochemical, vasculopathy and neuropathy indicators and the structure of the fecal microbiota during the intervention was analyzed.

Result: Glucose metabolism and diabetic complications showed superior remission in Group W with a 0.721 ± 0.742% decline of glycosylated hemoglobin after 4 months. The proportion of patients with diabetic peripheral neuropathy (Toronto Clinical Scoring System, TCSS ≥ 6) was significantly lower in Group W than in Group C. Both the left and right sural sensory nerve conduction velocity (SNCV-left sural and SNCV-right sural) slightly decreased in Group C and slightly increased in Group W. Additionally, the abundances of *Bifidobacterium*, *Faecalibacterium* and *Anaerostipes* were higher in Group W, and the abundances of *Weissella*, *Klebsiella*, *Cronobacter* and Enterobacteriaceae_unclassified were lower than those in Group C at month 2. At the end of month 4, *Bifidobacterium* remained more abundant in Group W.

Conclusion: To our knowledge, this is the first report of improvement to diabetes complications by using a dietary supplement in such a short-term period. The enrichment of SCFA-producing bacteria might be responsible for the attenuation of T2D and its complications.

Clinical trial registration number: http://www.chictr.org.cn/edit.aspx?pid=23309&htm=4, identifier ChiCTR-IOR-17013656

KEYWORDS

white common bean, type 2 diabetes, diabetic complication, gut microbiota, glucose and lipid metabolism

Introduction

Type 2 diabetes (T2D) remains one of the most problematic chronic metabolic disorders. Patients with T2D have a higher risk of macrovascular complications. Intensive glycemic control reduces microvascular complications (1) and exerts a modest improved effect on macrovascular outcomes (2).

Abbreviations: WCBE, White common bean extract; HbA1c, Glycosylated hemoglobin; UHP, Ultrahigh pressure; BMI, body mass index; TC, Total cholesterol.; TG, Triglycerides; FBG, Fasting blood glucose; 0.5-hPBG, 0.5-h blood glucose; 1h-PBG, 1-h blood glucose; 2-hPBG, 2-h blood glucose; 3-hPBG, 3-h blood glucose; HDL-c, High-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TCSS, Toronto Clinical Scoring System; DPN, diabetic peripheral neuropathy; NCS, Nerve conduction study; SNCV, Sensory nerve conduction velocity potential; ABI, Ankle-brachial pressure index; baPWV, brachial-ankle pulse wave velocity; RDP, Ribosomal Database Project; PCoA, Principal coordinates analysis.

Carbohydrates are vital macronutrients that provide primary calories for people, especially those in Asia and Africa. High carbohydrate intake can increase the risk of T2D (3, 4) and total mortality (5). However, the contradiction between the strong desire and rigid control of carbohydrate intake causes a dilemma for patients with T2D. Therefore, a regimen without restricting carbohydrate intake could be a promising antidiabetic approach for patients with T2D.

Carbohydrates can be degraded by α-amylase and α-glucosidase into absorbable monosaccharides in the small intestine. α-amylase can be utilized as a potential target for interventions, and the inhibition of this enzyme may be beneficial for weight loss and glycemic control (6, 7). α-amylase inhibitors are usually purified from white common bean (*Phaseolus vulgaris*). White common bean extract (WCBE) consumption showed a controversial effect on weight loss in animal or human experiment (8–11). In humans, the intake of WCBE was discovered to be able to regulate metabolic diseases, including hyperlipidemia and hyperglycemia (12). Either

naturally occurring peptides or hydrolysate fractions from WCBE exerted hypoglycemic activity in rodents (9, 13).

The gut microbiota has attracted considerable attention in recent years as a potentially malleable target for dietary interventions seeking to improve T2D (14). In addition to the direct effect of lowering glucose absorption in the small intestine, supplemental effects can be achieved through regulating the gut microbiota. These effects have deepened our understanding of the hypoglycemic effects of acarbose. 'Easily digestible' starches can be transformed by acarbose into 'slowly digestible' and 'long-acting' carbohydrates (15). Thus, more carbohydrates enter the large intestine (16) and can thereby initiate carbohydrate metabolism by the gut microbiota. Gut bacteria selected by carbohydrates entering the large intestine have capabilities of producing more SCFAs (14, 17). Then, SCFAs can induce intestinal L cells to secrete gut hormones, such as GLP-1 and PYY (14).Because of the similar effect of inhibiting the absorption of carbohydrates by α-amylase and α-glycosidase inhibitors, WCBE may show similar regulatory effects on the gut microbiota. In several animal experiments, WCBE administration has been found to attenuate obesity by modulating the gut microbiota (10, 18). Additionally, correlations have been reported between the regulation of gut microbiota and the improvement of oxidative stress, inflammatory response, and insulin resistance (19, 20), which influence the diabetic complications.

As *Phaseolus vulgaris* was found to exert a weak hypoglycemic effect in patients with T2D, this plant faces an obstacle in its use as an oral antidiabetic agent. Fairly high doses were recommended in clinical studies (21). Extracts of this plant have the potential prospect of modulating postprandial blood glucose levels, but heat treatment during processing aimed at destroying phytagglutinin influences its inhibitory activity. We previously developed a novel extraction method based on ultrahigh pressure (UHP) treatment in WCBE production that can reduce the heat-induced destruction of its inhibitory activities (22). Thus, we used this UHP-treated ready-to-use product of the crude WCBE powder as a food supplement for hypoglycemic purposes in patients with T2D. Furthermore, to date, there have been no reports about the influence of WCBE intervention on diabetic complications.

Here, We conducted a randomized double-blind placebo-controlled trial to explore the effects of WCBE on glucose metabolism and diabetic complications in patients with T2D. Furthermore, we considered the gut microbiota as the breakthrough point and analyzed the underlying important role of the gut microbiota in the improvement of glucose metabolism and diabetic complications by using WCBE.

Materials and methods

Study design and participants

The double-blinded, randomized, placebo-controlled 4-month trial was performed from January 2018 to November 2018 in the Third Affiliated Hospital, Nantong University (renamed later as the Affiliated Hospital of Jiangnan University), Wuxi, Jiangsu, China. The trial was approved by the ethical review board of the Third Affiliated Hospital, Nantong University (ID: IEC201711001) and registered on the Chinese Clinical Trial Register as ChiCTR-IOR-17013656. Written informed consent was obtained from all participants before the intervention.

Ninety-six patients with T2D aged 35–75 years were enrolled in this study because they met the following criteria: 6.5%≤ HbA1c ≤13.0%. Besides sulfonylureas and insulins, most hypoglycemic drugs have been reported to be able to modulate gut microbiota (23). Therefore, only patients treated with sulfonylureas or insulin were included. Patients were excluded if they had type 1 diabetes, malignant hypertension, severe cardiac disease, renal failure (eGFR<15), kidney replacement, inflammatory bowel disease, gastrointestinal ulcer, an autoimmune disease, or cancer. Exclusion criteria also included patients receiving medication or surgery for losing weight within 3 months, receiving the administration of antibiotics within one month, receiving gastrointestinal surgery, or during or preparing for pregnancy and lactation. Subjects with poor compliance or protocol violation or unwillingness to continue the clinical trial were asked to withdraw from this study. In the end, ninety participants were eligible and decided to participate in this study.

All subjects were randomly assigned in a 1:2 ratio to the control group (Group C) and WCBE group (Group W). After enrollment, demographic data, including sex, age, disease history, medication and lifestyle, of all subjects were recorded. Anthropometric data, including body mass index (BMI), waist

circumference, hip circumference, blood pressure, and pulse rate, were collected. Sample size was calculated based on the primary outcome (HbA1c), considering a 0.4% difference in HbA1c and a common standard deviation of 0.6% were required to detect a significant improvement in primary outcomes with 95% level and 80% power (24). Considering 10% dropout, withdrawal and non-compliance, a total of 90 subjects were needed in Group C and Group W at a ratio of 1:2.

A simple randomization scheme generated by the computer was created by the trial statistician. The clinical trial was double-blinded because neither the subjects nor researchers knew which group every subject was assigned to, and the grouping of all subjects was unblinded by a statistician after they had completed their experiment. The progression of diabetic complications generally occur over a greater time period than 3 months. Additionally, HbA1c can be used to evaluate the mean level of blood glucose in the recent 2-3 months. In our study, at the end of Month 2, HbA1c was measured after the intense intervention. Parameters of glucose metabolism and diabetic complications were monitored in a part of participant to at Month 4 to determine whether the intervention could ameliorate diabetic complications and maintain the improvement of glucose

metabolism. All of the participants received routine dietary guidance for diabetes. Subjects in Group W received 1.5 g WCBE rich in highly active α-amylase inhibitor (raw material preparation technology provided by Suzhou Langbang Nutrition Company and processed by Jiangsu Shouyuan Biotechnology Co. Ltd) half an hour before each meal. Subjects in Group C were given supplementation of 1.5 g maltodextrin as placebo After each participant was assessed for eligibility and assigned to one group, they experienced a 2-week wash-out phase in which their previous diet recipes were changed into dietary regimen for diabetic patient. Afterward, all participants received baseline biochemical and complication indicator measurements. This trial includes two phases. The first phase was a 2-month intense intervention. All participants received daily telephone follow-up, self-monitoring of fasting blood glucose and 2-hour postprandial blood glucose every 3 days, and a weekly face-to-face interview. All subjects only received biochemical examination at the end of this phase. As the progression of diabetic complications generally occur over a greater time period than 3 months, we then randomly selected 22 participants in Group C and 33 participants in Group W who were willing to continue to the next 2-month intervention phase. In this maintenance phase, participants received the intervention with the same dose of WCBE or maltodextrin as the first phase. During the second phase, they only received weekly telephone follow-up. At the end of Month 4, participants received biochemical examination for the third time and complication indicator measurement for the second time.

The primary and secondary outcomes

The change in the primary outcome, HbA1c, was detected during the intervention. Secondary outcomes included changes in the levels of fasting and postprandial plasma glucose, peripheral neuropathy nerve conduction, endothelial function and fecal microbiota. Outcomes representing lipid metabolism included changes in the levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c).

Sample collection and laboratory measurements

Feces and blood were collected from the subjects before the intervention and at the end of month 2 and 4. Venous blood was collected from the subjects after a 10-12 h fast, and the serum was separated for further laboratory measurements. Feces were immediately preserved in a -80°C freezer for further genome sequencing of the gut microbiota.

Clinical laboratory measurements were performed at Wuxi Third People's Hospital. Blood cell measurements were conducted on an automated hematology analyzer (Sysmex K4500; Sysmex Corporation, Japan). The measurement of biochemical indicators, including fasting blood glucose (FBG), 0.5-hour postprandial blood glucose (0.5 h-PBG), 1-hour postprandial blood glucose (1 h-PBG), 2-hour postprandial blood glucose (2 h-PBG), 3-hour postprandial blood glucose (3 h-PBG), TC, Trig, HDL-c and LDL-c, was performed on an automatic biochemical analyzer (Beckman Coulter au6800; Beckman Corporation, America). Insulin levels were detected on an immunoassay system (Immulite 1000; Siemens Healthcare Diagnostics Inc., Germany). Urine samples collected for urine-microalbumin detection were measured on a biochemical analyzer (Beckman Coulter au5800; Beckman Corporation, America). Fecal samples collected at month 0, 2 and 4 were used to analyze the 16S rRNA gene profile for the gut microbiota.

Toronto clinical scoring system

The TCSS is based on clinical symptoms, lower limb reflexes and sensory tests, and it was used to evaluate peripheral neuropathy according to a previous study (25). Patients with TCSS scores ≤5 were considered to have no neuropathy, while those with scores ≥6 indicated that they might suffer from diabetic peripheral neuropathy (DPN).

Nerve conduction study

The NCS was conducted using MedelecSynergy (VIASYS Health care, Philadelphia, PA, USA) based on standardized methodology for NCS (26). Four sensory nerves, including the median, ulnar, sural and superficial peroneal nerves, were tested bilaterally on all the participants. When conducting NCS, it was ensured that the skin temperature was maintained above 32°C over the upper limbs as well as the lower limbs. The parameters recorded in sensory NCS include sensory nerve conduction velocity potential (SNCV) and sensory nerve amplitude.

Endothelial function analysis

The measurements of ankle-brachial pressure index (ABI) indicate arterial sclerosis and the brachial-ankle pulse wave velocity (baPWV) indicates arterial stiffness and vascular damage. The measurement of these indices were conducted on a BP-203RPE III (Omron Health Co, Kyoto, Japan) according to the instructions for the instrument. The measurements were performed after at least 5 min of resting. Blood pressure of the upper and lower limbs was measured on oscillometric sensors. ABI was calculated bilaterally as the ratio of ankle SBP to arm SBP.

16S rRNA gene profiling

Fecal bacterial DNA extraction, NGS library preparation and sequencing were performed at Shanghai Honsun Biological Technology Co., Ltd. (Shanghai, China). Briefly, total DNA was extracted from the stool samples using the E.Z.N.A.® Soil DNA Kit (Omega Biotek, Norcross, GA, U.S.) according to the manufacturer's instructions. PCR for fecal DNA was performed to amplify the hypervariable V3-V4 region of the bacterial 16S rRNA gene using universal primers 338 F 5'-ACTCCTACGGGAGGCAGCAG-3' and 806 R 5'-GGACTACHVGGGTWTCTAAT-3'. After purification and quantification, PCR-amplified fragments were used for NGS library construction. 16S rRNA gene sequence tags were generated using Illumina MiSeq PE300 (Illumina, San Diego, CA, USA) and were clustered into operational taxonomic units (OTUs) with a 97% sequence similarity cutoff using the UPARSE v.7.0 platform. The QIIME (version 1.9.1) pipeline was used for 16S rRNA data analysis. Singletons and chimeras were identified and removed before the cluster analysis. Each sequence was taxonomically classified and annotated using Ribosomal Database Project (RDP) Classifier v.2.2 (http://rdp.cme.msu.edu/) against the Silva (SSU138) 16S rRNA database with a confidence threshold of 70%.

The dataset was rarified to 31237 reads for the analysis of α-diversity using four metrics: Shannon, Simpson, Chao and Ace diversity. For beta diversity analysis, principal coordinates analysis (PCoA) was performed on the abundance matrix based on Brary-Curtis distance by R version 3.1.1 (https://cran.r-project.Org/bin/windows/base/old/3.1.1/). The linear discriminant analysis (LDA) effect size (LEfSe) method was applied to determine the OTUs most likely to explain differences between groups at the same time point and between the same group pre- and post-intervention. The pheatmap package (https://cran.r-project.org/src/contrib/Archive/pheatmap/) was used for ecological analysis and heatmap depiction.

Statistical analysis

Prism 8 (GraphPad Prism, San Diego, CA) statistical software was used to analyze the data. A two-way repeated-measures analysis of variance (ANOVA) with a mixed effects model was used for intra- and intergroup comparisons. Statistical tests were two-sided, and a P value < 0.05 was considered to be statistically significant.

Results

Baseline characteristics

Ninety-six patients (37 males and 59 females) aged 56-72 years old with T2D who met the inclusion criteria were recruited for this study. Four volunteers who met the exclusion criteria and two volunteers who declined further screening were asked to quit the trial. Thirty subjects were randomly assigned to Group C and sixty subjects to Group W. At baseline, all subjects received measurements of anthropometric, biochemical and complication indicators. At the end of the intense intervention phase, 26 subjects in Group C and 57 subjects in Group W finished the second biochemical examination. We then randomly selected 22 participants in Group C and 33 participants in Group W who were willing to continue the further maintenance phase of intervention. At the end of the second intervention phase, 21 participants in Group C and 31 participants in Group W finished the third biochemical examination and the second complication indicator examination. In this trial, there is no adverse events were reported.The trial profile is shown in Supplementary Figure S1.

There was no significant difference in biochemical and diabetic complication indicators in subjects between the two groups at baseline, except for the levels of 0.5 hPBG, Trig, ABI on the left side, median nerve amplitude, and SCV-ulnar nerve (Table 1). In addition, there was no change in the participants' diet structure before and after the intervention (Supplementary Figure S2).

Effects of WCBE on glucose and lipid metabolism

The trial profile is shown in Figure 1. The processed WCBE inhibited the activity of α-amylase to reduce the digestion and absorption of carbohydrates, leading to a decrease in the serum glucose level. HbA1c was the primary outcome. There was a greater reduction in HbA1c levels in Group W than in Group C at the end of the 2-month intense intervention (0.660 ± 0.468% vs. 0.222 ± 0.763%, $p<0.05$) and at the end of the second 2-month intervention (0.721 ± 0.742% vs. 1.059×10^{-8} ± 0.942%, $p<0.05$) (Figure 1A). In OGTT glucose test, the FBG, 0.5 h PBG, 1 h PBG, 2 h PBG and 3 h PBG in Group W decreased after the 2-month and 4-month intervention, whereas almost all OGTT glucose parameters increased at the end of the 2nd month in Group C and continued to rise at the end of the 4th month. These results indicate an unsatisfactory glycemic control in Group C. Notably, the change in fasting and postprandial glucose levels were significantly different between the two groups at the end of 2nd and 4th month (Figure 1B). Accordingly, a significant reduction in the area under the curve (AUC) of glucose levels during the OGTT was observed in those administered WCBE, but this parameter was increased in those administered the placebo (Figure 1C). To evaluate the level of insulin resistance, HOMA-IR was calculated according to the fasting blood glucose and insulin levels at month 0, 2 and 4. After the 2-month intervention, HOMA-IR did not change significantly in either group. However, HOMA-IR was significantly increased after the 4-month intervention in Group C but remained steady compared with baseline in

10.3389/fendo.2022.999715

TABLE 1 Baseline characteristics of study participants.

Parameters	Group C (n=26)	Group W (n=57)	*P*
Basic indicators			
Age (y)	64.577 ± 1.352	63.912 ± 1.053	0.7142
Sex (M/F)	8/18	25/32	0.258
BMI (kg/m^2)	27.873 ± 0.432	25.086 ± 0.398	0.739
WHR	0.918 ± 0.009	0.919 ± 0.007	0.923
HbA1c (%)	7.842 ± 0.151	7.884 ± 0.168	0.864
Glucose metabolism indicators			
FBG (mmol/L)	7.903 ± 0.310	8.464 ± 0.214	0.173
0.5 h PBG (mmol/L)	10.893 ± 0.470	12.832 ± 0.33	0.001
1 h PBG (mmol/L)	16.187 ± 0.574	17.079 ± 0.308	0.159
2 h PBG (mmol/L)	17.920 ± 0.665	19.151 ± 0.453	0.157
3 h PBG (mmol/L)	16.794 ± 0.799	16.648 ± 0.54	0.883
Lipid metabolism indicators			
TC (mmol/L)	5.031 ± 0.194	4.794 ± 0.123	0.303
Trig (mmol/L)	2.040 ± 0.265	1.515 ± 0.161	0.034
HDL (mmol/L)	1.217 ± 0.055	1.344 ± 0.073	0.238
LDL (mmol/L)	3.050 ± 0.158	2.988 ± 0.109	0.758
Biochemical indicators			
GGT (mmol/L)	27.038 ± 3.254	34.000 ± 5.162	0.384
UA (μmol/L)	318.038 ± 19.806	311.475 ± 10.572	0.738
Testosterone (mmol/L)	12.828 ± 1.864	15.003 ± 0.895	0.238
Leukocytes (×10^9)	6.677 ± 0.363	6.095 ± 0.186	0.109
CRP (mmol/L)	1.769 ± 0.279	2.281 ± 0.259	0.199
mAlb (mg/L)	44.804 ± 25.025	54.621 ± 14.213	0.680
Complication indicators			
TCSS	5.158 ± 0.479	5.115 ± 0.420	0.885
baPWV-left (cm/s)	1780.471 ± 83.013	1747.115 ± 63.530	0.576
baPWV-right (cm/s)	1785.882 ± 65.705	1753.154 ± 57.600	0.543
ABI-left	1.196 ± 0.019	1.132 ± 0.016	0.025
ABI-right	1.186 ± 0.012	1.158 ± 0.033	0.087
Ulnar nerve amplitude (mV)	8.811 ± 0.837	7.050 ± 0.596	0.064
Median nerve amplitude (mV)	14.509 ± 1.930	7.050 ± 0.596	0.0002
Superficial peroneal nerve amplitude (mV)	12.894 ± 2.449	11.566 ± 1.096	0.8111
Sural nerve amplitude-left (mV)	7.146 ± 0.927	9.466 ± 0.764	0.0670
Sural nerve amplitude-right (mV)	6.858 ± 1.020	8.903 ± 0.884	0.1617
SNCV-ulnar nerve (m/s)	62.028 ± 1.082	56.295 ± 1.223	0.0029
SNCV- median nerve (m/s)	54.994 ± 2.147	51.714 ± 1.316	0.0859
SNCV- superficial peroneal nerve (m/s)	56.478 ± 2.494	52.649 ± 1.077	0.1758
SNCV- left sural nerve (m/s)	56.744 ± 2.094	52.570 ± 1.061	0.0573
SNCV- right sural nerve (m/s)	54.894 ± 2.261	54.042 ± 1.330	0.4086

Data are mean ± SEM. UA, uric acid; CRP, C-reactive protein; mAlb, microalbuminuria

Group W. At the end of the 4th month, WCBE tended to lower HOMA-IR levels (P=0.078) (Figure 1C).

No significant differences were found between the two groups for changes in the lipid metabolism parameters of BMI, waist to hip ratio (WHR), TC, Trig and LDL-c after the 2- and 4-month intervention. However, there was a greater increase in HDL-c after the 2- and 4-month WCBE intervention compared with placebo (P<0.05). BMI slightly decreased in both groups at the end of the 2nd month. Although BMI showed a greater increase in both groups at the end of the 4th month compared with the 2nd month, BMI remained relatively steady in Group W. γ-Glutamyl transpeptidase (GGT) was slightly increased in Group C and decreased in Group W, and the change in GGT after 4 months was significantly different between the two groups. Notably, there was a greater enhancement of testosterone in male

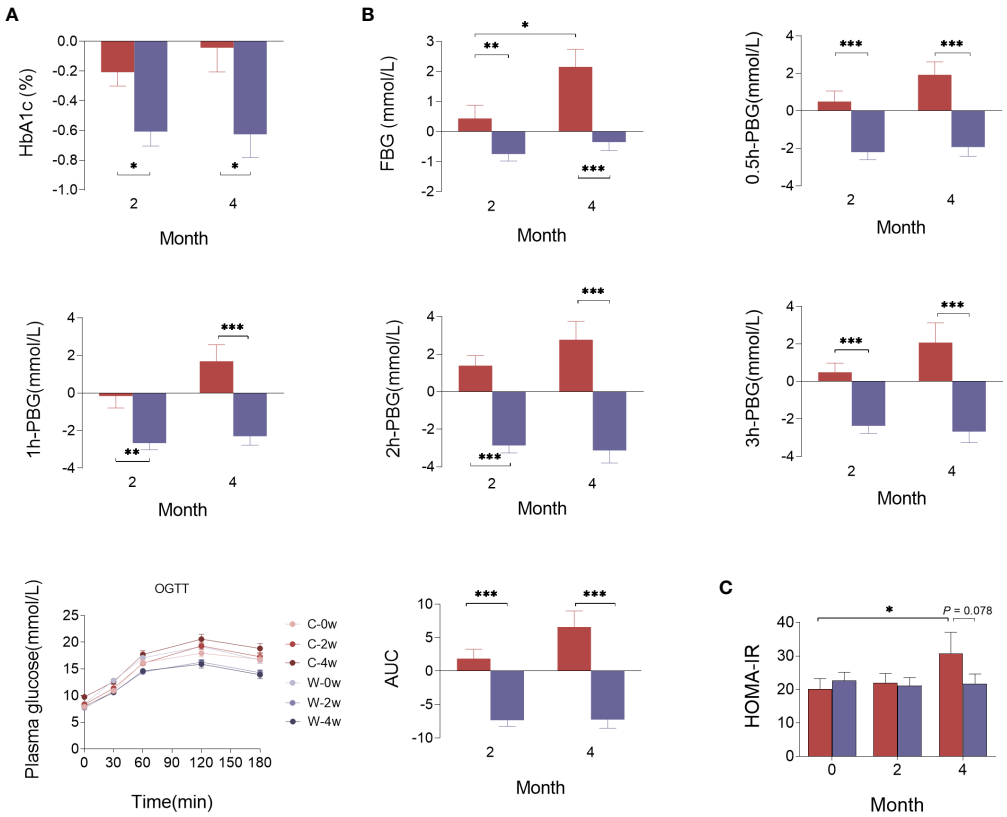


FIGURE 1
Effects of WCBE on glucose metabolism indices at the end of the 2nd month and 4th month. The change in HbA1c **(A)**, fasting and postprandial blood glucose levels **(B)**, and HOMA-IR **(C)**. *P < 0.05; **P < 0.01; ***P < 0.001.

patients in Group W than in Group C (Supplementary Figure S3).

Effects of WCBE on the progression of diabetic vasculopathy and neuropathy

TCSS, NCS and endothelial function analysis were used to assess diabetic vasculopathy and neuropathy. Considering that these diabetes complication indices could not be improved within a short time, we only conducted these measurements before and 4 months after the intervention. The decline in the Toronto score in Group W was greater than that in Group C (P<0.05) (Figure 2A). We further compared the proportion of patients with TCSS≥6 who could be diagnosed with diabetic peripheral neuropathy (DPN) pre- and post-intervention. We found that this proportion only significantly decreased in Group W after the intervention (P<0.01), but no change in this proportion was observed in Group C (P>0.05) (Figure 2B). Thus, the proportion of patients with TCSS≥6 was significantly lower in Group W than in Group C at the end of 4 months (P<0.05). ABI and baPWV are two sensitive markers of arterial stiffness. No difference in the change in ABI was observed between the two groups. As an index reflecting arterial stiffness in the arteries of the lower limbs, the baPWV level on the right side of the body showed greater reduction in Group W than in Group C after the 4-month intervention (P<0.05). However, there was no difference in the change of the baPWV level on the left side observed between the two groups (Figure 2C).

The NCS is considered the gold standard for the diagnosis of DPN. In this study, both the left and right sural sensory nerve conduction velocity (SNCV-left sural and SNCV-right sural) slightly decreased in Group C and slightly increased in Group W. There was a significant difference in the variation in the SNCV of the left sural nerve between the two groups after the intervention (P<0.05), and a slight but not significant difference in the variation in the SNCV of the right sural nerve was observed (P=0.0888) (Figure 2D). In addition, no difference in the variation in other motor or sensory NCVs were detected between the two groups (Supplementary Figure 4).

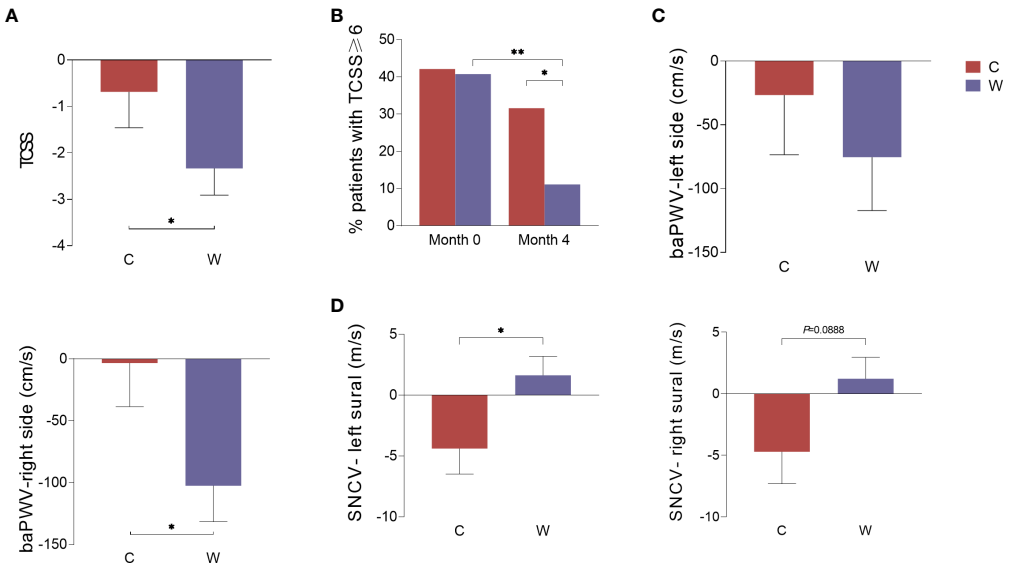


FIGURE 2
The change in indices representing diabetic complications during the intervention. Data were calculated according to the change in indices in Group C and Group W before and after the 4-month intervention. TCSS **(A)**, the percentage of patients with TCSS≥6 **(B)**, the baPWV on the left and right sides of the body **(C)**, and the conduction velocity of the left and right sural sensory nerves **(D)**. *P<0.05; **P<0.01.

Variation of α-diversity of gut microbiota

At baseline, parameters representing community richness and diversity, including the Shannon, Simpson, Chao and Ace index, were not different between participants in Group W and Group C. After 2 months and 4 months of intervention, these α-diversity indices did not change significantly (P > 0.05, Supplementary Figure S5).

Variation of β-diversity of gut microbiota

PCoA based on the Bray–Curtis distance was applied to evaluate the gut microbiota compositional discrimination between subjects in different groups at the same time point and in the same group at different time points. Before the intervention, there was no significant difference in gut microbiota structure between Group C and Group W (PERMANOVA, P>0.05). As expected, treatment with the WCBE resulted in a significant difference in the gut microbiota structure compared with Group C at the end of the 2nd month (PERMANOVA, P<0.01). At the end of the 4th month of intervention, the gut microbiota structure remained significantly different between Group C and Group W (PERMANOVA, P<0.05) (Figure 3).

We further compared the gut microbiota structure at pre-intervention with that at 2 and 4 months post-intervention in each group. Significant variations were discovered in Group W after treatment with the α-amylase inhibitor compared with pre-intervention (PERMANOVA, P<0.01). However, no variation in the gut microbiota structure could be observed pre- and post-intervention in Group C (PERMANOVA, P>0.05) (Figure 3A). In the gut microbial community, a higher abundance of *Faecalibacterium* was observed in Group W than in Group C 2 months after the intervention. However, 4 months after the intervention, no difference in the abundance of this genus was discovered between the two groups. The level of *Bifidobacterium* was only increased in Group W 2 and 4 months after the intervention (Figures 3A, B).

Key OTUs that discriminate the differences in the gut microbiota structure after intervention

LEfSe analysis was performed to identify bacterial taxa with differential abundance among the groups, and only those taxa with a log LDA score >2 were considered. At the end of the 2nd month of intervention, the abundances of *Bifidobacterium*, *Faecalibacterium* and *Anaerostipes* in participants in Group W were higher, whereas *Weissella*, *Klebsiella*, *Cronobacter* and Enterobacteriaceae_unclassified were less abundant than those in Group C (Figure 4A). After 4 months of intervention, *Bifidobacterium* remained more abundant in Group W than in

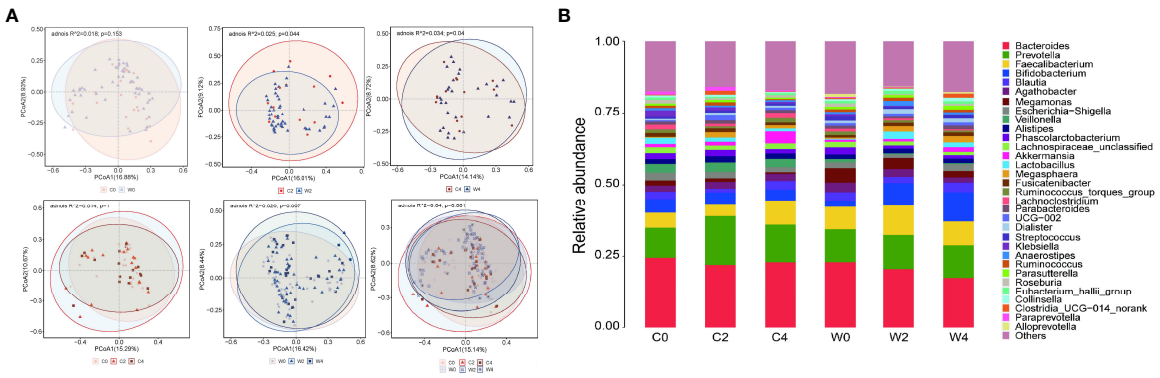


FIGURE 3
Effect of WCBE treatment on the gut microbiota structure. PcoA of fecal microbiota pre-intervention, 2 months post-intervention and 4 months post-intervention. Based on PERMANOVA statistical analysis, variations during the intervention, $P = 0.001$; C0 vs. W0, $P > 0.05$; C2 vs. W2, $P < 0.05$; C4 vs. W4, $P < 0.05$; variations during the placebo treatment, $P > 0.05$; variations during the WCBE treatment, $P < 0.01$ **(A)**. Microbial community changes at genus level **(B)**.

Group C. The genus of *Adlercreutzia* also showed higher abundance in participants after the 2- and 4-month α-amylase inhibitor intervention than in those who received placebo treatment. After the 4 months of intervention, *Citrobacter*, *Cronobacter* and Enterobacteriaceae_unclassified were less abundant in Group W. Notably, these less abundant genera after the intervention in Group W all came from the family Enterobacteriaceae, which contains many opportunistic pathogens (Figure 4B).

Differential gut bacteria were also screened pre- and post-intervention. In Group W, the abundance of *Lactobacillus* at the end of 2 months of intervention and *Bifidobacterium*, *Romboutsia* and *Faecalitalea* at the end of 4 months of intervention were higher than those before the intervention. The concentrations of *Fusobaterium*, *Roseburia*, *Citrobacter*, *Klebsiella* and Enterobacteriaceae decreased after 4 months of WCBE intervention (Figure 4C).

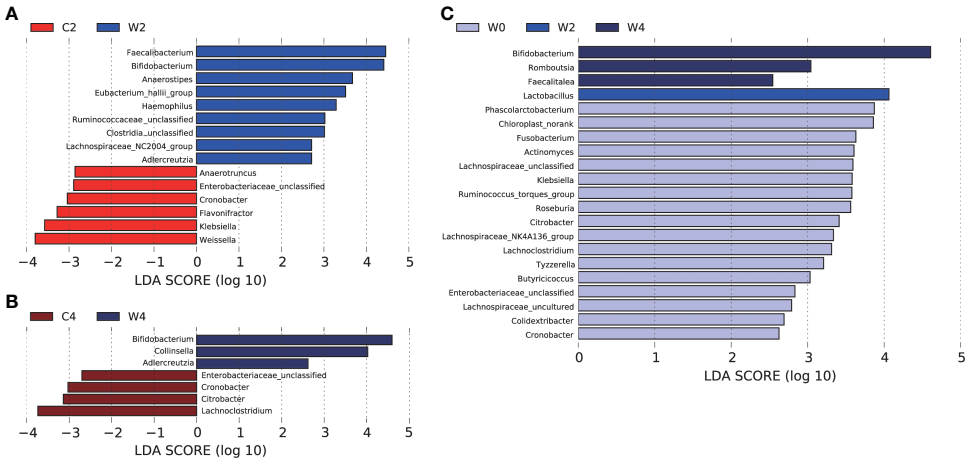


FIGURE 4
LEfSe analysis of differentially abundant taxa in the genus. Histogram of the LDA scores computed for features differentially abundant between gut microbiota. LEfSe scores can be interpreted as the degree of consistent difference in relative abundance between features in the two classes of analyzed microbial communities. The histogram thus identifies which clades among all those detected as statistically and biologically differential explain the greatest differences between communities.In this study, LDA=2 was used as the cut-off point. Differences in the gut microbiota in Groups C and Group W after 2 months of intervention **(A)**. Differences in the gut microbiota in Groups C and Group W after 4 months of intervention **(B)**.Differences in the gut microbiota between pre- and post-intervention in Group W **(C)**.

The dynamic variation of gut bacteria during the intervention

From the heatmap of the abundance of the key OTUs responsible for the different variations in the gut microbiota structure between the two groups after the intervention, we found that WCBE could enrich SCFA-producing bacteria, such as *Faecalibacterium* and *Bifidobacterium*, at the end of the 2nd month after the intervention. However, after 4 months of the intervention, only *Bifidobacterium* was greatly enriched. The other bacterial genera were not as enriched as those at the end of the 2nd month (Figure 5). Moreover, WCBE administration inhibited opportunistic pathogens, such as *Klebsiella*, after 2 and 4 months of intervention, but no significant change was observed in Group C.

Discussion

In the present study, WCBE that is rich in a highly active α-amylase inhibitor was found to alleviate glucose metabolism dysbiosis and diabetic complication indices. To our knowledge, this is the first time that vasculopathy and neuropathy in patients with T2D have been improved by using a dietary supplement in such a short-term period. Notably, after 2 months of an intense intervention with a WCBE treatment and in the following two-month maintenance period, the improvements to glycemic metabolism were preserved. This finding indicates that WCBE administration might be an ideal choice for the long-term management of glucose homeostasis. Numerous studies have demonstrated a connection between the gut microbiota and the occurrence of T2D. The regulation of the gut microbiota is also associated with improvements of metabolic parameters in patients with T2D (27–29). Since the improvement of some clinical indicators and the gut microbiota structure in Group W was less substantial at the end of the 4th month compared with the 2nd month, we speculate that the gradual diminished therapeutic effect might be related to the gradual diminished improvement of the gut microbiota. More causal relationships still need to be verified by experiments such as gut microbiota transplantation.

To explore the underlying 'intestinal mechanism' other than the conventional mechanism of 'reduced starch absorption' in glycemic control by the α-amylase inhibitor, we investigated the dynamic variations in the gut microbiota structure during the intervention. Lower α-diversity of the gut microbiota was found in patients with T2D compared with healthy controls (30, 31). In this study, no change in the α-diversity of the gut microbiota could be observed during the intervention. The β-diversity analysis of gut microbiota found that the structure of the gut microbiota was significantly altered by the administration of WCBE and showed significant difference compared with placebo treatment after 2 and 4 months of the intervention. At the end of the 4th month, patients in Group C even showed a trend toward the recovery of their bacterial structure to the pre-intervention status.

In the present study, according to the analysis of the results of LEfSe and heat map, the abundance of *Bifidobacterium*, *Faecalibacterium*, *Anaerostipes* and *Adlercreutzia* after the intense intervention was higher in Group W than in Group C. The higher abundance of *Bifidobacterium* and *Adlercreutzia* in Group W was preserved after the following 2-month maintenance intervention. It was reported that the increase in the abundance of *Bifidobacterium longum* negatively correlates with changes in HbA1c (32). Since many species in *Bifidobacterium* are capable of producing acetic acids with a given amount of carbohydrates, *Bifidobacterium* is often considered an acetic acid-producing genus (14). Acetic acid has been proven to participate in maintaining or improving glucose homeostasis (33). The continuous enrichment of *Bifidobacterium* suggests that this SCFA-producing genus may play an important role

FIGURE 5
The dynamic change in key OTU abundance during the intervention in both groups. The abundance of the OTUs identified based on LEfSe by comparing the two groups 2 months and 4 months post-intervention and the same group before and after the intervention were used to illustrate the dynamic variation of the key taxa during the α- glycosidase inhibitor intervention.

in the improvement of T2D during WCBE intervention. In our study, *Faecalibacterium* was more abundant in Group W at month 2. This well-known butyric acid-producing genus has often been inversely correlated with glycometabolism indicators (34). *Anaerostipes*, which has been reported to be capable of converting lactate and acetate to butyrate *via* the acetyl-CoA pathway (35), was higher in Group W at month 2. *Adlercreutzia* is associated with leanness and glucose tolerance (36). We found that the abundance of this genus increased after 2 and 4 months of WCBE intervention. The abundance of *Lactobacillus*, *Bifidobacterium*, *Romboutsia* and *Faecalitalea* significantly increased after the intervention in Group W. *Romboutsia*, a butyrate-producing genus, has been inversely associated with insulin resistance or T2D (37). Faecalitalea has been shown to promote insulin secretion and improve the insulin response (38). Therefore, α-amylase inhibitors can enrich a variety of SCFA producers that can resist systemic chronic inflammation, induce the secretion of beneficial gut hormones, and promote underlying beneficial bacteria that have been reported to be inversely associated with glycometabolism indicators.

Furthermore, the genera of *Klebsiella*, *Cronobacter*, *Citrobacter* and Enterobacteriaceae_unclassified were inhibited by the intake of WCBE. These genera belong to the family Enterobacteriaceae, which contains numerous opportunistic pathogens. *Klebsiella*, a common opportunistic pathogen, was increased in fecal samples from patients with T2D (39). *Cronobacter* can cause bacteremia and sepsis following adherence, invade the mucosa of the gastrointestinal tract and trigger the release of various proinflammatory cytokines and chemokines (40). *Citrobacter rodentium* has been related to defects in mucosal immunity and mucosal barrier integrity, resulting in systemic chronic low-grade inflammation and the further development of diabetes (41). *Weissella* and *Klebsiella* were increased in diabetic mice compared with a control group. They were also decreased after intervention using 1−deoxynojirimycin, which is an α-glucosidase inhibitor. The abundance of these with fasting blood glucose, fasting blood insulin and HOMA-IR (42). *Weissella* has been shown to produce lipoteichoic acids, which are responsible for the induction of host inflammatory responses (43). Thus, WCBE was able to reduce the abundance of opportunistic pathogens with the putative capability of impairing the integrity and immunity of intestinal mucosa and inducing systemic and chronic inflammation in patients with diabetes.

Glycemic control is recognized as an effective means for delaying the progression of diabetic complications. In the present study, WCBE alleviated the glycometabolism indices 2- and 4-months after the intervention. After 4 months of intervention, WCBE improved diabetic angiopathy and peripheral neuropathy, according to the analysis of TCSS, baPWV and left and right sural SNCV. To our knowledge, this is the first report of these effects of an α-amylase inhibitor on diabetic angiopathy and peripheral neuropathy. Accordingly, the gut microbiota was improved after 2 months of WCBE intervention, and these improvements remained after 4 months of intervention.

Recently, in a diabetic mouse model, the genus *Weissella* was inhibited by an extraction from cornuside, which is also a Chinese herbal medicine. The increased abundance of *Weissella confusa* might be closely related to the decreased level of testosterone and reproductive damage (44). *Weissella confusa* MBF8-1 can produce bacteriocin peptides that show spermicidal activity. In our study, WCBE enhanced the level of testosterone, and the genus *Weissella* was less abundant in Group W than in Group C, which is in accordance with a previous report.

Rotundic acid is a constituent in the bark of Ilex rotunda Thunb, and it can downregulate *Klebsiella* abundance. *Klebsiella* is negatively correlated with body weight and positively correlated with parameters of glycolipid metabolism, including glucose, insulin, HOMA-IR, TG, and indicators of cardiovascular function, including ANG-2, MAP, α-HBDH, CK-MB and LDH, in rats (45). In our study, the abundance of *Klebsiella* decreased after the intervention in Group W, which indicates that the inhibition of this genus may participate in the improvement of cardiovascular function. This study offers a novel perspective regarding the relationship among gut microbiota, blood glucose, and diabetic complications, especially the direct effect of the gut microbiota on diabetic complications.

However, there are some limitations in the present study. For example, this study is a randomized double-blind placebo-controlled trial and the sample size is a little small, which may result in the significant differences in levels of some complication indexes. Although the abundance of SCFA-producing genera was increased after the WCBE intervention, the levels of the different SCFAs were not measured. Four months might be too short of a period to obtain a significant improvement in diabetic complications, so significant changes in many indices indicating vasculopathy and neuropathy were difficult to observe in this study. To observe the combinative effects of WCBE on the regulation of glucose metabolic and gut microbiota, the relative small enrolled population may limit the application in a larger population. Later, we will perform further studies to evaluate the clinical effect of WCBE on diabetic patients treated with a variety of hypoglycemic drugs. Metagenomic sequencing would undoubtedly be a better methodology than 16S rRNA gene sequencing, which was used in this study, to analyze the improvements in functions of the gut microbiota and the association between the improvements in the gut microbiota and diabetes and its complications. In addition, whether the improvement of diabetic complications is mainly due to low absorption of carbohydrates or the modulation of the gut microbiota by WCBE needs further investigation.

In conclusion, WCBE, which is a valuable α-amylase inhibitor, could facilitate the improvement of the structure of the gut microbiota, especially the enrichment of SCFA-producing bacteria and inhibition of opportunistic pathogens. This might be a supplemental mechanism by which glycemic metabolism dysbiosis is alleviated in patients with T2D in addition to the direct inhibition of the absorption of saccharides. Furthermore, we speculate that the

continuous regulation of the gut microbiota for at least four months by WCBE might be related to the long-term improvement of diabetic complications. This α-amylase inhibitor could be considered a novel prebiotic antidiabetic agent for the regulation of glucose metabolism and gut microbiota homeostasis and may slightly ameliorate diabetic complications in patients with T2D. Notably, this convenient and valuable dietary supplement, WBCE, will meet the strong desire for carbohydrate intake in patients with T2D during long-term glucose control and complication prevention.

Data availability statement

The date presented in the study are deposited in the NCBI Bio Sample database accession number PRJNA872293.

Ethics statement

The studies involving human participants were reviewed and approved by Third Affiliated Hospital, Nantong University (Affiliated Hospital of Jiangnan University). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YuwF, FZ and QW collected, analyzed, and interpreted the data and co-wrote the manuscript. HC collected, analyzed, and interpreted the data. JieZ designed the study, collected, analyzed, and interpreted the data, and co-wrote the manuscript. WZ designed the study and interpreted the data. FaH collected, analyzed, and interpreted the data and co-wrote the manuscript. YG, DL, JuY, YX, YufZ, HZ, SS, AT, MJ, YD, JG, and YJ collected the data and followed-up on the trial. MD designed the study. FHe examined indices of diabetes complications. MC and JW examined indices of diabetes complications and interpreted the data. XD interpreted the data. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by National Natural Science Foundation of China (grant numbers 81870544, 81870594); the Natural Science Foundation of Jiangsu Province (grant numbers BK20181132, BK20210060, SBK2022023007); Scientific Research Project of Jiangsu Commission of Health (grant number M2021055); Science and Technology Program Project of Jiangsu Market Supervision and Administration (grant number KJ2022028); Jiangsu Scientific Research Project of Elderly Health (grant number LK2021035); Jiangsu Scientific Research Project of Women's and Children's Health (grant number F201741); Scientific Research Project of Wuxi Commission of Health (grant numbers ZZ003, Q201762); Wuxi Scientific and Technological Development Project (grant numbers N20192024, N20191001, Y20212001); Translational Medicine Research Program of Wuxi Translational Medicine Center (grant number 2020ZHYB08).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.999715/full#supplementary-material

References

1. . Intensive Blood-Glucose Control with Sulphonylureas or Insulin Compared with Conventional Treatment and Risk of Complications in Patients with Type 2 Diabetes (Ukpds 33). Uk Prospective Diabetes Study (Ukpds) Group. *Lancet* (1998) 352(9131):837–53.

2. Bethel MA, Mentz RJ, Merrill P, Buse JB, Chan JC, Goodman SG, et al. Microvascular and cardiovascular outcomes according to renal function in patients treated with once-weekly exenatide: Insights from the exscel trial. *Diabetes Care* (2020) 43(2):446–52. doi: 10.2337/dc19-1065

3. Ha K, Joung H, Song Y. Inadequate fat or carbohydrate intake was associated with an increased incidence of type 2 diabetes mellitus in Korean adults: A 12-year community-based prospective cohort study. *Diabetes Res Clin Pract* (2019) 148:254–61. doi: 10.1016/j.diabres.2019.01.024

4. Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K, Nagasawa SY, et al. Dietary carbohydrate intake, presence of obesity and the incident risk of type 2 diabetes in Japanese men. *J Diabetes Investig* (2016) 7(3):343–51. doi: 10.1111/jdi.12433

5. Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (Pure): A prospective cohort study. *Lancet* (2017) 390(10107):2050–62. doi: 10.1016/S0140-6736(17)32252-3

6. Ulbricht C, Bryan JK, Conquer J, Costa D, Stock T, Tanguay-Colucci S, et al. An evidence-based systematic review of amylase inhibitors by the natural standard research collaboration. *J Diet Suppl* (2010) 7(1):78–95. doi: 10.3109/19390210903535043

7. de Sales PM, de Souza PM, Dartora M, Resck IS, Simeoni LA, Fonseca-Bazzo YM, et al. Pouteria torta epicarp as a useful source of alpha-amylase inhibitor in the control of type 2 diabetes. *Food Chem Toxicol* (2017) 109:962–9. doi: 10.1016/j.fct.2017.03.015

8. Neil ES, McGinley JN, Fitzgerald VK, Lauck CA, Tabke JA, Streeter-McDonald MR, et al. White kidney bean (Phaseolus vulgaris l.) consumption reduces fat accumulation in a polygenic mouse model of obesity. *Nutrients* (2019) 11(11):2780. doi: 10.3390/nu11112780

9. Qin G, Wang F, Liang H, Tang S, Shekh K, Wang Y, et al. Subchronic study of a white kidney bean (Phaseolus vulgaris) extract with alpha-amylase inhibitory activity. *BioMed Res Int* (2019) 2019:9272345. doi: 10.1155/2019/9272345

10. Monk JM, Wu W, Lepp D, Pauls KP, Robinson LE, Power KA. Navy bean supplementation in established high-fat diet-induced obesity attenuates the severity of the obese inflammatory phenotype. *Nutrients* (2021) 13(3):757. doi: 10.3390/nu13030757

11. Wang S, Chen L, Yang H, Gu J, Wang J, Ren F. Regular intake of white kidney beans extract (Phaseolus vulgaris l.) induces weight loss compared to placebo in obese human subjects. *Food Sci Nutr* (2020) 8(3):1315–24. doi: 10.1002/fsn3.1299

12. Olmedilla-Alonso B, Pedrosa MM, Cuadrado C, Brito M, Asensio SMC, Asensio-Vegas C. Composition of two Spanish common dry beans (Phaseolus vulgaris), 'Almonga' and 'Curruquilla', and their postprandial effect in type 2 diabetics. *J Sci Food Agric* (2013) 93(5):1076–82. doi: 10.1002/jsfa.5852

13. Valencia-Mejia E, Batista KA, Fernandez JJA, Fernandes KF. Antihyperglycemic and hypoglycemic activity of naturally occurring peptides and protein hydrolysates from easy-to-Cook and hard-to-Cook beans (Phaseolus vulgaris l.). *Food Res Int* (2019) 121:238–46. doi: 10.1016/j.foodres.2019.03.043

14. Zhao L, Zhang F, Ding X, Wu G, Lam Y, Wang X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science* (2018) 359 (6380):1151–6. doi: 10.1126/science.aao5774

15. McCarty MF, DiNicolantonio JJ. Acarbose, lente carbohydrate, and prebiotics promote metabolic health and longevity by stimulating intestinal production of glp-1. *Open Heart* (2015) 2(1):e000205. doi: 10.1136/openhrt-2014-000205

16. Hiele M, Ghoos Y, Rutgeerts P, Vantrappen G. Effects of acarbose on starch hydrolysis. study in healthy subjects, ileostomy patients, and in vitro. *Dig Dis Sci* (1992) 37(7):1057–64. doi: 10.1007/BF01300287

17. Wan J, Wu Y, Pham Q, Li RW, Yu L, Chen MH, et al. Effects of differences in resistant starch content of rice on intestinal microbial composition. *J Agric Food Chem* (2021) 69(28):8017–27. doi: 10.1021/acs.jafc.0c07887

18. Shi Z, Zhu Y, Teng C, Yao Y, Ren G, Richel A. Anti-obesity effects of alpha-amylase inhibitor enriched-extract from white common beans (Phaseolus vulgaris l.) associated with the modulation of gut microbiota composition in high-fat diet-induced obese rats. *Food Funct* (2020) 11(2):1624–34. doi: 10.1039/c9fo01813a

19. Saad MJ, Santos A, Prada PO. Linking gut microbiota and inflammation to obesity and insulin resistance. *Physiol (Bethesda)* (2016) 31:283–93. doi: 10.1152/physiol.00041.2015

20. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* (2012) 490:55–60. doi: 10.1038/nature11450

21. Helmstadter A. Beans and diabetes: Phaseolus vulgaris preparations as antihyperglycemic agents. *J Med Food* (2010) 13(2):251–4. doi: 10.1089/jmf.2009.0002

22. Ma Y, Rang Y, Yang R, Zhao W. Effect of white kidney bean extracts on estimated glycemic index of different kinds of porridge. *LWT* (2018) 96:576–82. doi: 10.1016/j.lwt.2018.06.018

23. Feng Y, Cao H, Hua J, Zhang F. Anti-diabetic intestinal mechanisms: Foods, herbs, and Western medicines. *Mol Nutr Food Res* (2022) 66(13):e2200106. doi: 10.1002/mnfr.202200106

24. Firouzi S, Majid HA, Ismail A, Kamaruddin NA, Barakatun-Nisak MY. Effect of multi-strain probiotics (Multi-strain microbial cell preparation) on glycemic control and other diabetes-related outcomes in people with type 2 diabetes: A randomized controlled trial. *Eur J Nutr* (2017) 56(4):1535–50. doi: 10.1007/s00394-016-1199-8

25. Bril V, Perkins BA. Validation of the Toronto clinical scoring system for diabetic polyneuropathy. *Diabetes Care* (2002) 25(11):2048–52. doi: 10.2337/diacare.25.11.2048

26. Ng YT, Phang SCW, Tan GCJ, Ng EY, Botross Henien NP, UD MP, et al. The effects of tocotrienol-rich vitamin e (Tocovid) on diabetic neuropathy: A phase ii randomized controlled trial. *Nutrients* (2020) 12(5):1-15. doi: 10.3390/nu12051522

27. Karlsson F, Tremaroli V, Nookaew I, Bergström G, Behre C, Fagerberg B, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* (2013) 498(7452):99–103. doi: 10.1038/nature12198

28. Cani P, Bibiloni R, Knauf C, Waget A, Neyrinck A, Delzenne N, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* (2008) 57(6):1470–81. doi: 10.2337/db07-1403

29. Shin N, Lee J, Lee H, Kim M, Whon T, Lee M, et al. An increase in the akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut* (2014) 63(5):727–35. doi: 10.1136/gutjnl-2012-303839

30. Miao Z, Lin JS, Mao Y, Chen GD, Zeng FF, Dong HL, et al. Erythrocyte n-6 polyunsaturated fatty acids, gut microbiota, and incident type 2 diabetes: A prospective cohort study. *Diabetes Care* (2020) 43(10):2435–43. doi: 10.2337/dc20-0631

31. Menni C, Zhu J, Le Roy CI, Mompeo O, Young K, Rebholz CM, et al. Serum metabolites reflecting gut microbiome alpha diversity predict type 2 diabetes. *Gut Microbes* (2020) 11(6):1632–42. doi: 10.1080/19490976.2020.1778261

32. Gu Y, Wang X, Li J, Zhang Y, Zhong H, Liu R, et al. Analyses of gut microbiota and plasma bile acids enable stratification of patients for antidiabetic treatment. *Nat Commun* (2017) 8(1):1785. doi: 10.1038/s41467-017-01682-2

33. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* (2016) 7(3):189–200. doi: 10.1080/19490976.2015.1134082

34. Xu J, Lian F, Zhao L, Zhao Y, Chen X, Zhang X, et al. Structural modulation of gut microbiota during alleviation of type 2 diabetes with a Chinese herbal formula. *ISME J* (2015) 9(3):552–62. doi: 10.1038/ismej.2014.177

35. Shetty SA, Boeren S, Bui TPN, Smidt H, de Vos WM. Unravelling lactate-acetate and sugar conversion into butyrate by intestinal anaerobutyricum and anaerostipes species by comparative proteogenomics. *Environ Microbiol* (2020) 22 (11):4863–75. doi: 10.1111/1462-2920.15269

36. Ziętak M, Kovatcheva-Datchary P, Markiewicz LH, Ståhlman M, Kozak LP, Bäckhed F. Altered microbiota contributes to reduced diet-induced obesity upon cold exposure. *Cell Metab* (2016) 23(6):1216–23. doi: 10.1016/j.cmet.2016.05.001

37. Chen Z, Radjabzadeh D, Chen L, Kurilshikov A, Kavousi M, Ahmadizar F, et al. Association of insulin resistance and type 2 diabetes with gut microbial diversity: A microbiome-wide analysis from population studies. *JAMA Netw Open* (2021) 4(7):e2118811. doi: 10.1001/jamanetworkopen.2021.18811

38. Ma Q, Li Y, Wang J, Li P, Duan Y, Dai H, et al. Investigation of gut microbiome changes in type 1 diabetic mellitus rats based on high-throughput sequencing. *BioMed Pharmacother* (2020) 124:109873. doi: 10.1016/j.biopha.2020.109873

39. Zhao X, Zhang Y, Guo R, Yu W, Zhang F, Wu F, et al. The alteration in composition and function of gut microbiome in patients with type 2 diabetes. *J Diabetes Res* (2020) 2020:8842651. doi: 10.1155/2020/8842651

40. Feeney A, Kropp KA, O'Connor R, Sleator RD. Cronobacter sakazakii: Stress survival and virulence potential in an opportunistic foodborne pathogen. *Gut Microbes* (2014) 5(6):711–8. doi: 10.4161/19490976.2014.983774

41. Wang X, Ota N, Manzanillo P, Kates L, Zavala-Solorio J, Eidenschenk C, et al. Interleukin-22 alleviates metabolic disorders and restores mucosal immunity in diabetes. *Nature* (2014) 514(7521):237–41. doi: 10.1038/nature13564

42. Hu TG, Wen P, Shen WZ, Liu F, Li Q, Li EN, et al. Effect of 1-deoxynojirimycin isolated from mulberry leaves on glucose metabolism and gut microbiota in a streptozotocin-induced diabetic mouse model. *J Nat Prod* (2019) 82 (8):2189–200. doi: 10.1021/acs.jnatprod.9b00205

43. Hong YF, Lee YD, Park JY, Kim S, Lee YW, Jeon B, et al. Lipoteichoic acid isolated from weissella cibaria increases cytokine production in human monocyte-like thp-1 cells and mouse splenocytes. *J Microbiol Biotechnol* (2016) 26(7):1198–205. doi: 10.4014/jmb.1601.01047

44. Liu L, Shu A, Zhu Y, Chen Y. Cornuside alleviates diabetes mellitus-induced testicular damage by modulating the gut microbiota. *Evid Based Complement Alternat Med* (2021) 2021:5301942. doi: 10.1155/2021/5301942

45. Yan Z, Wu H, Yao H, Pan W, Su M, Chen T, et al. Rotundic acid protects against metabolic disturbance and improves gut microbiota in type 2 diabetes rats. *Nutrients* (2019) 12(1):67. doi: 10.3390/nu12010067

frontiers | Frontiers in Endocrinology

TYPE Systematic Review
PUBLISHED 13 December 2022
DOI 10.3389/fendo.2022.1069436

OPEN ACCESS

EDITED BY
Martha M Funnell,
University of Michigan, United States

REVIEWED BY
Jaclynn Hawkins,
University of Michigan, United States
Robin Nwankwo,
Michigan Medicine, University of Michigan, United States
Yu Kuei Lin,
University of Michigan, United States

*CORRESPONDENCE
Diana Sherifali
dsherif@mcmaster.ca

This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

SPECIALTY SECTION
RECEIVED 13 October 2022
ACCEPTED 28 November 2022
PUBLISHED 13 December 2022

CITATION
Racey M, Jovkovic M, Alliston P and Sherifali D (2022) Applying the RE-AIM implementation framework to evaluate diabetes health coaching in individuals with type 2 diabetes: A systematic review and secondary analysis. *Front. Endocrinol.* 13:1069436. doi: 10.3389/fendo.2022.1069436

Applying the RE-AIM implementation framework to evaluate diabetes health coaching in individuals with type 2 diabetes: A systematic review and secondary analysis

Megan Racey[1,2], Milos Jovkovic[1,2], Paige Alliston[1,2] and Diana Sherifali[1,2]*

[1]McMaster Evidence Review and Synthesis Team, McMaster University, Hamilton, ON, Canada, [2]School of Nursing, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

Background: Diabetes health coaching continues to emerge as an effective intervention to support diabetes self-management. While previous systematic reviews have focused on the effectiveness of diabetes health coaching programs in adults with type 2 diabetes (T2DM), limited literature is available on its implementation. This review examines what aspects of diabetes health coaching interventions for adults living with type 2 diabetes have been reported using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework to optimize implementation.

Methods: We examined the included studies from our recently completed systematic review, which searched 6 databases for randomized controlled trials (RCTs) of health coaching interventions delivered by a health professional for adults with T2DM. Reviewers screened citations and extracted data for study characteristics and the 5 dimensions (62 criteria) of the RE-AIM framework.

Results: 9 diabetes health coaching RCTs were included in this review. 12 criteria were reported by all the included studies and 21 criteria were not reported by any of the studies. The included studies all reported on more than 20 RE-AIM criteria, ranging from 21 to 27. While Reach was the best reported construct by the included studies, followed by Effectiveness and Implementation, the criteria within the Adoption and Maintenance constructs were rarely mentioned by these studies. In general, there was also wide variation in how each of the criteria were reported on by study authors

Conclusions: Due to the paucity of reporting of the RE-AIM components for diabetes health coaching, limited implementation and clinical practice implications can be drawn. The lack of detail regarding implementation approaches to diabetes health coaching greatly limits the interpretation and

comparisons across studies to best inform the application of this intervention to support diabetes self-management.

Systematic review registration: PROSPERO identifier, CRD42022347478

KEYWORDS

health coaching, systematic review, RE-AIM (reach, effectiveness, adoption, implementation and maintenance), type 2 diabetes

1 Introduction

Individuals living with type 2 diabetes (T2DM) are responsible for the majority of their self-management, spending only very limited time with their healthcare providers while the remaining time spent on self-management is completed by the individual outside of the healthcare setting. However, one's ability to self-manage chronic illnesses is dependent on several factors, including sociodemographic variables (e.g. income, culture, literacy, environment), behavioural considerations (e.g. eating and activity habits), and comorbidities (1). Despite the availability of diabetes education programs, engagement with such programs has been challenged by a) limited availability, offerings, and duration of education, support, and specialized programming and b) minimal individualized or tailored education and support (2–5).

Diabetes health coaching is increasingly viewed as an effective strategy to support self-management. According to Wolever et al., health coaching may be described as: a) patient centred; b) includes patient determined goals; c) incorporates self-discovery and active learning processes; d) encourages accountability for behavioural goals; e) provides some education alongside coaching; f) a health professional who is trained in behaviour change, communication, and motivational interviewing skills (6). Health coaching may also be timely and relevant health related education, behaviour change promotion, and psychosocial support to enhance the well-being of individuals and facilitate the achievement of their health-related goals (7, 8). More recently, health coaching models have been proposed to help describe and define these interventions (9). This model is comprised of four components: (i) personal case management and monitoring, emphasizing process of care issues and system navigation related to diabetes; (ii) diabetes self-management education and support, highlighting the need for knowledge, skill acquisition, and problem solving related to day-today management; (iii) behaviour modification, goal setting and reinforcement, using motivational interviewing and theories to facilitate goal setting, attainment, and behaviour change; and (iv) general psychosocial support, leveraging active listening and empathy to provide support. Any of these components may be involved in health coaching programs.

Several reviews show a consistent statistically significant reduction in glycated hemoglobin (A1C) of approximately 0.24% to 0.66% with exposure to a diabetes health coach (10–12). But despite the rapid interest in this diabetes health coaching, the description of the role of coaches and how these interventions are implemented and evaluated remains limited. Moreover, the implementation (e.g. training, delivery) and the short and long term evaluation measures related to diabetes health coaching has not been fully described and reported in the literature (9). A previous review conducted in 2015 found that although eight trials reported effectiveness on glycemic control, details of the implementation and evaluation of diabetes health coaching were limited and mainly pertained to the specific training requirements of health care professionals (11).

Regardless of the availability of many implementation theories, checklists, and strategies, to date, no implementation frameworks have been applied to the diabetes health coaching literature, with only scant discussions related to implementation in the literature. The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework was created to improve the transparency in reporting of the essential components of an intervention, with the goal of ultimately supporting the adoption and implementation of evidence-based interventions (13). Although the RE-AIM framework is generally used as a planning tool for scaling up and sustaining the spread of interventions, it has not been applied to the diabetes health coaching literature to date.

Therefore, the application of the RE-AIM framework to diabetes health coaching intervention components will further elucidate the critical aspects of the intervention to ensure the adoption, scaling, and maintenance of an intervention that is effective in supporting diabetes self-management support. Leveraging the findings of a recently completed systematic review and meta-analysis on the effectiveness of diabetes health coaching trials by Racey et al., the goal of this systematic review is to examine the application and reporting of the RE-AIM components in the included studies, which will inform the feasibility and scalability of future diabetes health coaching work.

10.3389/fendo.2022.1069436

2 Methods

This review is a secondary research question to a systematic review and meta-analysis (12). This paper examines the implementation components of health coaching interventions in adults with T2DM from the registered protocol (PROSPERO-CRD42022347478).

2.1 Search strategy

The search terms, databases, and strategy were developed in consultation with a research librarian at McMaster University and informed by a previous systematic review (11) (Supplemental Material 1). We searched MEDLINE, Embase/Emcare, Cumulative Index of Nursing and Allied Health Literature (CINAHL), PsycINFO, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to December 2021. We manually searched reference lists of relevant reviews and included studies for citations that were not captured in our search. Results from the search were deduplicated, and citations were uploaded to a secure internet-based platform for screening (DistillerSR, Evidence Partners Inc., Ottawa, Canada).

2.2 Study selection and eligibility

The eligibility criteria were established for the primary systematic review and have been previously explained (12). Briefly, studies had to be written in English, been published in a peer-reviewed journal, and meet the following criteria: 1) be a randomized controlled trial at the patient-level; 2) report data on adults ≥18 years of age with T2DM; 3) be a health coaching intervention (beyond one-dimensional education programs and including components as defined by Wolever et al. and Sherifali et al.) that was delivered, led, and/or implemented by a regulated healthcare professional, one who would routinely see patients with diabetes for care or management in a healthcare setting such as a clinician, nurse, or diabetes educator in primary care, community care, or hospital-based programs; and 4) include a control group which was defined as treatment as usual, standard care, or minimal contact that did not contain intervention components. Outcomes were not used for inclusion or exclusion of the studies. Studies were excluded if: 1) they reported data on participants younger than 18 years of age, who did not have type 2 diabetes, or who were pregnant; 2) health coaching was not the primary intervention; and 3) they were not randomized controlled trials, used a quasi-randomization methodology, including cluster randomization, or were pilot or feasibility trials.

2.3 Data extraction and quality assessment

A team of researchers conducted the screening and data extraction (MR, MJ, PA, DS). A minimum of two reviewers were required to independently and in duplicate screen titles and abstracts of all potentially eligible studies. Articles marked for inclusion by either team member went on to full-text screening which was completed independently and in duplicate by 2 team members and required consensus for inclusion or exclusion. We developed, piloted, and deployed standardized forms for data extraction. All relevant data was extracted using standardized forms. For each study, one team member extracted study characteristics and the 5 dimensions (62 criteria) of RE-AIM (13, 14) and a different team member verified the extraction. Studies were assessed for Risk of Bias in our complementary review (12). All conflicts for screening and data extraction were resolved by the lead researcher of this review (M.R.).

For the RE-AIM data extraction, reviewers used an adapted extraction tool designed specifically for conducting systematic reviews using RE-AIM (14). The tool outlined each RE-AIM criteria and their definitions for consistent extraction of each component. Reach was evaluated by 12 criteria including descriptions of the target population, inclusion, and exclusion criteria, who participated or was exposed to the intervention, participation rates, and characteristics of those who participated and those who did not. Effectiveness (or efficacy) was evaluated by 9 RE-AIM criteria including reporting of mediators and moderators, how data were treated, quality of life, unintended or negative consequences, and attrition. Adoption was assessed at both the setting and provider/staff levels by 10 and 11 criteria, respectively. The Adoption construct included criteria such as the number and proportion of setting and staff members who agreed to participate in delivering the intervention, description of target locations or providers, how these settings and staff members were recruited, and how representative they were of the intended audience in terms of setting and staff. Implementation was assessed by 11 criteria as our research team added 2 criteria (engagement to inform intervention development and tailoring of intervention). We adapted the tool by including two additional components from the template for intervention description and replication (TIDieR) checklist and guide (15), as these are not covered by RE-AIM: details about tailoring the intervention for participants and the engagement of practitioners, participants, and/or caregivers in the development of the intervention. These components were added to investigate the personalized and tailored nature of health coaching interventions and to reflect our previous systematic review (12) which looked at quadruple aim outcomes beyond the patient level. Other existing criteria included whether interventions were theory-based, detailed descriptions of intervention protocols and how well these protocols were adhered to (fidelity), costs, and the completion rates of intervention participants. Maintenance was evaluated by 8 RE-

AIM criteria including sustained impact of the intervention after termination for the participants and at the setting/staff level. See Supplemental Material 2 for RE-AIM components and definitions of each criteria.

3 Results

From 3,612 citations, we assessed 137 full-text articles for eligibility and included 9 randomized controlled trials (RCTs) (Figure 1) (16–24). The studies were published from 2014 to 2021. Studies were conducted across the globe in North America, Europe, and Australia, and intervention duration was between 3 months to 3 years, with most being 6 or 12 months in duration (n=7). Characteristics of the included studies can be found in Table 1 and further details from studies can be found in Supplemental Material 3. A total sample of 2,498 adults with T2D were included in this review with a mean age ranging from 51.0 to 66.6 years and percentage of women in the studies ranging from 10% to 78%. The mean A1C at baseline ranged from 5.5% to 9.9%.

There was diversity in how our included studies aligned with definitions and models of diabetes health coaching (6, 9). While all the studies included intervention components related to self-management and education and eight studies also addressed behaviour modification, psychosocial support and case management and monitoring were less common health coaching components. Within these components, studies used a variety of techniques and approaches from general counselling to specialized cognitive behaviour therapy or motivational interviewing. As per our inclusion criteria, all studies used healthcare professionals to deliver the health coaching intervention. For most studies (n=7), just one type of coach was used but in 2 studies (19, 22), a team of health professionals worked together for the delivery of different components of the intervention. Coaches included a certified diabetologist, nurses, psychologists, doctoral students, community health workers, pharmacists, social workers, certified diabetes nurse educators, and a dietitian (Supplemental Material 3). Telephone-only strategies were used by 6 studies, while telephone and face-to-face was used in one study, and two studies used in-person or face-to-face strategies only. All the studies were focused on individual or one-on-one interactions and only one study also included group components. Sessions and interactions with the coaches ranged from weekly, to bi-weekly, to as infrequent as one session every 4 to 6 weeks. The duration of these sessions also varied from as short as 15 minutes to as long as 90 minutes; however, most seemed to average around 30 minutes. Any in-person components of the health coaching interventions took place in outpatient healthcare settings such as clinics, healthcare centres, primary care offices, and doctors offices (Supplemental File 3).

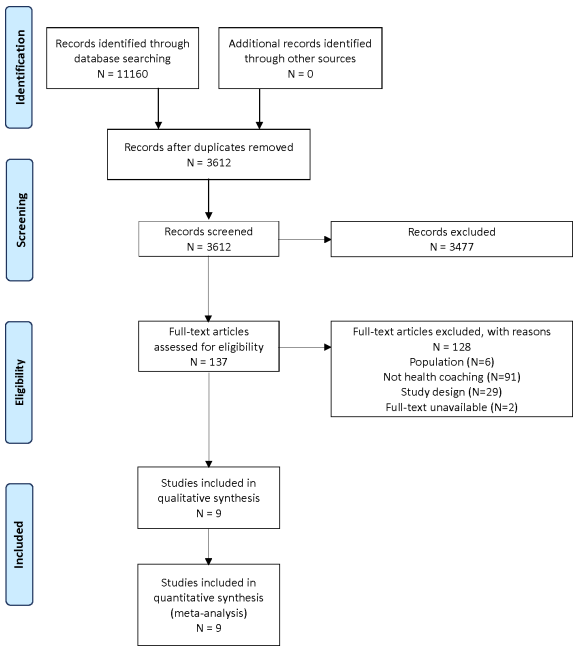


FIGURE 1
PRISMA flowchart.

3.1 Overall RE-AIM summary

A summary of the RE-AIM results by each element can be found in Table 2 (detailed extraction results are available in Supplemental File 4). Every study reported on at least one of the 61 RE-AIM criteria; 12 criteria were reported by all 9 included studies and 21 criteria were not reported by any of the studies. Of the 12 criteria reported by all studies, 5 of these were in the Reach element and many are consistent with CONSORT guidelines (25). These criteria include target population, population demographics, inclusion/exclusion criteria for participants, invited participants and sample size numbers, attrition rates, level of expertise of providers, the number, timing, and duration of intervention contacts, and the tailoring of the coaching interventions to individual participant needs. The included studies all reported on more than 20 RE-AIM criteria, ranging from 21 to 27 (Table 2). The study that reported the most criteria (27 out of 61) was a one-year RCT which assessed the effectiveness of health coaching over mobile phones and self-monitoring of health parameters with a remote patient monitoring system using trained health coaches (24).

3.2 RE-AIM criteria

3.2.1 Reach

Reach was the most thoroughly reported RE-AIM construct by the included studies. Eight of the 12 criteria were described by almost all the studies in our review (n=8 or 9). All studies described the target population, provided demographic information about the

10.3389/fendo.2022.1069436

TABLE 1 Characteristics of included studies.

Author, Year	N[1]	Age, mean y (SD)	Gender[2] (% F/M)	Intervention Description	Delivery person(s)	Location/ Site of Delivery	Control Description	Study Duration[3]
Balducci, 2019 (16)	300	I: 61.0 (9.7) C: 62.3 (10.1)	39/61	Behavioural intervention through counselling sessions	Certified exercise specialist/ diabetologist	Outpatient diabetes clinics	General recommendations for increasing daily physical and decreasing sedentary time	3 years
Cummings, 2019 (22)	139	O: 52.6 (9.6) I: 51.0 (9.0) C: 53.0 (9.0)	78/22	Cognitive behavioral therapy (CBT) plus lifestyle counseling	Team: behavioural providers consisting of a nurse care manager, psychologist, clinical health psychology doctoral student and a community health worker	A large academic family medicine practice	Standard care	12 months
Jutterström, 2016 (20)	327	O: 64.5 (9.58) I: 64.9 (11.10) Internal C: 62.6 (10.61) External C: 66.2 (8.75)	37/63	Group and/or individual sessions to discuss self-management of disease	Diabetes specialist nurses	9 health care centers	Standard care	I: 2-6 months C: 6 months
Karhula, 2015 (24)	287	I: 66.6 (8.2) C: 65.5 (9.6)	44/56	Health coaching over mobile phones and self-monitoring of health parameters with a remote patient monitoring system	Trained personal health coaches	Virtual/ phone	Standard care	12 months
Naik, 2019 (19)	225	O: 61.9 (8.3)	10/90	Goal setting for diabetes and depression	Trained health professionals or coaches including psychologists, nurses, pharmacists and social workers	Virtual/ phone	Usual care	6 months
Odnoletkova, 2016 (17)	3115	I: 63.8 (8.7) C: 62.4 (8.9)	39/61	COACH model (a continuous quality improvement cycle)	Diabetes nurse educators	Virtual/ phone	Usual care	6 months
Sherfali, 2021 (23)	365	I: 56.82 (11.69) C: 59.05 (11.79)	50/50	Diabetes health coaching using case management and monitoring, diabetes self-management education and support with behaviour modification, goal setting and reinforcement in addition to general psychosocial support	Trained registered nurse/ certified diabetes educator	Virtual/ phone	Usual diabetes education	12 months
Varney, 2014 (21)	94	I: 59 (56–62)[4] C: 64 (61-66)[4]	32/68	Telephone coaching with encouragement to follow a specified diet and exercise 150 min per week	Dietitian	Virtual/ phone	Usual care	6 months
Young, 2020 (18)	319	O: 59.07 (11.4) I: 58.96 (11.3) C: 59.18 (11.5)	47/53	Individual coaching sessions using motivational interviewing to promote mutual goal setting, enhance self-efficacy in health behaviour change, and assist individuals to derive meaning from the data to reinforce choices and behaviours	Registered nurses	Primary care clinics and virtual/ phone	Usual care	3 months

O = overall population; I = intervention; C = control.

1. Number of participants randomized at start of study; 2. Values for gender are based on reported baseline which may not equal N randomized but rather the number of participants who completed the intervention; 3. Not including follow-up, if applicable; 4. Reported by the study as mean (95% CI).

TABLE 2 RE-AIM criteria included in each study.

RE-AIM Element	Criteria	Study									Total
		Balducci 2019	Cummings 2019	Jutterström 2016	Karhula 2015	Naik 2010	Odnoletkova 2016	Sherifali 2021	Varney 2014	Young 2020	
Reach	Described target population	x	x	x	x	x	x	x	x	x	**9**
	Demographic, behavioral information about target population	x	x	x	x	x	x	x	x	x	**9**
	Method to identify the target population	x	x	x	x	x	x		x	x	**8**
	Recruitment strategies	x		x	x	x	x	x	x	x	**8**
	Inclusion/exclusion criteria for individuals	x	x	x	x	x	x	x	x	x	**9**
	Eligible, invited (exposed to recruitment) potential participants	x	x	x	x	x	x	x	x	x	**9**
	Sample size	x	x	x	x	x	x	x	x	x	**9**
	Individual participation rate (sample size/eligible invited potential participants)	x	x	x	x	x	x	x	x	x	**9**
	Comparisons between the target population and the study sample			x	x				x		**3**
	Statistical comparisons between the target population and the study sample			x	x				x		**3**
	Cost of recruitment										**0**
	Qualitative methods to measure reach						x				**1**
Effectiveness	Report of mediators	x	x							x	**3**
	Report of moderators	x	x	x	x			x	x	x	**7**
	Intent-to-treat	x	x		x	x	x	x		x	**7**
	Imputation procedures	x	x		x	x		x	x	x	**7**
	Quality-of-life measures				x		x	x		x	**4**
	Unintended consequences measures/results	x						x			**2**
	Percent attrition (at program completion)	x	x	x	x	x	x	x	x	x	**9**
	Cost-effectiveness										**0**
	Qualitative methods to measure efficacy/effectiveness						x			x	**2**
Adoption, setting	Eligible, invited potential settings			x							**1**
	Number of participating settings	x		x		x					**3**
	Setting participation rate			x							**1**
	Description of the targeted location										**0**
	Inclusion/exclusion criteria of the setting										**0**
	Description of intervention location	x	x	x		x				x	**5**
	Method to identify the setting										**0**

(Continued)

10.3389/fendo.2022.1069436

TABLE 2 Continued

RE-AIM Element	Criteria	Study									Total
		Balducci 2019	Cummings 2019	Jutterström 2016	Karhula 2015	Naik 2010	Odnoletkova 2016	Sherifali 2021	Varney 2014	Young 2020	
	Comparisons between the targeted and participating settings										**0**
	Statistical comparisons between the targeted and participating settings										**0**
	Average number of persons served per setting										**0**
Adoption, provider/staff	Eligible, invited potential providers (staff)				x						**1**
	Number of participating providers (staff)			x	x	x				x	**4**
	Provider (staff) participation rate				x						**1**
	Method to identify target providers										**0**
	Level of expertise of providers	x	x	x	x	x	x	x	x	x	**9**
	Inclusion/exclusion criteria for providers										**0**
	Comparisons between targeted and participating providers (staff)										**0**
	Statistical comparisons between targeted and participating providers (staff)										**0**
	Measures of cost adoption										**0**
	Dissemination beyond originally planned										**0**
	Qualitative methods to measure adoption						x				**1**
Implementation	Theory-based	x	x	x	x			x		x	**6**
	Engagement to inform intervention										**0**
	Number of intervention contacts	x	x	x	x	x	x	x	x	x	**9**
	Timing of intervention contacts	x	x	x	x	x	x	x	x	x	**9**
	Duration of intervention contacts	x	x	x	x	x	x	x	x	x	**9**
	Extent protocol delivered as intended (fidelity)	x	x		x		x	x			**5**
	Consistency of implementation across settings or providers				x		x			x	**3**
	Tailoring of intervention	x	x	x	x	x	x	x	x	x	**9**
	Participant attendance/completion rates	x	x	x	x	x	x	x	x		**8**
	Measure of intervention cost										**0**
	Qualitative methods to measure implementation										**0**
Maintenance	Follow-up outcome measures at some duration after intervention termination			x		x	x		x	x	**5**
	Attrition/loss to follow-up of individuals			x		x	x		x	x	**5**

(Continued)

10.3389/fendo.2022.1069436

10.3389/fendo.2022.1069436

TABLE 2 Continued

RE-AIM Element	Criteria	Study										Total
		Balducci 2019	Cummings 2019	Jutterström 2016	Karhula 2015	Naik 2010	Odnoletkova 2016	Sherifali 2021	Varney 2014	Young 2020		
	Qualitative methods to measure individual maintenance of the intervention											0
	Intervention alignment with the organization's mission											0
	Institutionalization of program after completion of study											
	Maintenance of the program after completion of the study											0
	Attrition/loss to follow-up of settings											0
	Qualitative methods to measure organizational maintenance/sustainability						x					1
TOTAL FOR STUDY		24	21	26	27	22	25	21	21	26		

The 'x' means that the variable (row) is present in the Citation (Column). The bold values are to contrast the headings and total counts at the bottom of the table.

target population, outlined inclusion/exclusion criteria for screening participants, and provided the number of invited participants, participant rate, and overall sample size of the study. Eight of the 9 included studies also described their methods to identify the target population and their recruitment strategies. Demographic information was not reported consistently across studies, with studies reporting different sample characteristics. For example, while all studies reported on the gender and age of their participants, there was variation in reporting of ethnicity/race (n=5), socioeconomic status (n=5), and chronic diseases/comorbidities (n=4). Only 3 studies compared the target population to their study sample and made statistical comparisons (20, 21, 24). While Jutterstrom et al., and Karhula et al., found no differences in their populations, Karhula et al., did note that those who did not complete the intervention had unfamiliarity with mobile phones. Varney et al., found that their study population was younger and less likely to require an interpreter than the population attending the diabetes clinic from which they recruited. No studies measured the cost of their recruitment and only one study qualitatively measured reach, which was reported in a secondary publication that conducted focus groups and interviews with participants, nurses, and general practitioners (GPs) (17, 26).

3.2.2 Effectiveness

Effectiveness was also well reported by the studies included in our review. All the studies reported on attrition at program completion and most (n=7) reported on moderators, outlined their imputation methods for missing data, and conducted intention-to-treat analysis. Four studies reported on quality of life outcomes and only 2 studies reported adverse events (16, 23). Balducci et al., reported any elective surgeries and medical conditions that occurred outside of the intervention and hypoglycemic episodes, arrythmias, and musculoskeletal injuries or discomfort that occurred during intervention visits or sessions. Sherifali et al., reported on hospitalizations (for any reason), emergency department visits, and hypo- and hyper-glycemic episodes requiring hospitalizations. There were no statistically significant differences in proportion of participants with adverse events between the 2 groups. Two studies used qualitative methods to measure intervention efficacy (17, 18). Both had high rates of participant satisfaction and acceptance with their coaching interventions.

3.2.3 Adoption

Overall, adoption was poorly reported by all studies in our review. While all 9 studies did report the level of expertise of intervention providers, this is likely reflective of our inclusion criteria and selection of studies that used healthcare professionals to deliver the intervention. Five studies did describe the location of the intervention; however, many of our included studies were conducted virtually, *via* the telephone, and therefore did not have a physical intervention location to engage with participants. The rest of the adoption

criteria at both the setting and provider/staff level were poorly described as our included studies lacked details about how they selected study locations/settings (eligibility, participation rates, comparisons between settings) and how they selected providers to be involved in intervention delivery (eligibility, participant rates, comparisons between participating and non-participating staff). No studies measured the cost of adoption or if there was dissemination beyond what was originally planned. Only Odnoletkova reported on qualitative methods to measure adoption and found nurses and GPs to be generally accepting and supportive of the intervention (17, 26).

3.2.4 Implementation

Implementation was another well reported RE-AIM construct. All of our included studies reported the number, timing, and duration of intervention contacts (visits or telephone calls) and the tailoring of intervention components to the needs of the participant. This personalization of the intervention is likely reflective of the individual nature of coaching interventions and the fact that our included studies involved mostly one-on-one coaching interactions, rather than group based sessions. Eight of the 9 included studies provided details about participant attendance and completion of the intervention by measuring sessions attended, calls received, and duration of these interactions. Six studies mentioned basing their intervention on a theory or model such as social cognitive theory (16), health belief model (16), cognitive behaviour theory (22), motivational interviewing (18, 23), and others. Fidelity, or the extent the intervention protocol was delivered as intended, was reported by 5 studies using checklists, protocols and manuals, and quality control measures such as supervision or observations by study authors and listening to recordings of interactions between coaches and participants. Three studies also reported on the consistency of implementation across settings and/or providers (different coaches). No studies used any engagement with providers or participants to inform their intervention, and no studies reported on the cost of implementing the intervention or used qualitative methods to measure their implementation.

3.2.5 Maintenance

This construct was poorly reported by all studies in this review. Beyond immediate post-intervention measurements, 5 studies assessed outcomes at a follow-up timepoint and all these studies also reported on the loss of participants during this follow-up period (17–21). Both Jutterstrom et al., and Young et al., did not provide reasons for the loss of participants and the detail provided by Varney et al., for dropouts was vague. Only 1 study used qualitative measures to investigate maintenance and sustainability of such a program (17). No studies assessed or reported on any of the other criteria such as maintenance of the program, modifications made to maintain the program, or alignment of the intervention with the organization's mission.

4 Discussion

This review leverages a recently completed systematic review and meta-analysis examining the effectiveness of diabetes health coaching interventions (12) and examines the application and reporting of the RE-AIM framework to inform future research. Generally, we found good reporting on the reach, effectiveness, and implementation components of the RE-AIM framework, with limited reporting on adoption, and a dearth of reporting on maintenance constructs. The RE-AIM framework was developed to bolster the transparency of reporting of complex interventions, specifically behavioural interventions (13). Ensuring consistent reporting across interventions would lead to an improved understanding of the exact components and implementation of interventions such as diabetes health coaching. However, to date, the application of RE-AIM framework to the diabetes health coaching literature only highlights the gaps in reporting, diversity how these interventions align with health coaching definitions, and exposes limitations in its practical implementation.

From our review of the 9 trials that examined the effectiveness of diabetes health coaching, we found components that addressed the adoption and maintenance criteria were poorly reported. Adoption (e.g. diffusion) relates to the setting and staffing required for the intervention to be deployed. As most studies offered diabetes health coaching virtually (i.e., telephone or technology), it is difficult to ascertain the specific setting-related and staffing requirements that supported the adoption of the intervention. Moreover, the studies were heterogeneous in the descriptions of who could be a health coach (e.g. nurse, physician, exercise physiologist, etc.) and the required training to deliver the coaching intervention (e.g. 120 minutes compared to 8 days of training with credentialed courses). The variability of maintenance, related to the individual or organization implementing diabetes health coaching, was extremely limited in the literature, suggesting that the longer-term impact of diabetes health coaching is not described and has not been evaluated. This corresponds to the limited data on longer term effectiveness of diabetes health coaching beyond 6 months (12), thus making it difficult to understand the impact of diabetes health coaching and the sustained impact of such interventions.

The findings of this review lead to a greater understanding of the evidence and the true impact of interventions, which are behavioural and contextualized to persons and settings. Unfortunately, the evidence related to the implementation of diabetes health coaching and the nature of translating interventions provides gaps in our understanding of and ability translate findings and scale diabetes health coaching interventions to larger populations (27–29). Historically, effectiveness studies and implementation studies have been considered separate entities. Preferably, studies and systematic reviews would be able to report

on the effectiveness of the diabetes health coaching intervention and situate the findings within an implementation framework (e.g. RE-AIM), which would better inform stakeholders about practice changes and policies (30).

These latest considerations for merging effectiveness and implementation studies has advanced since the early 2000s, in response to minimizing research waste and the need for bridging the gap from efficacy to effectiveness to implementation into clinical practice (29, 31). With a greater emphasis on effectiveness and implementation focused trials, we will further understand the impact of diabetes health coaching on a variety of health outcomes under 'usual care' settings (31). A lack of the studies in this review fulfilling the RE-AIM framework related to diabetes health coaching may suggest that researchers have limited consideration or knowledge of implementation issues when assessing effectiveness of interventions (30). This conceptual incongruency of thinking about "beginning with the end in mind" further perpetuates a delay in uptake and implementation of effective interventions such as diabetes health coaching. Thus, a hybrid approach of effectiveness and implementation designs are only increasing, with the hope that greater transparency and concise reporting with such frameworks as RE-AIM, will evolve the scientific thinking and form a greater appreciation of implementing behavioural interventions like diabetes health coaching in real-world settings.

While our review comprised a comprehensive literature, we did not search grey literature or unpublished industry reports about diabetes health coaching. The exclusion of studies with non-traditional RCT randomization methods may have led to missing implementation trials and thus an under-reporting of studies meeting the Adoption and Maintenance criteria. However, our review leveraged a previous high quality systematic review (11) and we followed rigorous systematic review processes for this update. To this end, this review is a secondary analysis to a recently conducted systematic review and meta-analysis, which explored the effectiveness of diabetes health coaching (12).

5 Conclusions

The findings of our review confirm that need for more detailed and transparent reporting related to the implementation of diabetes health coaching. Because of the highly contextualized factors related to behavioural interventions such as diabetes health coaching, it is crucial that research focuses not only on the effectiveness of such interventions but also the implementation. Our review highlights major gaps and a paucity of high-quality evidence related to crucial components of adoption and maintenance of diabetes health coaching. More standardized reporting on external validity is needed to determine whether diabetes health coaching interventions can be effectively delivered, in what setting, by whom it can be delivered, and whether it is sustainable long-term in clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

All authors were involved in conception and design of the study and approved the protocol; MR, DS were responsible for overseeing the search of databases and literature. MR handled management of database and deduplication or records. MR, MJ, PA, DS were involved in the screening of citations; MR, MJ, PA were responsible for data extraction; MR, DS were responsible for data verification, analysis of data and interpretation of data. All authors supported in the drafting of the manuscript which was led by MR and all authors supported in revising and formatting of the manuscript. All authors have provided final approval of the version of the manuscript submitted for publication, and all authors agree to be accountable for all aspects of the work.

Funding

This research was funded by the McMaster Evidence Review and Synthesis Team (MERST). DS holds the Heather M Arthur Population Health Research Institute/Hamilton Health Sciences Chair in Interprofessional Health Research which supported her role in this work.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1069436/full#supplementary-material

References

1. Kimenai DM, Pirondini L, Gregson J, Prieto D, Pocock SJ, Perel P, et al. Socioeconomic deprivation: An important, largely unrecognized risk factor in primary prevention of cardiovascular disease. *Circulation* (2022) 146(3):240–8. doi: 10.1161/CIRCULATIONAHA.122.060042

2. Holland SK, Greenberg J, Tidwell L, Malone J, Mullan J, Newcomer R. Community-based health coaching, exercise, and health service utilization. *J Aging Health* (2005) 17(6):697–716. doi: 10.1177/0898264305277959

3. Kogan AJ. Overcoming obstacles to effective care of type 2 diabetes. *Am J Managed Care* (2009) 15(9 Suppl):S255–62.

4. Hiss RG. The concept of diabetes translation: Addressing barriers to widespread adoption of new science into clinical care. *Diabetes Care* (2001) 24 (7):1293–6. doi: 10.2337/diacare.24.7.1293

5. Shah BR, Booth GL. Predictors and effectiveness of diabetes self-management education in clinical practice. *Patient Educ Counseling* (2009) 74(1):19–22. doi: 10.1016/j.pec.2008.08.005

6. Wolever RQ, Dreusicke M, Fikkan J, Hawkins TV, Yeung S, Wakefield J, et al. Integrative health coaching for patients with type 2 diabetes: a randomized clinical trial. *Diabetes Educator* (2010) 1(4):629–39. doi: 10.1177/0145721710371523

7. Huffman M. Health coaching: A new and exciting technique to enhance patient self-management and improve outcomes. *Home Healthcare Now* (2007) 25 (4):271–4. doi: 10.1097/01.NHH.0000267287.84952.8f

8. Wong-Rieger D. *Health coaching for chronic conditions engaging and supporting patients to self-manage*. Toronto, ON: Institute for Optimizing Health Outcomes (2011).

9. Sherifali D. Diabetes coaching for individuals with type 2 diabetes: A state-of-the-science review and rationale for a coaching model. *[Review]* (2017) 1(6):547–54. doi: 10.1111/1753-0407.12528

10. Pirbaglou M, Katz J, Motamed M, Pludwinski S, Walker K, Ritvo P. Personal health coaching as a type 2 diabetes mellitus self-management strategy: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Educator* (2018) 1 (7):1613–26. doi: 10.1177/0890117118758234

11. Sherifali D, Bai JW, Kenny M, Warren R, Ali MU. Diabetes self-management programmes in older adults: a systematic review and meta-analysis. *Diabetic Med* (2015) 32(11):1404–14. doi: 10.1111/dme.12780

12. Racey M, Jovkovic M, Alliston P, Ali MU, Sherifali D. Diabetes health coach in individuals with type 2 diabetes: A systematic review and meta analysis of quadruple aim outcomes. *Front Endocrinol* (2022).

13. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health* (1999) 89(9):1322–7. doi: 10.2105/ajph.89.9.1322

14. Harden SM, Gaglio B, Shoup JA, Kinney KA, Johnson SB, Brito F, et al. Fidelity to and comparative results across behavioral interventions evaluated through the RE-AIM framework: a systematic review. *Systematic Rev* (2015) 4(1):155. doi: 10.1186/s13643-015-0141-0

15. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ Br Med J* (2014) 348:g1687. doi: 10.1136/bmj.g1687

16. Balducci S, D'Errico V, Haxhi J, Sacchetti M, Orlando G, Cardelli P, et al. Effect of a behavioral intervention strategy on sustained change in physical activity and sedentary behavior in patients with type 2 diabetes: The IDES_2 randomized clinical trial. *JAMA: J Am Med Assoc* (2019) 321(9):880–90. doi: 10.1001/jama.2019.0922

17. Odnoletkova I, Goderis G, Nobels F, Fieuws S, Aertgeerts B, Annemans L, et al. Optimizing diabetes control in people with type 2 diabetes through nurse-led telecoaching. *Diabetic Med* (2016) 33(6):777–85. doi: 10.1111/dme.13092

18. Young HM, Miyamoto S, Dharmar M, Tang-Feldman Y. Nurse coaching and mobile health compared with usual care to improve diabetes self-efficacy for persons with type 2 diabetes: randomized controlled trial. *JMIR mhealth uhealth* (2020) 8(3):e16665. doi: 10.2196/16665

19. Naik AD, Hundt NE, Vaughan EM, Petersen NJ, Zeno D, Kunik ME, et al. Effect of telephone-delivered collaborative goal setting and behavioral activation vs enhanced usual care for depression among adults with uncontrolled diabetes: a randomized clinical trial. *JAMA network Open* (2019) 2(8):e198634. doi: 10.1001/jamanetworkopen.2019.8634

20. Jutterström L, Hörnsten Å, Sandström H, Stenlund H, Isaksson U. Nurse-led patient-centered self-management support improves HbA1c in patients with type 2 diabetes-a randomized study. *Patient Educ Counseling* (2016) 99(11):1821–9. doi: 10.1016/j.pec.2016.06.016

21. Varney JE, Weiland TJ, Inder WJ, Jelinek GA. Effect of hospital-based telephone coaching on glycaemic control and adherence to management guidelines in type 2 diabetes, a randomised controlled trial. *Internal Med J* (2014) 44(9):890–7. doi: 10.1111/imj.12515

22. Cummings DM, Lutes LD, Littlewood K, Solar C, Carraway M, Kirian K, et al. Randomized trial of a tailored cognitive behavioral intervention in type 2 diabetes with comorbid depressive and/or regimen-related distress symptoms: 12-month outcomes from COMRADE. *Diabetes Care* (2019) 42(5):841–8. doi: 10.2337/dc18-1841

23. Sherifali D, Brozic A, Agema P, Punthakee Z, McInnes N, O'Reilly D, et al. Effect of diabetes health coaching on glycemic control and quality of life in adults living with type 2 diabetes: a community-based, randomized, controlled trial. *Can J Diabetes* (2021) 45(7):594–600. doi: 10.1016/j.jcjd.2020.11.012

24. Karhula T, Vuorinen AL, Rääpysjärvi K, Pakanen M, Itkonen P, Tepponen M, et al. Telemonitoring and mobile phone-based health coaching among Finnish diabetic and heart disease patients: randomized controlled trial. *J Med Internet Res* (2015) 17(6):e153. doi: 10.2196/jmir.4059

25. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* (2010) 340:c332. doi: 10.1136/bmj.c332

26. Odnoletkova I, Buysse H, Nobels F, Goderis G, Aertgeerts B, Annemans L, et al. Patient and provider acceptance of telecoaching in type 2 diabetes: a mixed-method study embedded in a randomised clinical trial. *BMC Med Inf Decision Making* (2016) 16:142–. doi: 10.1186/s12911-016-0383-3

27. Tomoaia-Cotisel A, Scammon DL, Waitzman NJ, Cronholm PF, Halladay JR, Driscoll DL, et al. Context matters: The experience of 14 research teams in systematically reporting contextual factors important for practice change. *Ann Family Med* (2013) 11(Suppl 1):S115. doi: 10.1370/afm.1549

28. Wolfenden L, Foy R, Presseau J, Grimshaw JM, Ivers NM, Powell BJ, et al. Designing and undertaking randomised implementation trials: guide for researchers. *BMJ* (2021) 372:m3721. doi: 10.1136/bmj.m3721

29. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: Combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care* (2012) 50 (3):217–26. doi: 10.1097/MLR.0b013e3182408812

30. World Health O. ExpandNet. In: *Beginning with the end in mind: planning pilot projects and other programmatic research for successful scaling up*. Geneva: World Health Organization (2011).

31. Wells KB. Treatment research at the crossroads: The scientific interface of clinical trials and effectiveness research. *Am J Psychiatry* (1999) 156(1):5–10. doi: 10.1176/ajp.156.1.5

frontiers | Frontiers in Endocrinology

TYPE Systematic Review
PUBLISHED 16 December 2022
DOI 10.3389/fendo.2022.1069401

OPEN ACCESS

EDITED BY
Hiroshi Okada,
Matsushita Memorial Hospital, Japan

REVIEWED BY
Hanako Nakajima,
Kyoto Prefectural University of Medicine, Japan
Gillian Hood,
Queen Mary University of London, United Kingdom

*CORRESPONDENCE
Diana Sherifali
dsherif@mcmaster.ca

SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 13 October 2022
ACCEPTED 28 November 2022
PUBLISHED 16 December 2022

CITATION
Racey M, Jovkovic M, Alliston P, Ali MU and Sherifali D (2022) Diabetes health coach in individuals with type 2 diabetes: A systematic review and meta analysis of quadruple aim outcomes. *Front. Endocrinol.* 13:1069401. doi: 10.3389/fendo.2022.1069401

Diabetes health coach in individuals with type 2 diabetes: A systematic review and meta analysis of quadruple aim outcomes

Megan Racey[1], Milos Jovkovic[1], Paige Alliston[1], Muhammad Usman Ali[2] and Diana Sherifali[1]*

[1]McMaster Evidence Review and Synthesis Team; and School of Nursing, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, ON, Canada, [2]McMaster Evidence Review and Synthesis Team; and Department of Clinical Epidemiology & Biostatistics, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, ON, Canada

Background: As diabetes self-management necessitates life-long learning, behaviour change, support, and monitoring, health coaching is a promising intervention to assist individuals in more than just meeting glycemic goals and glycated hemoglobin (A1C) targets. Currently, studies of health coaching for type 2 diabetes (T2DM) are limited due to their emphasis on glycemic control. The goal of this systematic review and meta-analysis is to determine the effects of health coaching on adults with T2DM based on quadruple aim outcomes and to assess the implementation of these interventions.

Methods: We searched 6 databases for randomized controlled trials of health coaching interventions delivered by a health professional for adults with T2DM. Reviewers screened citations, extracted data, and assessed risk of bias and certainty of evidence (GRADE). We assessed statistical and methodological heterogeneity and performed a meta–analysis of studies.

Results: Nine studies were included in this review. Our meta-analysis showed a significant reduction of A1C [0.24 (95% CI, -0.38 to -0.09)] after exposure to diabetes health coaching, and small to trivial significant benefits for BMI, waist circumference, body weight, and depression/distress immediately post intervention based on moderate certainty of evidence. However, long term benefit of these clinical outcomes were not maintained at follow-up timepoints. There was a small significant benefit for systolic blood pressure which was maintained after the completion of health coaching exposure at follow-up, but there was no statistically significant benefit in other secondary outcomes such as diastolic blood pressure and lipid profile measures (e.g. triglycerides). Very few studies reported on other quadruple aim measures such as patient-reported outcomes, cost of care, and healthcare provider experience.

Conclusions: Our systematic review and meta-analysis shows that health coaching interventions can have short term impact beyond glucose control on cardiometabolic and mental health outcomes. Future studies should try to examine quadruple aim outcomes to better assess the benefit and impact of

these interventions at longer time points and following termination of the coaching program.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero, identifier (CRD42022347478).

KEYWORDS

health coaching, systematic reveiw, meta analysis, quadruple aim, type 2 diabetes

1 Introduction

Diabetes is increasingly a major health issue worldwide (1), with 1 in 10 adults living with diabetes in 2021. The rise in global rates of diabetes prevalence has led to challenges in managing diabetes at the health systems and societal levels, costing 966 billion USD in health care expenditures (2). The day-to-day management of diabetes is centred around the individual and ideally supported by a multi-disciplinary team to facilitate a patient's ability to manage one's own diabetes care through ongoing self-management education and support (3). Self-management education and support are most effective when tailored according to: the individual's ability for learning and readiness for change; the context of one's cultural beliefs, health beliefs and preferences; socioeconomic barriers and other health challenges (3).

In recent years, health coaching has emerged as an effective intervention to support diabetes self-management. According to Wolever et al., health coaching may be described as: a) patient centred; b) includes patient determined goals; c) incorporates self-discovery and active learning processes; d) encourages accountability for behavioural goals; e) provides some education alongside coaching; f) a health professional who is trained in behaviour change, communication, and motivational interviewing skills (4). Health coaching may also be timely and relevant health related education, behaviour change promotion, and psychosocial support to enhance the well-being of individuals and facilitate the achievement of their health-related goals (5, 6).

Although previously marred by small pilot studies, underpowered trials, and high attrition, a growing body of quality evidence for type 2 diabetes (T2DM) suggests that individuals achieve better health outcomes with health coaching than traditional education and support programs (4, 7–9). A scan of the literature identified a few systematic reviews related to health coaching (9, 10). The first review in 2003 synthesized the effect of health coaching components; it reviewed 25 individual health coaching studies for individuals with chronic illnesses and found that while education and behaviour change are important, they are not sufficient (10). Therefore the need for coach interactions that move a patient to a stage of action were evident, as was the need to consider the emotional state of the patient (10). The second review, completed in 2010, examined the evidence for health coaching on lifestyle behaviours (9). The review included relevant studies published between 1998 and 2008, of which 15 studies included, and only 7 were randomized controlled trials (RCTs). Although the review was also not specific to diabetes health coaching, the review did note that there were significant improvements in lifestyle behaviours (diet, physical activity, weight management), as well as medication adherence. Methodological limitations were identified in the review for the 7 trials, such as small sample sizes and incomplete follow-up (9). More recently, Sherifali et al., completed a review of 8 diabetes health coaching trials and determined that coaching interventions led to an overall reduction of glycated hemoglobin (A1C) by 0.32 (95% CI, -0.50 to -0.15) (11). Exposure to diabetes health coaching for more than 6 months led to a 0.57% reduction in A1C levels (95% CI, -0.76 to -0.38), compared to exposure to a diabetes health coach for ≤6 months (–0.23%; 95% CI, -0.37 to -0.09) (11). Finally, in 2018, Pirbaglou and colleagues reviewed the literature to consider the impact of diabetes health coaching on A1C, as well as on quality of life and self-efficacy (12). Health coaching interventions were also successful in reducing A1C levels at all time points, with the largest magnitude of reduction between 4 to 9 months, but found inconsistent benefits on psychosocial findings (12).

As diabetes self-management necessitates life-long learning, behaviour change, support, and monitoring, health coaching is a promising intervention to assist individuals in more than just meeting glycemic goals and A1C targets. At present, despite the growing body of evidence, studies of health coaching for T2DM are limited due to their emphasis on glycemic control. Therefore, we will explore the literature to determine the impact of diabetes health coaching on patient-reported outcomes, clinical outcomes, provider satisfaction, and cost-effectiveness, specifically the quadruple aim goals (13). As an adaptation of a 2015 systematic review and based on the evolution of health coaching (11), the goal of this systematic review and meta-analysis is to determine the effects of health coaching on adults

with type 2 diabetes based on quadruple aim outcomes and subsequently, to assess the implementation of these interventions, including describing the diabetes health coaching intervention and in what context.

2 Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (14) from a registered protocol (PROSPERO-CRD42022347478). Our methods followed the Cochrane Handbook for Systematic Reviews of Interventions Version 6, 2019 (15).

2.1 Search strategy

The search terms, databases, and strategy were developed in consultation with a research librarian at McMaster University and informed by a previous systematic review (11) (Supplemental Material 1). We searched MEDLINE, Embase/Emcare, Cumulative Index of Nursing and Allied Health Literature (CINAHL), PsycINFO, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to December 2021. We manually searched reference lists of relevant reviews and included studies for citations that were not captured in our search. Results from the search were deduplicated, and citations were uploaded to a secure internet-based platform for screening (DistillerSR, Evidence Partners Inc., Ottawa, Canada).

2.2 Study selection and eligibility

To be included, studies had to be written in English, been published in a peer-reviewed journal, and meet the following criteria: 1) be a RCT (randomized at the patient-level); 2) report data on adults ≥18 years of age with T2DM; 3) be a health coaching intervention (beyond one-dimensional education programs) that was delivered, led, and/or implemented by a regulated healthcare professional, one who would routinely see patients with diabetes for care or management in a healthcare setting such as a clinician, nurse, or diabetes educator in primary care, community care, or hospital-based programs; and 4) include a control group which was defined as treatment as usual, standard care, or minimal contact that did not contain intervention components. There were no criteria for diagnosis of T2DM; however, studies with general adult populations or mixed populations but which have subgroup analysis for participants with T2DM were also considered. Without subgroup analysis, a mixed population must have at least 80% of participants with our targeted condition (T2DM) to be included in our review. Outcomes were not used for inclusion or exclusion of the studies. Studies were excluded if: 1) they reported data on participants younger than 18 years of age, who did not have type 2 diabetes or who were pregnant; 2) health coaching was not the primary intervention; and 3) they were not RCTs, used a quasi-randomization methodology, including cluster randomization, or were pilot or feasibility trials.

2.3 Data extraction and quality assessment

A team of researchers conducted the screening and data extraction (MR, MJ, PA, DS). A minimum of 2 reviewers were required to independently and in duplicate screen titles and abstracts of all potentially eligible studies. Articles marked for inclusion by either team member went on to full-text screening which was completed independently and in duplicate by 2 team members and required consensus for inclusion or exclusion. We developed, piloted, and deployed standardized forms for data extraction. For each study, one team member extracted study characteristics, risk of bias (RoB) assessment (using the Cochrane Collaboration RoB tool (16) for RCTs), template for intervention description and replication (TIDieR) checklist and guide (17), and outcome data using electronic forms housed in a web-based systematic review software program. Two team members independently verified all extracted data and disagreements were resolved through discussion and/or third party consultation. All outcomes as they relate to the Quadruple Aim framework were considered. This framework was developed to optimize health system performance and includes improved patient experience (patient-reported outcomes), better population health (clinical population health outcomes), lower costs (cost of care outcomes) and improved clinical experience (healthcare provider experience) (13). In cases where studies had multiple measures for the same outcome, we extracted the primary or direct measures before using secondary outcomes or subgroup analysis data. All extraction was independently verified by the statistician (MA). Conflicts were resolved by the lead researcher of this review (MR).

We independently evaluated the certainty of the body of evidence using the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) method (18) with GRADEpro software (19). GRADE rates the certainty of a body of evidence as high, moderate, low, or very low and ratings are based on an assessment of 5 conditions: 1) methodological quality, 2) consistency across effect estimates/statistical heterogeneity, 3) directness of the body of evidence to the populations, interventions, comparators and/or outcomes of interest, 4) precision of results, and 5) indications of reporting bias.

2.4 Statistical analysis

All data analyses were planned a priori. A meta-analysis was used to combine the results across studies by outcome using the published data from included studies. For continuous outcomes, we used change from baseline to immediate post-treatment (means, standard deviations) and the longest follow-up data (means, standard deviations). We used a random effects multi-level meta-analytic approach to account for dependency between effect sizes (i.e., the correlation between effect sizes due to multiple measures or sub-measures of the same outcome within a study or comparison of multiple interventions to a single control group). In such cases, multiple measures and comparisons from the same study were nested within studies first and variance in observed effect sizes was decomposed into sampling variance, within study variance and between-study variance to account for intra-cluster (or intraclass) correlation in the true effects true effects (20, 21). For the pooling of patient-reported outcomes such as quality of life, depression and distress, the direction of effect was adjusted to ensure consistency of desirable outcome responses. The summary measures of effect were generated in the form of standardized mean differences (SMD) (22). The SMD is interpreted based on its magnitude according to Cohen d recommended thresholds (~0.2 = small effect, ~0.5 = medium effect, ~0.8 = large effect) (23). For studies where measure of variance was reported as confidence intervals, standard error, or p-values, we used Cochrane recommended methods to convert this data to standard deviation (24). The statistical heterogeneity I^2 statistic was also estimated in the context of multi-level meta-analytical approach i.e., within-cluster heterogeneity (multiple comparisons from same study) and between-cluster heterogeneity (effect sizes across studies). Overall I^2 for each summary effect size was estimated to represent the heterogeneity not attributable to sample error and is the sum of within-cluster and between-cluster heterogeneity. The Cochran's Q (α=0.05) was employed to detect statistical heterogeneity and I^2 statistic to quantify the magnitude of statistical heterogeneity between studies where I^2 >50% represents moderate and I^2 >75% represents substantial heterogeneity across studies. The primary subgrouping in each analysis was based on length of follow-up i.e. immediate post-treatment and long-term follow up. All analyses were performed using R software (metafor (25) and dmetar (26) packages).

3 Results

Our search strategy yielded 3,612 citations after duplicates were removed. We assessed 137 full-text articles for eligibility and included 9 RCTs in this review (Figure 1) (27–35). The studies were published from 2014 to 2021. We searched databases from inception and considered all studies based on the above inclusion/exclusion criteria as these criteria were updated from our similar, previous review (11) and warranted thorough screening of the literature. However, we excluded studies that were published before 2015 (one-year overlap with our previous review) which met our inclusion/exclusion criteria as they were already described in our previous review as included studies. Based on the updated inclusion/exclusion criteria of this review, some studies published before 2015 were included in this review as they were excluded in the previous review based mostly on the inclusion requirement of A1C as a reported outcome and this was no longer an exclusion criteria of this review. Likewise, some studies from our 2015 review which were described as pilot of feasibility studies were excluded in this update due to the increased rigor of our study design criteria. The PICO of this review was updated from the 2015 review to reflect the evolution of the health coaching literature and topic area.

A total sample of 2,498 adults with T2DM were included in this review with a mean age ranging from 51.0 to 66.6 years and percentage of women in the studies ranging from 10% to 78%. The mean A1C at baseline ranged from 5.5% to 9.9%. Studies were conducted across the globe in North America, Europe, and Australia, and intervention duration was between 3 months to 3 years, with most being 6 or 12 months in duration (n=7). A total of 5 studies measured outcomes beyond immediate post-treatment and 4 of these studies conducted follow-up measurements 6 months after intervention completion (29–32) while 1 study completed measurements 12 months post-intervention (28). Adverse events were only reported by 2 studies (27, 34). Balducci et al., 2019 reported any elective surgeries and medical conditions that occurred outside of the intervention and hypoglycemic episodes, arrythmias, and musculoskeletal injuries or discomfort that occurred during intervention visits or sessions (27). Sherifali et al., 2021 reported on hospitalizations (for any reason), emergency department visits, and hypo- and hyper-glycemic episodes requiring hospitalizations (34). There were no statistically significant differences in proportion of participants with adverse events between the 2 groups. Study characteristics are shown in Table 1 and more fulsome details can be found in Supplemental Material 2.

3.1 Diabetes coaching intervention characteristics

The objective or rationale for the health coaching interventions was either to directly affect glycemic control or to influence glycemic control and/or diabetes management through other self-care behaviours and reducing risk factors (Table 1). As per our inclusion criteria, all studies used healthcare professionals to deliver the health coaching intervention. For most studies (n=7), just one type of coach was used but in 2 studies (30, 33), a team of health professionals worked together for the delivery of different components of the intervention. Coaches across the

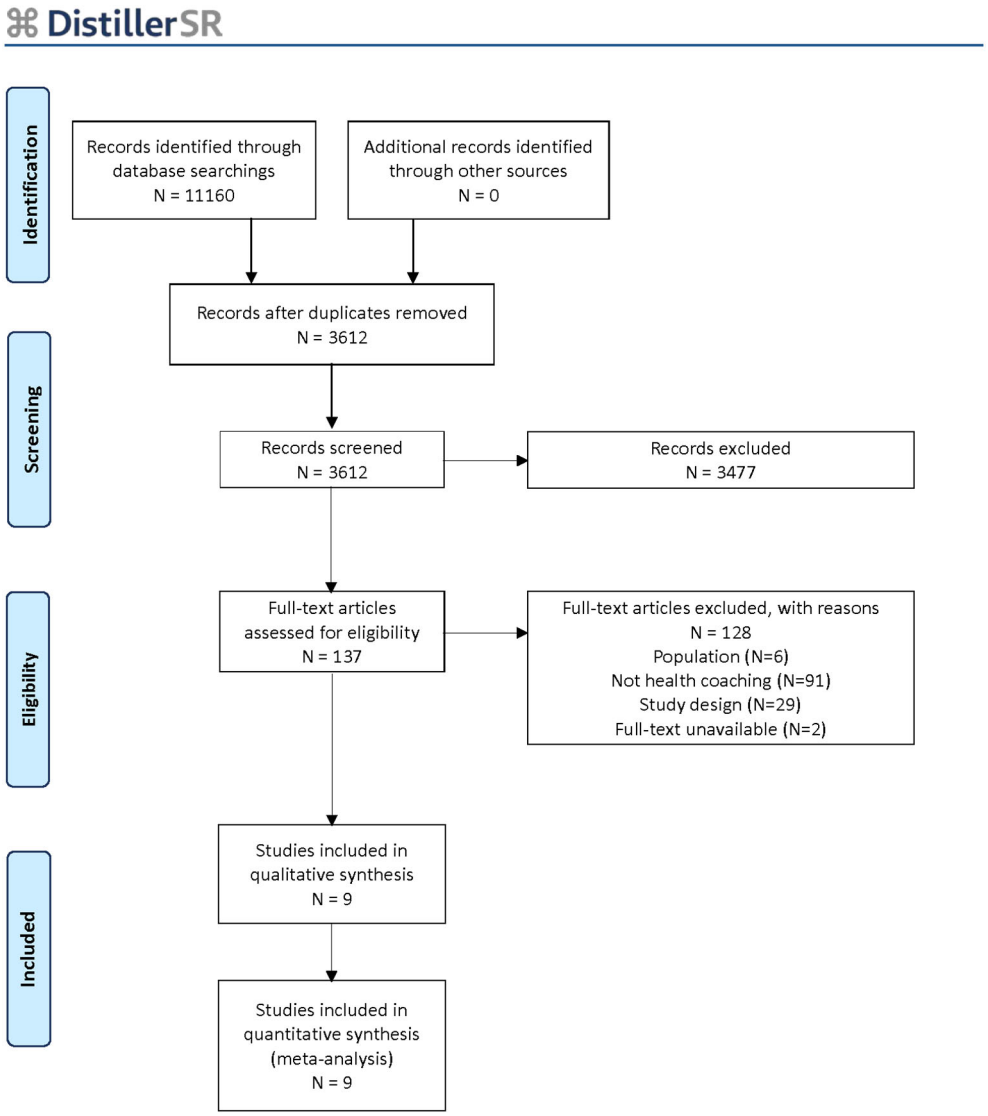


FIGURE 1
PRISMA Flow chart.

studies included a certified diabetologist, nurses, psychologists, doctoral students, community health workers, pharmacists, social workers, certified diabetes nurse educators, and a dietitian (Supplemental Material 2).

Coaching interventions were deployed using various strategies (Supplemental Materials 2, 3). Telephone-only strategies were used by 6 studies (28, 30, 32–35), while telephone and face-to-face was used in 1 study (29), and 2 studies used in-person or face-to-face strategies only (27, 31). All the studies were focused on individual or one-on-one interactions and only 1 study also included group components. Sessions and interactions with the coaches ranged from weekly, to bi-weekly, to as infrequent as one session every 4 to 6 weeks. The duration of these sessions also varied from as short as 15 minutes to as long as 90 minutes; however, most seemed to average around 30 minutes. Any in-person components of the health coaching interventions took place in outpatient healthcare settings such as clinics, centres, primary care offices, and doctors offices (Supplemental Material 3). One study did not provide any details about the location of the intervention beyond geographical area, but it was a telephone/virtual program (34). The fact that over 60% of the included studies consisted of telephone-only interactions means that many of the intervention components and exchanges between the coaches and participants occurred from wherever the participant was at that time.

TABLE 1 Characteristics of Included Studies.

Study	Balducci (2019) Italy (27)
Objective	To investigate whether a behavioral intervention strategy can produce a sustained increase in physical activity and reduction in sedentary time among individuals with type 2 diabetes (T2D).
Methods	Design: Randomized clinical superiority trial Inclusion criteria: 1) T2D for at least 1 year; 2) age 40 to 80 years; 3) body mass index of 27 to 40; 4) physical inactivity; 5) sedentary lifestyle for at least 6 months; 6) ability to walk 1.6 km without assistance; 7) and clearance by a cardiologist Exclusion criteria: not stated
Participants	Sample: N= 300; Intervention: n= 150; Control: n= 150 Follow up n: Intervention: n= 133; Control: n= 134 Mean age (SD): Overall: not stated; Intervention: 61.0 (9.7); Control: 62.3 (10.1) Gender (male): Intervention: n= 91 (60.7%); Control: n= 93 (62.0%) Race/ethnicity: not stated Mean BMI (SD): Intervention: n= 30.0 (4.9); Control: n= 30.1 (5.3) Baseline A1C % (SD): Intervention: n= 7.4 (1.6); Control: n= 7.3 (1.4)
Intervention	Intervention duration: 3 years Description of intervention: 1 individual theoretical counseling session, conducted by a diabetologist, and 8 biweekly individual theoretical and practical counseling sessions, conducted by a certified exercise specialist, per year. Description of control group: General physician recommendations for increasing daily physical activity and decreasing sedentary time. Length of follow up: NA
Quadruple Aims Outcomes	Clinical population health
Study	**Cummings** (2019) **USA** (33)
Objective	To evaluate the effect of cognitive behavioral therapy (CBT) plus lifestyle counseling in primary care on hemoglobin A1c (HbA1c) in rural adult patients with T2D and comorbid depressive or regimen-related distress (RRD) symptoms.
Methods	Design: Randomized controlled trial Inclusion criteria: 1) adult patients (18–75 years) with a medical record–established history of T2D with an HbA1c at screening >7.0% (53 mmol/mol) and with a positive screen for symptoms of distress using the Diabetes Distress Scale 2 (DDS-2) item screener and/or a positive screen for symptoms of depression on the Patient Health Questionnaire 2 (PHQ-2) item screener Exclusion criteria: 1) medical record–established diagnosis of advanced disease or the presence of alcoholism, cognitive impairment, or major psychiatric illness that would preclude active participation
Participants	Sample: N= 139; Intervention: n= 67; Control: n= 72 Follow up n: Intervention: n= 58; Control: n= 62 Mean age (SD): Overall: 52.6 (9.6); Intervention: 51.0 (9.0); Control: 53.0 (9.0) Gender (male): Intervention: n= 14 (21%); Control: n= 17 (24%) Race/ethnicity (%): African American: I: 77; C: 67 Mean BMI (SD): not stated Baseline A1C % (SD): Intervention: n= 9.88 (2.1); Control: n= 9.35 (1.7)
Intervention	Intervention duration: 12 months Description of intervention: The CBT subgroup intervention focused on the reduction of depressive and/or RRD symptoms through modification of negative thoughts and problematic behaviors as well as improvement of diabetes self-management strategies. Sessions were delivered by a clinical health psychologist as well as a doctoral student in clinical health psychology. CBT intervention components were guided by two evidence-based treatment manuals for behavioral activation. Description of control group: Standard care Length of follow up: NA
Quadruple Aims Outcomes	Patient-reported/experience; Clinical population health
Study	**Jutterström** (2016) **Sweden** (31)
Objective	To evaluate the effect of a patient-centered self-management support, in T2D with regard to metabolic changes
Methods	Design: Randomized controlled trial Inclusion criteria: 1) diagnosed with T2D within three years; 2) aged 40–80 years; 3) Swedish speaking; 4) and no diagnosed cognitive impairment or other severe illnesses; 5) had not received patient education other than information given to newly diagnosed T2D patients Exclusion criteria: not stated
Participants	Sample: N= 195; Intervention: n= 70, 35; Control: n= 36; External Control (EC): n=54 Follow up n: Intervention: n= 59, 33; Control: n= 32; EC: n= 47 Mean age (SD): Overall: 64.5 (9.58); Intervention: 64.0 (8.72), 64.9 (11.10); Control: 62.6 (10.61); EC: 66.2 (8.75) Gender (male): Intervention: n= 43 (68.3%), 21 (61.8%); Control: n= 18 (52.9%); EC: n= 32 (62.7%) Race/ethnicity: not stated

(Continued)

TABLE 1 Continued

Study	Balducci (2019) Italy (27)
	Mean BMI (SD): Intervention: n= 30.22 (5.22), 31.76 (5.73); Control: n= 30.56 (5.81); EC: n= 29.62 (5.27) Baseline A1C % (SD): Intervention: n= 6.0 (0.93), 5.8 (0.87); Control: n= 5.8 (0.77); EC: n= 5.5 (0.84)
Intervention	Intervention duration: 6 months Description of intervention: Participants in the group intervention (GI) and individual intervention (II) groups were invited to six sessions of 45–90 min each. In the GI group, the patients reflected aspects of living with type 2 diabetes together and the diabetes specialist nurses (DSNs) acted as a moderator. The II participants met the local diabetes nurse one-on-one. Description of control group: Standard care Length of follow up: 12 months#
Quadruple Aims Outcomes	Clinical population health
Study	**Karhula** (2015) **Finland** (35)
Objective	To study whether a structured mobile phone-based health coaching program, which was supported by a remote monitoring system, could be used to improve the health-related quality of life (HRQL) and/or the clinical measures of T2D and heart disease patients.
Methods	Design: Randomized controlled trial Inclusion criteria: 1) diagnosis of T2D, glycosylated hemoglobin (HbA1c) level, which needed to be above 6.5% within 1 year prior to the screening; 2) diagnosed with diabetes at least 3 months earlier; 3) 18 years of age or older; 4) ability to fill in questionnaires in Finnish; 5) ability to use the RPM system and the devices provided; 6) having adequate cognitive capacities to participate, being able to walk Exclusion criteria: not stated
Participants	Sample: N= 287; Intervention: n= 208; Control: n= 79 Follow up n: Intervention: n= 162; Control: n= 63 Mean age (SD): Overall: not stated; Intervention: 66.6 (8.2); Control: 65.5 (9.6) Gender (male): Intervention: n= 99 (55%); Control: n= 40 (57%) Race/ethnicity: not stated Mean BMI (SD): Intervention: n= 31.1 (5.4); Control: n= 30.9 (5.7) Median Baseline A1C %: Intervention: n= 7.25; Control: n= 7.20
Intervention	Intervention duration: 12 months Description of intervention: Health coaching over mobile phones and self-monitoring of health parameters with the help of a remote patient monitoring (RPM) system. Description of control group: Standard care Length of follow up: NA
Quadruple Aims Outcomes	Patient-reported/experience; Clinical population health
Study	**Naik** (2019) **USA** (30)
Objective	To evaluate the effectiveness of proactive population screening plus telephone delivery of a collaborative goal-setting intervention among high-risk patients with uncontrolled diabetes and depression.
Methods	Design: Randomized clinical trial Inclusion criteria: 1) Veterans with uncontrolled diabetes (defined by International Classification of Diseases and HbA1c of > or =7.5% for 1 year before the study) who lived at least 20 miles from the main Veterans Health Administration hospital in Houston, Texas, or who received primary care services within a MEDVAMC satellite community-based clinic across Southeast Texas Exclusion criteria: 1) severe cognitive impairment or mental health condition; 2) hearing or visual impairment; 3) active suicidal ideation; 4) presence of significant hypoglycemic events; 5) substance abuse
Participants	Sample: N= 225; Intervention: n= 136; Control: n= 89 Follow up n: Intervention: n= 90; Control: n= 68 Mean age (SD): Overall: 61.9 (8.3); Intervention: not stated; Control: not stated Gender (male): Intervention: n= 121 (89%); Control: n= 81 (91%) Race/ethnicity n (%): White - I: 73 (53.7); C: 51 (57.3); non-Hispanic black - I: 41 (30.1); C: 16 (18.0); Hispanic - I: 12 (8.8); C: 11 (12.4); Other - I: 10 (7.4); C: 11 (12.4) Mean BMI (SD): not stated Baseline A1C % (SD): Intervention: n= 9.2 (1.4); Control: n= 9.3 (1.5)
Intervention	Intervention duration: 6 months Description of intervention: Nine sessions across 6 months in which coaches focused on goal setting, discrete skill modules (increasing pleasant activities, using thoughts to improve wellness, diet, physical activity, medication management, and relaxation) and maintenance skills customized to meet their diabetes and depression goals. Description of control group: Usual care Length of follow up: 12 months#

(Continued)

TABLE 1 Continued

Study	Balducci (2019) Italy (27)
Quadruple Aims Outcomes	Patient-reported/experience; Clinical population health; Cost of care/system-level
Study	**Odnoletkova** (2016) **Belgium** (28)
Objective	To investigate the effect of the COACH programme on HbA1c and other modifiable diabetes risk factors in people with T2D in a primary care setting.
Methods	Design: Randomized controlled trial Inclusion criteria: 1) adults aged 18–75 years; 2) diagnosis of T2D; 3) received glycose-lowering oral and/or injectable therapy Exclusion criteria: 1) corticoid therapy and/or a debilitating coexisting medical condition, such as dialysis, mental illness or cancer; 2) residence in long-term care facilities; 3) pregnancy; 4) insufficient proficiency in Dutch
Participants	Sample: N= 574; Intervention: n= 287; Control: n= 287 Follow up n: Intervention: n= 240; Control: n= 246 Mean age (SD): Overall: not stated; Intervention: 63.8 (8.7); Control: 62.4 (8.9) Gender (male): Intervention: n= 173 (60%); Control: n= 180 (63%) Race/ethnicity: not stated Mean BMI (SD): Intervention: n= 30.2 (4.9); Control: n= 30.6 (5.2) Baseline A1C % (SD): Intervention: n= 7.0 (1.0); Control: n= 7.9 (0.9)
Intervention	Intervention duration: 6 months Description of intervention: The underlying 'COACH model' is a continuous quality improvement cycle, which includes bridging the knowledge gap, assertiveness training, setting an action plan and (re)assessment. The COACH programme consisted of five telephone sessions of a mean (range) duration of 30 (10–45) min, delivered at a mean (range) interval of 5 (3–8) weeks by a certified diabetes nurse educator. Description of control group: Usual care Length of follow up: 18 months#
Quadruple Aims Outcomes	Patient-reported/experience; Clinical population health; Healthcare provider experience; Cost of care/system-level
Study	**Sherifali** (2021) **Canada** (34)
Objective	To evaluate the effect of a 12-month telephone diabetes health coaching (DHC) intervention on glycemic control in persons living with T2D.
Methods	Design: Community-based randomized controlled trial Inclusion criteria: 1) ≥18 years of age; 2) T2D diagnosis; 3) A1C level >7.5% within 6 months before randomization; 4) ability to read and write in English; 5) telephone access Exclusion criteria: 1) pregnancy; 2) debilitating coexisting conditions (i.e., mental illness, impaired cognition); 3) underlying medical conditions that could provide misleading A1C levels
Participants	Sample: N= 365; Intervention: n= 188; Control: n= 177 Follow up n: Intervention: n= 186; Control: n= 171 Mean age (SD): Overall: not stated; Intervention: 56.82 (11.69); Control: 59.05 (11.79) Gender (male): Intervention: n= 99 (52.66%); Control: n= 83 (46.89%) Race/ethnicity n (%): Caucasian: I: 150 (79.79); C: 144 (81.36) Mean BMI (SD): Intervention: n= 34.71 (7.80); Control: n= 35.36 (8.35) Baseline A1C % (SD): Intervention: n= 9.10 (1.65); Control: n= 8.86 (1.50)
Intervention	Intervention duration: 12 months Description of intervention: Diabetes health coaching comprised of care that included: 1) case management and monitoring; 2) diabetes self-management education and support; 3) behaviour modification, goal setting and reinforcement; and 4) general psychosocial support. Description of control group: Usual diabetes education (individual or group) provided by nurses and/or dietitians, typically every 3 to 6 months, along with community resources and a study provided accelerometer. Length of follow up: NA
Quadruple Aims Outcomes	Patient-reported/experience; Clinical population health
Study	**Varney** (2014) **Australia** (32)
Objective	To measure the effect of a 6-month telephone coaching intervention on glycaemic control, risk factor status and adherence to diabetes management practices at the intervention's conclusion (6 months) and at 12 months.
Methods	Design: Randomized controlled trial Inclusion criteria: 1) adults with T2D and HbA1C >7% Exclusion criteria: 1) unable to provide consent; 2) non-English speaking; 3) cognitively impaired; 4) receiving palliative care; 5) severely hearing impaired or without telephone access
Participants	Sample: N= 94; Intervention: n= 47; Control: n= 47 Follow up n: Intervention: n= 35; Control: n= 36 Mean age (95% CI): Overall: not stated; Intervention: 59 (56–62); Control: 64 (61–66)

(Continued)

TABLE 1 Continued

Study	Balducci (2019) Italy (27)
	Gender (male): Intervention: n= 34 (72%); Control: n= 30 (64%) Race/ethnicity n (%): Caucasian I: 46 (98); C: 37 (79); Asian/Indian I: 1 (2); C: 8 (17); Afro-Caribbean I: 0 (0); C: 2 (4) Mean BMI (95% CI): Intervention: n= 32.1 (30.3-33.9); Control: n= 30.9 (29.1-32.6) Baseline A1C % (SD): Intervention: n= 8.2 (8.0-9.7); Control: n= 8.5 (8.1-8.9)
Intervention	Intervention duration: 6 months Description of intervention: Participants were encouraged to follow a low saturated fat, high-fibre diet, with 50% of energy from carbohydrates, and were encouraged to exercise for 150 min per week. During subsequent telephone coaching sessions, progress towards treatment goals, risk factor status, adherence to self-care and monitoring requirements were reassessed. If goals were not achieved, barriers to goal attainment were identified, an action plan addressing these barriers was agreed and new goals were established. Description of control group: Received telephone calls to arrange baseline, 6- and 12-month assessment appointments. Could access usual care services, including a diabetes clinic staffed by endocrinologists, diabetes educators and dietitians. Length of follow up: 12 months#
Quadruple Aims Outcomes	Patient-reported/experience; Clinical population health
Study	**Young** (2020) **USA** (29)
Objective	To evaluate the effectiveness of a nurse coaching program using motivational interviewing paired with mobile health (mHealth) technology on diabetes self-efficacy and self-management for persons with T2D.
Methods	Design: Randomized controlled trial Inclusion criteria: 1) aged 18 years or above; 2) receiving care at 1 of the 3 clinics; 3) living with T2D and having HbA1c of 6.5% (48 mmol/mol) or higher; and 4) able to speak English Exclusion criteria: 1) no access to a telephone; 2) were not able to consent because of cognitive impairment, or were pregnant
Participants	Sample: N= 319; Intervention: n= 158; Control: n= 161 Follow up n: Intervention: n= 132; Control: n= 155 Mean age (SD): Overall: 59.07 (11.4); Intervention: 58.96 (11.3); Control: 59.18 (11.5) Gender (male): Intervention: n= 81 (52.6%); Control: n= 84 (52.8%) Race n (%) - Caucasian I: 96 (63.2); C: 100 (62.9), African American I: 21 (13.8); C: 18 (11.3), Asian I: 11 (7.2); C: 16 (10.1), Other I: 16 (10.5); C: 14 (8.8), More than 1 race I: 8 (5.3); C: 11 (6.9) Ethnicity n (%) - Hispanic or Latino I: 24 (17.5); C: 18 (12.9), Not Hispanic or Latino I: 113 (82.5); C: 122 (87.1) Mean BMI (SD): not stated Baseline A1C % (SD): not stated
Intervention	Intervention duration: 3 months Description of intervention: Each participant was paired with a nurse health coach who delivered 6 individual sessions using a counseling style based on the concepts of motivational interviewing. Sessions were structured to promote mutual goal setting, enhance self-efficacy in health behaviour change, and assist individuals to derive meaning from the data to reinforce choices and behaviours. Description of control group: Usual care comprised standard health care visits with providers and access to classes, resources, and services (i.e., diabetes management and weight loss education, electronic learning videos, and care coordination). Length of follow up: 9 months#
Quadruple Aims Outcomes	Patient-reported/experience

NA, not applicable.
#, follow up reported as time from baseline.

We described the diabetes health coaching intervention using the TIDieR checklist (17); reporting on the 12 domains were inconsistent with limited reporting on implementation fidelity (planned vs. actual) (Figure 2). Almost all the included studies specifically mentioned tailoring and personalization of the intervention to the participants needs (n=8), which is likely reflective of the personal nature of health coaching (Figure 2). While Balducci et al., did consist of individual face-to-face sessions with the coach (27), there was no explicit mention of how these sessions were tailored to the participant. Three studies mentioned the modification of the intervention from what was originally planned. Balducci et al., created a two-step scaled intensity for physical activity to support behaviour change (27). Based on feedback and study measures, Karhula et al., adjusted the length coaching phone calls to be shorter in duration (35). Young et al., had an unexpected recall of equipment that resulted in the use of a different activity tracker (29). Moreover, very few studies assessed how well the intervention was delivered (Figure 2). Four studies outlined plans to assess intervention fidelity, consisting of quality control measurements, listening to recordings of participant-coach interactions, and auditing of sessions, but only 1 included this as an outcome in their paper. Odnoletkova et al., conducted interviews with healthcare providers to assess intervention implementation (28). It is

FIGURE 2
Spider chart of the total reporting of TIDieR Tool Items.

important to note that this component of TIDieR goes beyond attendance and adherence of the intervention by participants.

Studies were also mapped to the proposed Sherifali Diabetes Coaching Model (36). This model is comprised of four components: (i) personal case management and monitoring, emphasizing process of care issues and system navigation related to diabetes; (ii) diabetes self-management education and support, highlighting the need for knowledge, skill acquisition, and problem solving related to day-today management; (iii) behaviour modification, goal setting and reinforcement, using motivational interviewing and theories to facilitate goal setting, attainment, and behaviour change; and (iv) general psychosocial support, leveraging active listening and empathy to provide support. The studies in our review all included intervention components related to self-management and education (n=9) and almost all the studies also addressed behaviour modification (n=8). Psychosocial support was included in 66% of the studies (n=6), while only one third of the studies addressed personal case management and monitoring.

3.2 Risk of bias and quality of included studies

The Cochrane RoB tool showed mixed quality of study methodology: 4 studies were low risk of bias (27–30), 4 were unclear risk of bias (31–34), and 1 was high risk of bias (35) mostly due to issues regarding blinding of participants, providers, and/or outcome assessment (Table 2).

The certainty of evidence, as assessed by GRADE, ranged from very low to moderate due to concerns regarding risk of bias (studies rated as unclear risk of bias), inconsistency (direction of effect is not consistent with substantial heterogeneity observed across studies), and imprecisions (inadequate sample size and imprecise effect estimates with confidence intervals the include no effect) (Supplemental Material 4).

3.3 Benefits of treatment

We extracted and categorized outcomes based on the Quadruple Aim framework (13) and were able to meta-analyze outcomes for patient-reported and clinical population health outcomes. For the remaining outcomes, there was insufficient data and number of studies for meta-analysis, therefore, these are described narratively.

3.3.1 Patient-reported outcomes

Patient-reported outcomes included satisfaction, diabetes empowerment, quality of life, and depression/distress. Only 1 study reported on satisfaction using the Diabetes Treatment Satisfaction Questionnaire (28) and 1 reported on empowerment with the Diabetes Empowerment Scale (29). Quality of life outcomes were reported by 4 studies post-intervention and 2 studies at long-term follow-up using a variety of standardized tools/questionnaires; however, there was no significant effects between intervention or control groups at either time point (Supplemental Material 5). Five studies reported the effect of the coaching intervention on depression/distress. At immediate post-treatment, health coaching interventions showed a significant decrease of small magnitude in depression/distress levels of 0.21 (95% CI, -0.41 to -0.02) based on moderate certainty of evidence (Figure 3; Supplemental Material 4). At long-term follow-up, the 4 studies with data did not show a significant effect.

3.3.2 Clinical population health

Glucose control was measured by glycosylated hemoglobin (A1C) and fasting blood glucose (FBG). Eight of the nine studies reported the effect of the coaching intervention on A1C levels. At immediate post-treatment, data from 7 health coaching interventions showed a significant decrease of small magnitude in A1C levels of 0.24 (95% CI, -0.38 to -0.09) based on moderate certainty of evidence (Figure 4; Supplemental Material 4). At long-term follow-up, the 4 studies with A1C data did not show a significant effect. FBG was reported in 2 studies (27, 32). Immediately post-treatment, both studies found significant improvements in FBG; however, this effect was not maintained at long-term follow-up in Varney et al.

Studies also measured anthropometric outcomes including body mass index (BMI), waist circumference, and body weight. Two studies measured BMI post-intervention and 3 studies measured BMI at long-term follow-up. At immediate post-treatment, health coaching interventions showed a significant decrease of small magnitude in BMI of 0.19 (95% CI, -0.35 to -0.03) based on moderate certainty of evidence (Figure 5A; Supplemental Material 4); however, this effect was not maintained at long-term follow-up. Similarly, at immediate post-treatment, data from 3 health coaching interventions showed a significant decrease in waist circumference of small

TABLE 2 Risk of bias.

Author, year (ref)	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PATIENTS/ PARTICIPANTS & PROVIDERS/ PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER BIAS
Balducci 2019 (27)	L	L	H	L	L	L	L
Cummings 2019 (33)	L	L	U	U	L	L	L
Jutterström 2016 (31)	L	L	U	U	U	L	L
Karhula 2015 (35)	L	L	U	U	H	L	L
Naik 2019 (30)	L	L	U	L	L	L	L
Odnoletkova 2016 (28)	L	L	U	L	L	L	L
Sherifali 2021 (34)	L	L	U	U	L	L	L
Varney 2014 (32)	L	L	H	U	L	L	L
Young 2020 (29)	L	U	L	U	L	L	L

U=unclear risk.
L=low risk.
H=high risk.

magnitude of 0.24 (95% CI -0.41 to -0.07) based on moderate certainty of evidence (Figure 5B; Supplemental Material 4); however, this effect was not maintained at long-term follow-up with data from 2 studies. Lastly, the data from 5 studies on body weight at post-intervention and 2 studies at long-term follow-up showed similar trends. At immediate post-treatment, health coaching interventions showed a significant decrease of small magnitude in body weight of 0.19 (95% CI -0.30 to -0.08) based on moderate certainty of evidence (Figure 5C; Supplemental Material 4). At long-term follow-up, the data did not show a significant effect.

Blood pressure was reported as both systolic and diastolic in our included studies. At immediate post-treatment, data from 5 health coaching interventions showed a significant decrease of small magnitude in systolic blood pressure of 0.28 (95% CI -0.40 to -0.16) based on moderate certainty of evidence (Figure 6; Supplemental Material 4) and this effect was maintained at long-term follow-up based on data from 3 studies with a significant decrease of small magnitude of 0.38 (95% CI -0.53 to -0.23) based on moderate certainty of evidence (Figure 6; Supplemental Material 4). Diastolic blood pressure data came from 4 studies at post-treatment and 3 studies at long-term follow-up; however, health coaching interventions did not show significant effects at either time point (Supplemental Material 5).

Lastly, many of our included studies measured other cardiometabolic outcomes from blood triglycerides and cholesterol levels. Data from 4 studies at immediate post-treatment and 3 studies at long-term follow-up showed no significant effects from the coaching interventions on total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), or triglycerides (Supplemental Material 5).

3.3.3 Cost of care

Outcomes related to cost of care were measured in 2 studies (28, 30) as the use of health care services. Both studies measured clinic visits including mental health clinic visits, primary care/general practitioner clinic visits, and other healthcare specialist visits such as endocrinologists, cardiologists, and ophthalmologists. Naik et al., did not see any significant differences in health care use or clinic visits between treatment and control groups, but Odnoletkova did find significant differences between treatment and control groups. Those randomized to the coaching intervention sought out healthcare services and specialist visits and tests more than those in the control group. There was no data from our included studies on the cost of care such as cost of the coaching interventions, or any cost savings due to the intervention programs.

3.3.4 Healthcare provider experience

Odnoletkova was the only study in our included articles to report on healthcare provider experience and this was described in a mixed-method study embedded in their clinical trial (37). Through both questionnaires and interviews, the study explored the perceptions of participants, nurses, and general practitioners

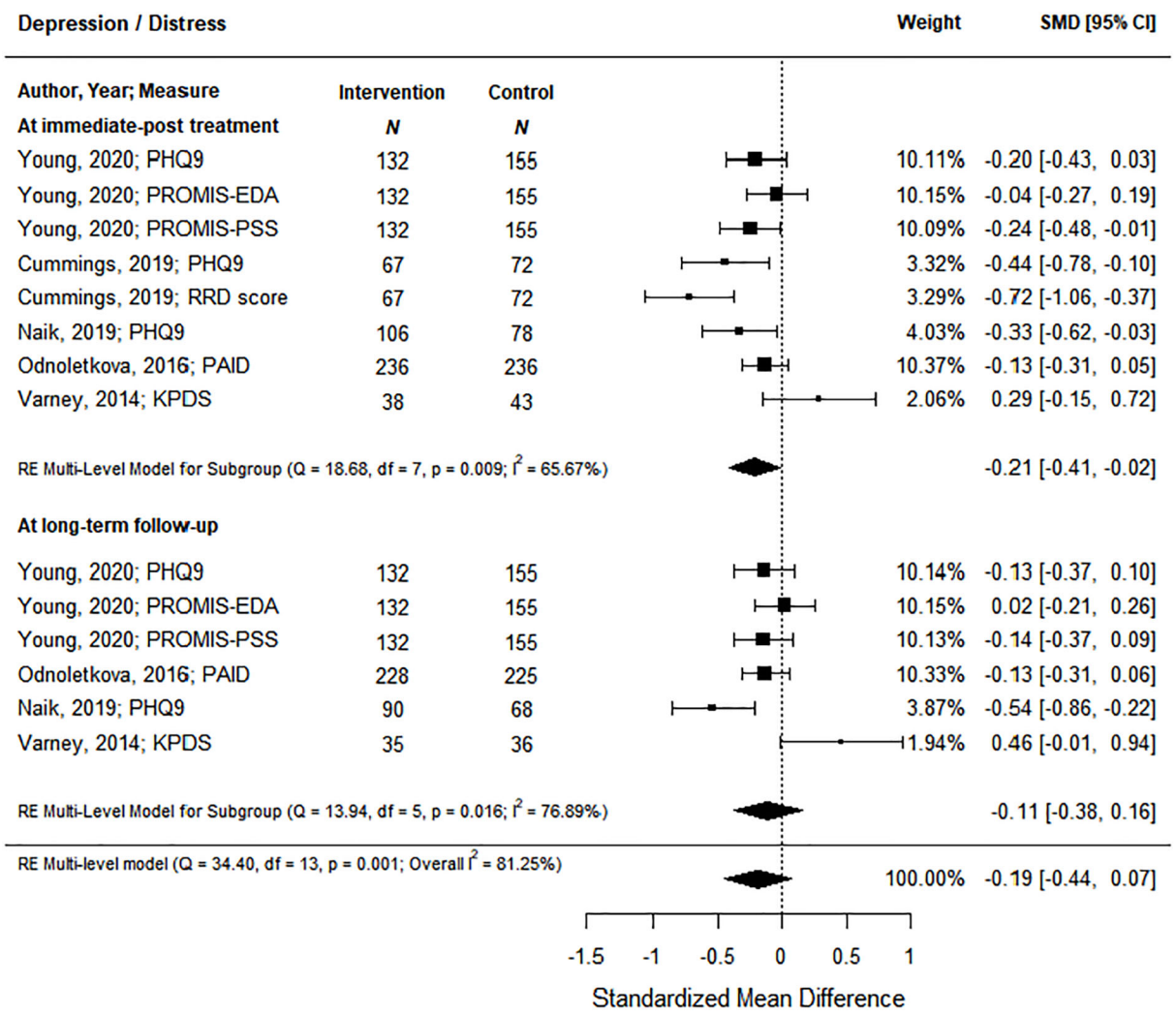


FIGURE 3
The effect of coaching interventions on depression/distress.

(GPs) regarding the telecoaching intervention. Overall, both GPs and nurses found the coaching intervention to be sufficient and facilitated their work and noted that diabetes education is lacking in their training. According to most GPs, work still needs to be done to identify the groups of patients who would benefit from coaching programs using different methods (i.e. in person vs telephone). Healthcare providers agreed that a combination of phone and face-to-face consultations is necessary.

4 Discussion

We examined the literature to determine the impact of diabetes health coaching on the quadruple aim outcomes of patient-reported outcomes, clinical outcomes, provider satisfaction, and cost-effectiveness, and to describe the implementation and context of diabetes health coaching interventions. A total of 9 trials from Europe, Australia, and North America were included and the description of what comprised diabetes health coaching as an intervention was consistent across studies and previously published literature (11, 12). While 8 of the 9 studies reported on the impact of diabetes health coaching on glycemic control, there was limited evidence on patient-reported outcomes, provider satisfaction, and cost of care.

Similar to other reviews (11, 12, 38), our review of the literature found that diabetes health coaching interventions are still diverse with respect to the delivery personnel, mode of delivery, and most notably when it comes to the frequency, duration, and location of coaching interactions and sessions. The differences in the mode of delivery and length of interventions

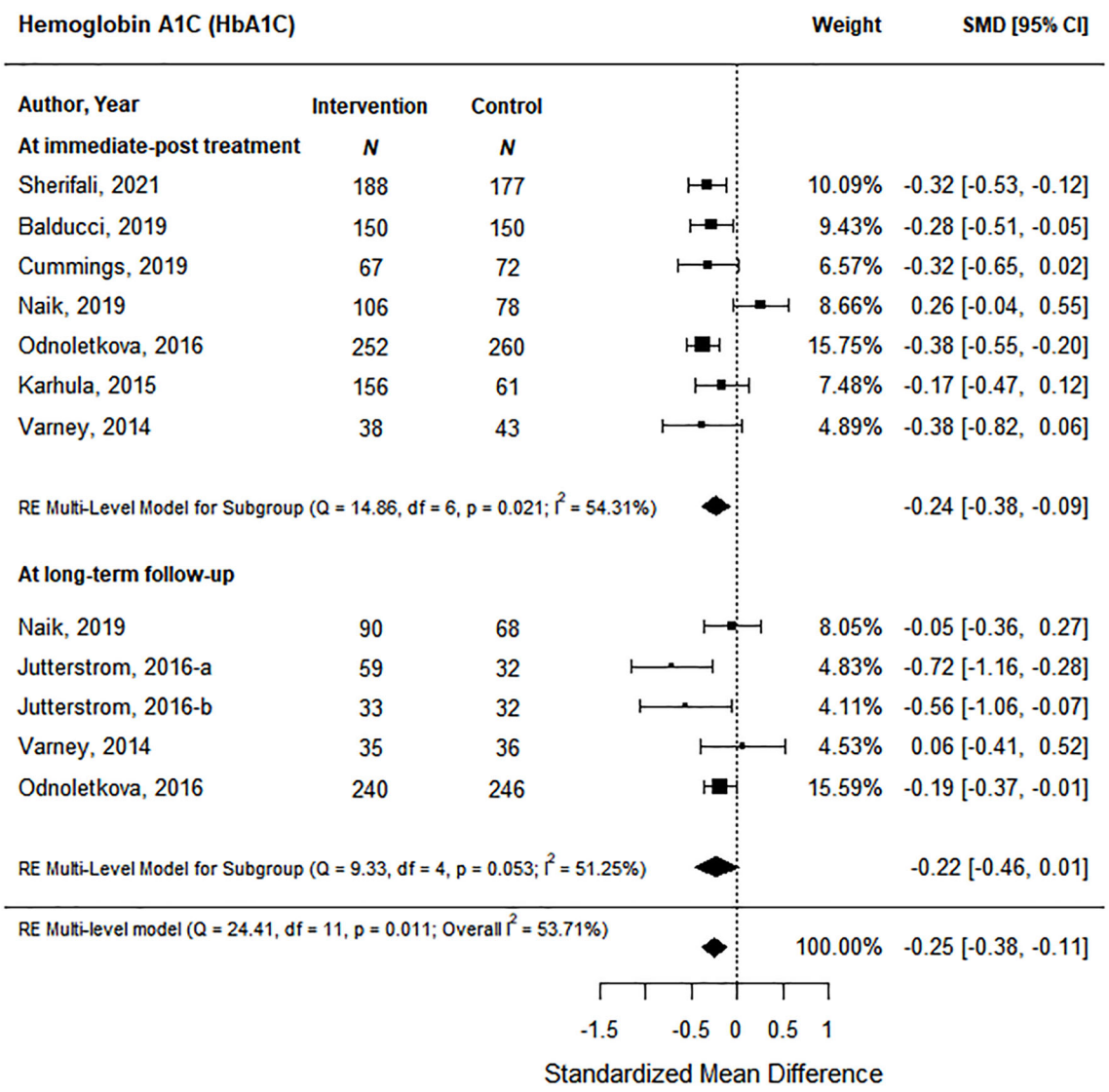


FIGURE 4
The effect of coaching interventions Hba1c levels.

raises the need for further research into which study-level factors are most effective for all the quadruple aim outcomes. There was great variability in the individual components of the coaching interventions; however, they still aligned well to the Sherifali Coaching model (36) and definitions of health coaching more broadly (4–6). The reporting of intervention components also aligned with standard reporting guidelines such as CONSORT (39). The studies in our review provided details related to the why, what, who, how, where, and when of diabetes health coaching interventions, but components related to intervention fidelity were lacking.

Our meta-analysis showed a statistically and clinically significant reduction of A1C [0.24 (95% CI, -0.38 to -0.09)] after exposure to diabetes health coaching, and small to trivial benefits for BMI, waist circumference, body weight, and depression/distress at post treatment. However, long term benefit was not seen across all clinical outcomes, following the completion of the diabetes health coaching intervention. Although there was a small benefit noted for systolic blood pressure, which was maintained following diabetes health coaching exposure, there was no statistically significant benefit in other secondary outcomes such as diastolic blood pressure and lipid profile measures (e.g. triglycerides). It is important to note that there is heterogeneity and imprecision in the health coaching interventions and associated data from our included studies which downgrades our confidence in the generalizability

10.3389/fendo.2022.1069401

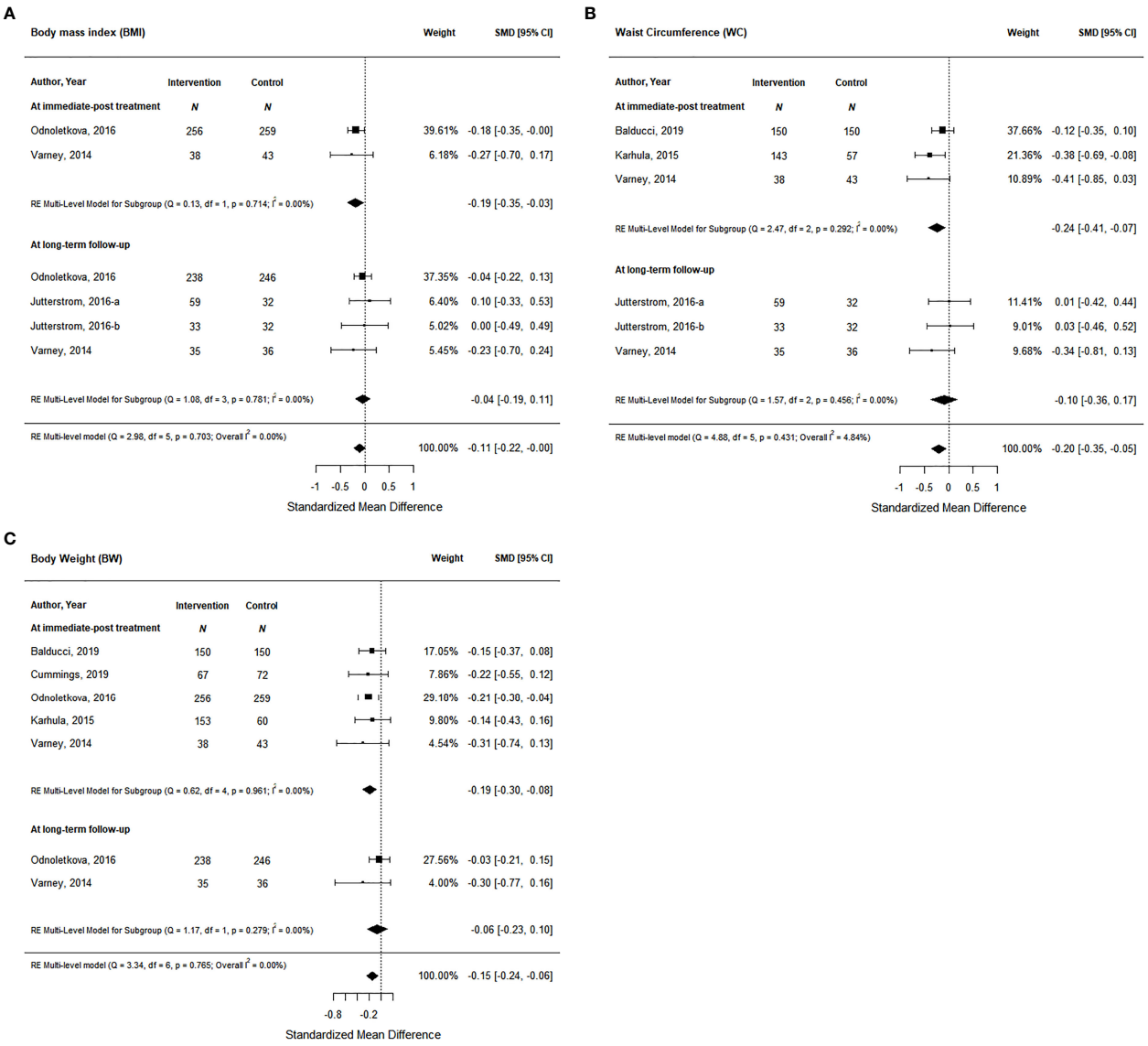


FIGURE 5
The effort of coaching interventions on anthropometric outcomes ((**A**). BMI; **(B)** Waist circumtances; **(C)** Body Weight).

of these treatment effects and lowers the overall certainty of evidence rating (GRADE) for specific outcomes. In such cases, these results and their generalizability should be interpreted with caution, warranting future high quality research with adequate sample sizes to further affirm the findings of our systematic review and meta-analysis.

The pooled treatment effect of diabetes health coaching on A1C is smaller in magnitude than previous reviews which have estimated approximately a 0.5% reduction in A1C following a six month diabetes health coaching intervention (11, 12). The decrease in pooled treatment effect size in our review may be due to the changing nature of diabetes self-management, with many diabetes clinical guidelines and standards of practice placing a greater emphasis on self-management support, particularly starting around 2015 (3). Furthermore, as the development, implementation, and evaluation of diabetes health coaching as an intervention gains greater attention, fewer pilot studies are being conducted. Pilot studies often yield larger and less precise effect sizes, whereas full-scale RCTS with powered sample sizes and larger trials are yielding more precise, real-world estimates of diabetes health coaching in a variety of contexts. However, longer duration intervention studies are required to fully assess the implementation, impact on clinical population health outcomes, cost of care,

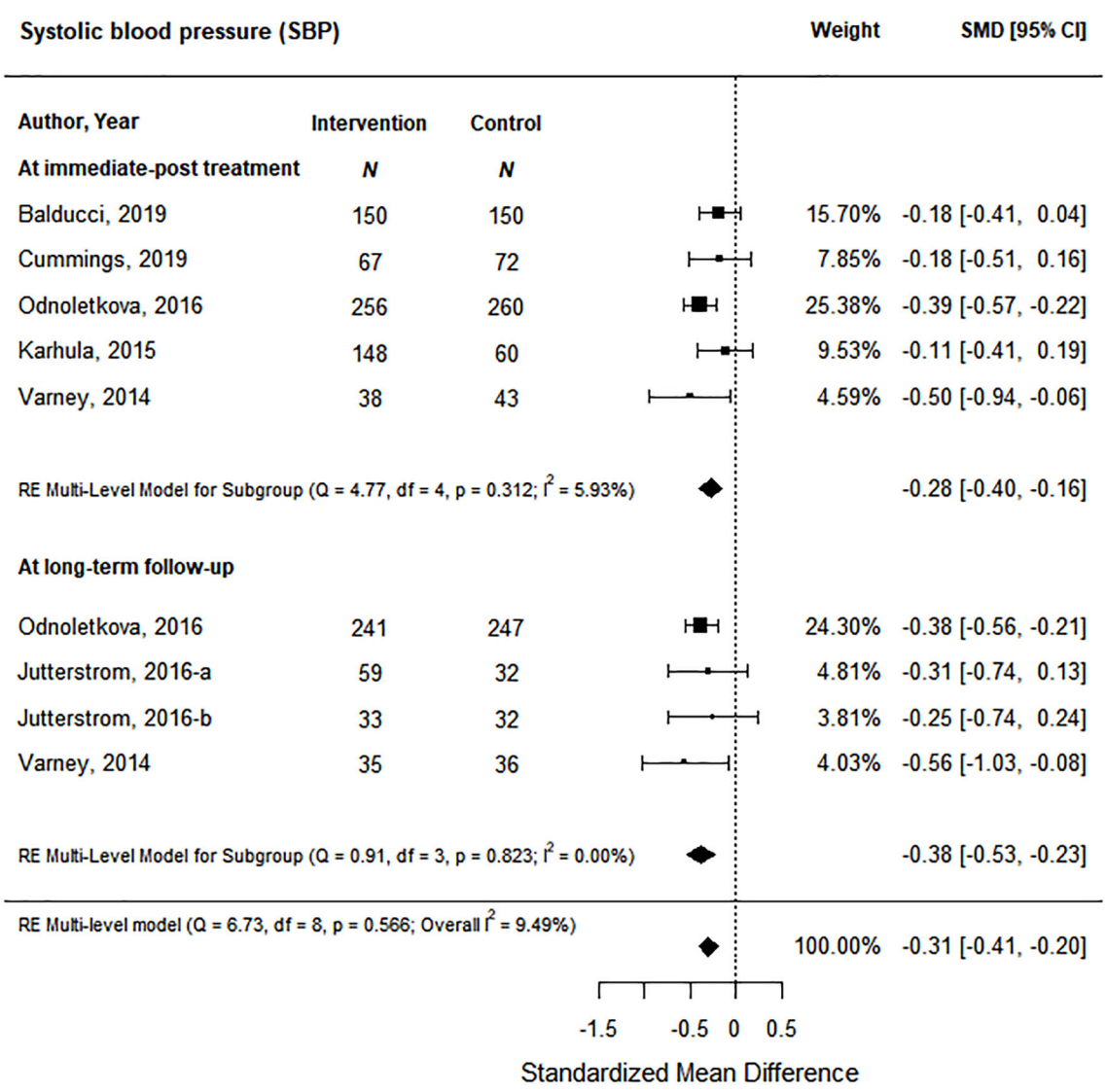


FIGURE 6
The effect of coaching interventions on systolic blood pressure.

sustainability, and legacy effect of diabetes health coaching since other reviews also found a reduced effectiveness of these interventions with longer study durations beyond one year (12).

The examination of quadruple aim goals in the context of diabetes health coaching demonstrated a paucity of evidence. Specifically, clinical outcomes related to blood pressure and lipid management may require longer duration studies, beyond 6 months, to yield observed clinical benefits. Other reviews have also failed to find a significant benefit of health coaching interventions for these cardiometabolic clinical outcomes (38). Beyond these clinical outcomes, we also found there was limited evidence on patient-reported outcomes, provider satisfaction, and cost of care. The few studies that did report on these outcomes showed mixed results, and while we found a significant decrease of small magnitude in depression/distress levels of 0.21 (95% CI, -0.41 to -0.02), other reviews have not seen the same significance in their analyses (12, 38). One explanation for these findings may be the emphasis that diabetes health coaching interventions currently place on metabolic control of T2DM. The patient-reported outcomes may require more psychologically focussed programming. Based on the Sherifali Coaching model (36), we found psychosocial support was included in only 66% of the studies (n=6), while only one third of the studies addressed personal case management and monitoring.

Our review was comprehensive, having searched multiple databases and leveraged a comprehensive search strategy from a previous review. However, we did not search grey literature and

we only included studies that met our predetermined inclusion criteria. We have noted that there is heterogeneity in our included studies but unfortunately, we could not perform any meta-regression analysis based on study-level factors (such as coaching intervention type, length of intervention, or population) as there were too few studies to conduct such analysis. We also applied a transparent definition of diabetes health coaching which may be excluding studies in which diabetes health coaching was delivered by a non-health care professional. However, by applying the TIDieR checklist to the descriptions of the study interventions, we are contributing to the greater understanding of what comprises diabetes health coaching.

5 Conclusions

Findings from this systematic review and meta-analysis showed that the diabetes health coaching literature continues to evolve, adding more evidence from larger trials of longer duration on the benefit on glucose control (such as A1C). Health coaching interventions can have short term impact beyond glucose control on cardiometabolic and mental health outcomes. As diabetes health coaching continues to be implemented as a self-management support intervention, future research should continue to explore the impact of health coaching on patient reported outcomes, other metabolic health outcomes, provider satisfaction, and cost to better assess the impact of these interventions at longer time points following the termination of the coaching program. More broadly, this systematic review provides a road map of gaps and opportunities for future research in diabetes health coaching evaluation and implementation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

All authors were involved in conception and design of the study and approved the protocol; MR, DS were responsible for overseeing the search of databases and literature. MR handled management of database and deduplication or records. MR, MJ, PA, DS were involved in the screening of citations; MR, MJ, PA were responsible for data extraction; MR, MA, DS were responsible for data verification and analysis of data. MR, MA, DS were involved in interpretation of data. All authors supported in the drafting of the manuscript which was led by MR and all authors supported in revising and formatting of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This research was funded by the McMaster Evidence Review and Synthesis Team (MERST). Diana Sherifali holds the Heather M Arthur Population Health Research Institute/Hamilton Health Sciences Chair in Interprofessional Health Research which supported her role in this work.

Acknowledgments

The authors thank Angela Eady for developing the search strategy and Saira Khalid for supporting in creation of tables and figures for the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1069401/full#supplementary-material

References

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes - global burden of disease and forecasted trends. *J Epidemiol Global Health* (2020) 10((1):107–. doi: 10.2991/jegh.k.191028.001

2. *Diabetes around the world in 2021: IDF diabetes atlas* (2021). Available at: https://diabetesatlas.org/.

3. Sherifali D, Berard LD, Gucciardi E, MacDonald B, MacNeill G. Self-management education and support. *Can J Diabetes.* (2018) 42:S36–41. doi: 10.1016/j.jcjd.2017.10.006

4. Wolever RQ, Dreusicke M, Fikkan J, Hawkins TV, Yeung S, Wakefield J, et al. Integrative health coaching for patients with type 2 diabetes: a randomized clinical trial. *Diabetes educator.* (2010) 36(4):629–39. doi: 10.1177/0145721710371523

5. Huffman M. Health coaching: A new and exciting technique to enhance patient self-management and improve outcomes. *Home Healthcare Now.* (2007) 25 (4):271–4. doi: 10.1097/01.NHH.0000267287.84952.8f

6. Wong-Rieger D. *Health coaching for chronic conditions engaging and supporting patients to self-manage.* Toronto, ON: Institute for Optimizing Health Outcomes (2011).

7. Ruggiero L, Moadsiri A, Butler P, Oros SM, Berbaum ML, Whitman S, et al. Supporting diabetes self-care in underserved populations: a randomized pilot study using medical assistant coaches. *Diabetes Educator.* (2010) 36(1):127–31. doi: 10.1177/0145721709355487

8. Whittemore R, Melkus GD, Sullivan A, Grey M. A nurse-coaching intervention for women with type 2 diabetes. *Diabetes Educator.* (2004) 30 (5):795–804. doi: 10.1177/014572170403000515

9. Webb TL, Joseph J, Yardley L, Michie S. Using the Internet to promote health behavior change: A systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. *J Med Internet Res* (2010) 12(1):e4. doi: 10.2196/jmir.1376

10. Lindner H, Menzies D, Kelly J, Taylor S, Shearer M. Coaching for behaviour change in chronic disease: A review of the literature and the implications for coaching as a self-management intervention. *Aust J Primary Health* (2003) 9 (3):177–85. doi: 10.1071/PY03044

11. Sherifali D, Bai JW, Kenny M, Warren R, Ali MU. Diabetes self-management programmes in older adults: a systematic review and meta-analysis. *Diabetic Med* (2015) 32(11):1404–14. doi: 10.1111/dme.12780

12. Pirbaglou M, Katz J, Motamed M, Pludwinski S, Walker K, Ritvo P. Personal health coaching as a type 2 diabetes mellitus self-management strategy: A systematic review and meta-analysis of randomized controlled trials. *Am J Health Promot* (2018) 1(7):1613–26. doi: 10.1177/0890117118758234

13. Bodenheimer T, Sinsky C. From triple to quadruple aim: Care of the patient requires care of the provider. *Ann Family Med* (2014) 12(6):573. doi: 10.1370/afm.1713

14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* (2009) 339: b2535. doi: 10.1136/bmj.b2535

15. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane handbook for systematic reviews of interventions version 6.3. 2nd Edition.* Chichester, UK: John Wiley & Sons (2022).

16. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* (2011) 343:d5928. doi: 10.1136/bmj.d5928

17. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ Br Med J* (2014) 348:g1687. doi: 10.1136/bmj.g1687

18. Schünemann H BJ, Guyatt G, Oxman A. *GRADE handbook for grading quality of evidence and strength of recommendations.* The GRADE Working Group (2013). Available at: https://gdt.gradepro.org/app/handbook/handbook.html.

19. *GDT g. GRADEpro guideline development tool [Software].* McMaster University (2015).

20. Pastor DA, Lazowski RA. On the multilevel nature of meta-analysis: A tutorial, comparison of software programs, and discussion of analytic choices. *Multivariate Behav Res* (2018) 53(1):74–89. doi: 10.1080/00273171.2017.1365684

21. Assink M, Wibbelink CJM. Fitting three-level meta-analytic models in r: A step-by-step tutorial. *Quantitative Methods Psychol* (2016) 12(3):154–74. doi: 10.20982/tqmp.12.3.p154

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials.* (1986) 7(3):177–88. doi: 10.1016/0197-2456(86)90046-2

23. Cohen J. *Statistical power analysis for the behavioral sciences (2nd ed.).* Hillsdale, NJ: Lawrence Erlbaum Associates, Publishers (1988).

24. Higgins JPT LT, Deeks JJ. Choosing effect measures and computing estimates of effect. In: Higgins JPT LT, Deeks JJ, editors. *Cochrane handbook for systematic reviews of interventions* (2019). 143–76. Available at: https://training.cochrane.org/handbook/current/chapter-06.

25. Viechtbauer W. Conducting meta-analyses in r with the metafor package. *J Stat Software* (2010) 36(3). doi: 10.18637/jss.v036.i03

26. Harrer M CP, Furukawa T. *Ebert DD dmetar: Companion r package for the guide 'Doing meta-analysis in r'. r package version 0.0.9000.* (2019).

27. Balducci S, D'Errico V, Haxhi J, Sacchetti M, Orlando G, Cardelli P, et al. Effect of a behavioral intervention strategy on sustained change in physical activity and sedentary behavior in patients with type 2 diabetes: The IDES_2 randomized clinical trial. *JAMA: J Am Med Assoc* (2019) 321(9):880–90. doi: 10.1001/jama.2019.0922

28. Odnoletkova I, Goderis G, Nobels F, Fieuws S, Aertgeerts B, Annemans L, et al. Optimizing diabetes control in people with type 2 diabetes through nurse-led telecoaching. *Diabetic Med* (2016) 33(6):777–85. doi: 10.1111/dme.13092

29. Young HM, Miyamoto S, Dharmar M, Tang-Feldman Y. Nurse coaching and mobile health compared with usual care to improve diabetes self-efficacy for persons with type 2 diabetes: randomized controlled trial. *JMIR mhealth uhealth.* (2020) 8(3):e16665. doi: 10.2196/16665

30. Naik AD, Hundt NE, Vaughan EM, Petersen NJ, Zeno D, Kunik ME, et al. Effect of telephone-delivered collaborative goal setting and behavioral activation vs enhanced usual care for depression among adults with uncontrolled diabetes: a randomized clinical trial. *JAMA network Open* (2019) 2(8):e198634. doi: 10.1001/jamanetworkopen.2019.8634

31. Jutterström L, Hörnsten Å, Sandström H, Stenlund H, Isaksson U. Nurse-led patient-centered self-management support improves HbA1c in patients with type 2 diabetes-a randomized study. *Patient Educ Counseling.* (2016) 99(11):1821–9. doi: 10.1016/j.pec.2016.06.016

32. Varney JE, Weiland TJ, Inder WJ, Jelinek GA. Effect of hospital-based telephone coaching on glycaemic control and adherence to management guidelines in type 2 diabetes, a randomised controlled trial. *Internal Med J* (2014) 44(9):890–7. doi: 10.1111/imj.12515

33. Cummings DM, Lutes LD, Littlewood K, Solar C, Carraway M, Kirian K, et al. Randomized trial of a tailored cognitive behavioral intervention in type 2 diabetes with comorbid depressive and/or regimen-related distress symptoms: 12-month outcomes from COMRADE. *Diabetes Care* (2019) 42(5):841–8. doi: 10.2337/dc18-1841

34. Sherifali D, Brozic A, Agema P, Punthakee Z, McInnes N, O'Reilly D, et al. Effect of diabetes health coaching on glycemic control and quality of life in adults living with type 2 diabetes: a community-based, randomized, controlled trial. *Can J Diabetes* (2021) 45(7):594–600. doi: 10.1016/j.jcjd.2020.11.012

35. Karhula T, Vuorinen AL, Rääpysjärvi K, Pakanen M, Itkonen P, Tepponen M, et al. Telemonitoring and mobile phone-based health coaching among Finnish diabetic and heart disease patients: randomized controlled trial. *J Med Internet Res* (2015) 17(6):e153. doi: 10.2196/jmir.4059

36. Sherifali D. Diabetes coaching for individuals with type 2 diabetes: A state-of-the-science review and rationale for a coaching model. *[Review]* (2017) 1 (6):547–54. doi: 10.1111/1753-0407.12528

37. Odnoletkova I, Buysse H, Nobels F, Goderis G, Aertgeerts B, Annemans L, et al. Patient and provider acceptance of telecoaching in type 2 diabetes: a mixed-method study embedded in a randomised clinical trial. *BMC Med Inf Decision Making.* (2016) 16:142–. doi: 10.1186/s12911-016-0383-3

38. Radwan NM, Al Khashan H, Alamri F, El Olemy AT. Effectiveness of health coaching on diabetic patients: A systematic review and meta-analysis. (Edinburgh, Scotland: WDEC 2020, 2nd World Congress on Diabetes and Endocrinology) (2019).

39. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* (2010) 340:c332. doi: 10.1136/bmj.c332

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 16 January 2023
DOI 10.3389/fendo.2022.1019390

OPEN ACCESS

EDITED BY
Lingling Xu,
Peking Union Medical College Hospital (CAMS), China

REVIEWED BY
Yoshifumi Saisho,
Saisho Diabetes Clinic, Japan
Shinya Furukawa,
Ehime University, Japan

*CORRESPONDENCE
Hiroshi Okada
conti@koto.kpu-m.ac.jp

SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 15 August 2022
ACCEPTED 28 December 2022
PUBLISHED 16 January 2023

CITATION
Matsui T, Okada H, Hamaguchi M, Kurogi K, Murata H, Ito M and Fukui M (2023) The association between the reduction of body weight and new-onset type 2 diabetes remission in middle-aged Japanese men: Population-based Panasonic cohort study 8.
Front. Endocrinol. 13:1019390.
doi: 10.3389/fendo.2022.1019390

The association between the reduction of body weight and new-onset type 2 diabetes remission in middle-aged Japanese men: Population-based Panasonic cohort study 8

Takaaki Matsui[1], Hiroshi Okada[1,2]*, Masahide Hamaguchi[1], Kazushiro Kurogi[3], Hiroaki Murata[4], Masato Ito[3] and Michiaki Fukui[1]

[1]Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan, [2]Department of Diabetes and Endocrinology, Matsushita Memorial Hospital, Moriguchi, Japan, [3]Department of Health Care Center, Panasonic Health Insurance Organization, Moriguchi, Japan, [4]Department of Orthopaedic Surgery, Matsushita Memorial Hospital, Moriguchi, Japan

Aim: This study aimed to investigate the association between change in body weight (BW) and type 2 diabetes remission in Japanese men with new-onset type 2 diabetes.

Methods: This study enrolled 1,903 patients with new-onset type 2 diabetes between 2008 and 2013 from a medical health checkup program conducted by the Panasonic Corporation, Osaka, Japan. The baseline was defined as the year of new-onset diabetes. We assessed the type 2 diabetes remission five years after baseline and the association between the change in BW and type 2 diabetes remission using logistic regression analyses. To evaluate the predictive performance of the change in BW, we employed the receiver operating characteristic curves and the area under the receiver operating characteristic (ROC) curve (AUC).

Results: The BW loss was associated with type 2 diabetes remission in the participants with a BMI ≥25 kg/m^2 but not in the participants with a BMI <25 kg/m^2. The odds ratios were 1.96 (95% CI: 1.19–3.29) and 3.72 (95% CI: 2.14–6.59) in the participants with a loss of 5–9.9% and loss of ≥10% for five years, respectively, in the participants with a BMI ≥25 kg/m^2 (reference; stable group [0.9% gain to 0.9% loss]). The AUC and cut-off values for the rate of change in BW for type 2 diabetes remission were 0.59 and 5.0%.

Discussion: Body weight loss of ≥5% effectively achieved diabetes remission in Japanese men with a BMI ≥25 kg/m^2 and new-onset type 2 diabetes.

KEYWORDS

type 2 diabetes, body weight loss, diabetes remission, medical health checkup, obesity

Introduction

There are several well-known risk factors for the onset of diabetes in the Japanese population, such as hyperlipidemia, hypertension, aging, weight gain, smoking history, impaired glucose tolerance (IGT), and family history (1–8). One of the goals in clinical care is the prevention of diabetes by focusing on these risk factors. However, in recent decades, the number of patients with diabetes and medical costs of diabetes have been increasing worldwide. Therefore, diabetes remission is as important as diabetes prevention.

Several Japanese studies have reported the association between body weight loss and diabetes prevention in patients with IGT. Kosaka et al. (9) conducted an intervention trial on whether body weight reduction by diet and exercise could prevent progression to diabetes among male patients with IGT in an outpatient clinic. Their study showed that the reduction in risk of diabetes was 67.4% lower in the intervention group than in the control group, and body weight loss was higher in the intervention group than in the control group (loss of 2.18 kg versus 0.39 kg) for 4 years. Kawahara et al. (10) conducted an intervention trial on whether a short-term hospital program of diabetes education could prevent progression to diabetes in patients with IGT. They reported that the incidence of diabetes was 42% lower in the intervention group than in the control group for 3 years. They also observed that body weight loss was higher in the intervention group than in the control group (loss of 2.1 kg versus gain of 0.4 kg). Furthermore, Saito et al. (11) conducted an intervention trial involving patients with IGT in an outpatient clinic. They reported that the risk of incident diabetes was 59% lower in the intervention group than that in the control group and that body weight loss was higher in the intervention group than in the control group (loss of 2.5 kg versus 1.1 kg). Thus, the association between body weight loss and prevention of type 2 diabetes in patients with IGT might be obvious. However, to our knowledge, there are no studies that assessed the association between change in body weight and diabetes remission in Japanese patients with type 2 diabetes. The findings of such studies may help in setting strategies to achieve type 2 diabetes remission. This is the first study to investigate the association between change in body weight and type 2 diabetes remission in Japanese men with new-onset type 2 diabetes.

Materials and methods

Study design and data collection

This retrospective cohort study included participants of a physical examination program at Panasonic Corporation, Osaka, Japan. This study was named Panasonic cohort study and used 2008–2018 data from Panasonic Corporation's database. All the participants partook in the physical examination program yearly from 2008 to 2018. The baseline was defined as the year of new-onset diabetes. The participants' baseline characteristics were evaluated using a self-administered questionnaire. The participants were classified into current smokers, past smokers, and non-smokers based on smoking habits. The participants who regularly practiced any sport twice a week for more than one year were classified as regular exercisers.

The study was approved by the local ethics committee of Panasonic Health Insurance Organization (Approval number: 2021-001) and was conducted in accordance with the principles of the Declaration of Helsinki.

Change in body weight

Body weight and height of all participants were recorded using an automatic machine yearly. We collected body weight five years after baseline to evaluate the change in this variable. Change in body weight was calculated as follows: body weight five years after baseline – body weight at baseline. The rate of change in body weight (%) was calculated as follows: (body weight five years after baseline – body weight at baseline) × 100/body weight at baseline.

Definitions of onset and remission of type 2 diabetes

Participants with a fasting plasma glucose concentration ≥126 mg/dL and/or who were on antihyperglycemic medication were considered as having type 2 diabetes. Participants with a fasting plasma glucose concentration <126 mg/dL and who were not taking antihyperglycemic medication were considered as having type 2 diabetes remission. We calculated the incidence of new-onset type 2 diabetes between 2008 and 2013 among the participants who did not have diabetes in 2008 and type 2 diabetes remission five years after baseline to evaluate the association between the change in body weight and type 2 diabetes remission in the participants with new-onset type 2 diabetes.

Exclusion criteria

Overall, 84,997 men partook in the physical examination program in 2008. We excluded the participants with diabetes in 2008 (n = 4943). Of 80,054 men without diabetes in 2008, 3,264 men developed type 2 diabetes between 2008 and 2013. Of 3,264 men with new-onset type 2 diabetes, we excluded 1361 men who did not partake in the physical examination program five years after baseline. The final analysis involved the data of 1,903 men with new-onset diabetes between 2008 and 2013.

Statistical analyses

The differences in the general characteristics at baseline (the year of new-onset diabetes) according to the type 2 diabetes remission were evaluated using Student's t-test and chi-square test, as appropriate. The association between the change in body weight and type 2 diabetes remission was assessed by logistic regression analyses. The multivariate analysis was adjusted for the factors related to type 2 diabetes, such as body mass index (BMI), age, systolic blood pressure (SBP), serum high-density lipoprotein (HDL) cholesterol concentrations, serum low-density lipoprotein (LDL) cholesterol concentrations, serum triglycerides concentrations, serum fasting plasma glucose concentrations, serum uric acid concentrations, smoking status, physical exercise habits, and change in body

weight. The categorical values of the change in body weight and the rate of change in body weight were added into multivariate models to assess the association between categorical values and type 2 diabetes remission. The five groups according to change in body weight (gain [≥ 1 kg gain], stable [0.9 kg gain to 0.9 kg loss], loss of 1–4.9 kg, loss of 5–9.9 kg, and loss of ≥10 kg) and the rate of change in body weight (gain [≥ 1% gain], stable [0.9% gain to 0.9% loss], loss of 1–4.9%, loss of 5–9.9%, and loss of ≥10%) were added to the multivariate analyses of data of all the participants and participants with obesity (BMI ≥25 kg/m^2) at baseline, respectively. The four groups according to change in body weight (gain [≥ 1 kg gain], stable [0.9 kg gain to 0.9 kg loss], loss of 1–4.9 kg, and loss of ≥5 kg) and the rate of change in body weight (gain [≥ 1% gain], stable [0.9% gain to 0.9% loss], loss of 1–4.9%, and loss of ≥5%) were added to the multivariate analyses of data of non-obese participants (BMI <25 kg/m^2) at baseline, respectively. A receiver operating characteristic curve analysis was performed for change in body weight to assess the ability to identify patients with type 2 diabetes remission. We used JMP software (SAS Institute, NC, USA) to performe all statistical analyses. Continuous variables are expressed as mean ± standard deviation or absolute numbers. P values <0.05 were considered statistically significant. The associations are presented as hazard ratios with 95% confidence intervals (CIs).

Results

The baseline characteristics of all the participants with new-onset type 2 diabetes are shown in Table 1. In total, 619 participants (32.5%) had type 2 diabetes remission five years after baseline. In the participants with a BMI ≥25 kg/m^2 and BMI < 25 kg/m^2, 298 (27.1%) and 321 (40.0%) participants had type 2 diabetes remission five years after baseline. The average change in body weight was -2.3 ± 4.9 kg, -3.3 ± 5.5 kg, and -0.9 ± 3.8 kg in the overall participants, participants with BMI ≥25 kg/m^2, and participants with BMI <25 kg/m^2. The proportions of participants with type 2 diabetes remission in the overall study population are shown in Figures 1 and 2. The proportion of type 2 diabetes remission varied with the degree of change in body weight loss in the overall participants and the participants with a BMI ≥25 kg/m^2.

The unadjusted and adjusted odds ratios in the multivariate models for type 2 diabetes remission are shown in Table 2. For every 1 kg reduction in body weight for 5 years, the odds ratio of type 2 diabetes remission increased by 6% in the overall participants. The adjusted odds ratios in the multivariate models for type 2 diabetes remission according to BMI category are shown in Table 3. For every 1 kg reduction in body weight for 5 years, the odds ratio of type 2 diabetes remission increased by 9% in the participants with a BMI ≥25 kg/m^2. Conversely, the degree of reduction in body weight was not associated with type 2 diabetes remission in the participants with a BMI <25 kg/m^2. The BMI, LDL cholesterol, fasting plasma glucose, and smoking habit were associated with type 2 diabetes remission in the participants with a BMI <25 kg/m^2.

The multiple adjusted odds ratios of change in body weight and rate of change in body weight according to the categorical values for type 2 diabetes remission with the body weight stable group as reference are shown in Figures 1 and 2. In the participants with a BMI ≥25 kg/m^2, the odds ratios were 2.05 (95% CI, 1.27–3.36; P = 0.003) and 4.50 (95% CI, 2.46–8.32; P <0.0001) in the participants with a loss of 5–9.9 kg and ≥10 kg, respectively. In the participants with a BMI <25 kg/m^2, change in body weight, and rate of change in body weight was not associated with type 2 diabetes remission. The results were almost identified with the change in body weight when we evaluated odds ratios regarding the rate of change in body weight. When diabetes remission was defined as < 110mg/dl, the results was almost same as definition of diabetes remission < 126 mg/dl. In the participants with a BMI ≥25 kg/m^2, the odds ratios were 7.96 (95% CI, 3.72–17.69; P < 0.0001) in the participants with a loss of ≥10 kg. When diabetes remission was defined as < 110mg/dl, change in body weight was not associated with type 2 diabetes remission in the participants with a BMI <25 kg/m^2.

TABLE 1 Characteristics of participants at baseline according to type 2 diabetes remission.

	All	Remission of diabetes (-)	Remission of diabetes (+)	P value
N	1,903	1,284	619	–
Age (y)	48.3 (5.3)	48.3 (5.0)	48.1 (5.8)	0.35
Body mass index (kg/m^2)	26.3 (4.2)	26.8 (4.2)	25.1 (4.0)	<0.0001
Systolic blood pressure (mmHg)	128.0 (14.5)	128.2 (14.7)	127.5 (14.2)	0.29
Diastolic blood pressure (mmHg)	81.5 (10.4)	82.0 (10.3)	80.5 (10.5)	0.004
LDL cholesterol (mg/dL)	134.0 (33.8)	137.0 (33.0)	127.7 (34.5)	<0.0001
HDL cholesterol (mg/dL)	51.9 (12.8)	50.9 (12.2)	54.1 (13.9)	<0.0001
Triglycerides (mg/dL)	184.9 (154.6)	188.7 (144.5)	177.0 (173.4)	0.12
Glucose (mg/dl)	136.6 (25.4)	138.4 (28.4)	132.9 (17.1)	<0.0001
Uric acid (mg/dL)	6.1 (1.5)	6.2 (1.4)	6.1 (1.7)	0.41
Smoking (none/past/current)	714/412/777	468/283/533	246/129/244	0.38
Physical exercise (+/-)	342/1561	232/1,052	110/509	0.87

Data are presented as mean (standard deviation) or absolute number.
LDL, low-density lipoprotein; HDL, high-density lipoprotein.

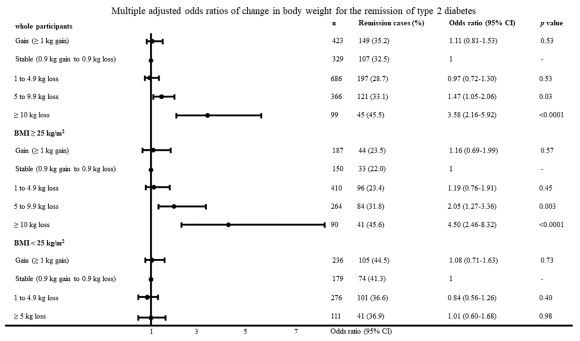


FIGURE 1
Multiple adjusted odds ratios of change in body weight for the remission of type 2 diabetes adjusted for age, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, fasting plasma glucose, uric acid, smoking habit and physical activity.

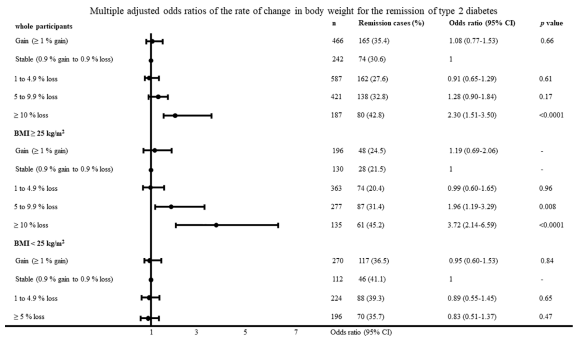


FIGURE 2
Multiple adjusted odds ratios of change in body weight for the remission of type 2 diabetes adjusted for age, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, fasting plasma glucose, uric acid, smoking habit and physical activity.

The area under the curve and cut-off values of the change in body weight and rate of change in body weight for type 2 diabetes remission were 0.58 and 3.9 kg loss, and 0.59 and 5.0% loss in the participants with a BMI ≥25 kg/m^2, respectively.

Discussion

This study assessed the association between the change in body weight and type 2 diabetes remission in participants with new-onset diabetes. The major findings of our study were as follows: (1) body weight loss was associated with new-onset type 2 diabetes remission in the participants with a BMI ≥25 kg/m^2 (obese) but not in the participants with a BMI <25 kg/m^2 (non-obese); and (2) in patients with a BMI ≥25 kg/m^2 (obese), a body weight loss of ≥3.9 kg or ≥5.0% might be effective for new-onset type 2 diabetes remission. Our findings are largely consistent with the guidelines of the Japan Society for the Study of Obesity, which recommends a body weight loss of ≥3.0% in the participants with a 25 ≤ BMI < 35 kg/m^2 and a body weight loss of ≥5.0% in the participants with a BMI ≥35 kg/m^2.

Body weight is strongly associated with the development of diabetes in Western people and Japanese people (12). Several studies have reported the association between body weight loss and diabetes remission. The Diabetes Remission Clinical Trial (DiRECT) was conducted to assess effective body weight management for diabetes remission (13). DiRECT showed that almost half of the participants achieved diabetes remission at 12 months in the intervention group, whose average body weight loss was −10.0 ± 8.0 kg (13). However, because eligible participants in DiRECT had a BMI of ≥27 kg/m^2, it is unclear whether those findings were similar to persons with a BMI <27 kg/m^2. An observational study in Scotland reported that more than 5 kg of body weight loss was associated with

TABLE 2 Unadjusted and adjusted odds ratios for type 2 diabetes remission.

	Crude		Multiple	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age (per 10years)	0.92 (0.76-1.10)	0.35	0.72 (0.59-0.88)	0.001
Body mass index (per 1kg/m^2)	0.90 (0.88-0.92)	<0.0001	0.89 (0.86-0.92)	<0.0001
Systolic blood pressure (per 10mmHg)	0.96 (0.90-1.03)	0.29	1.03 (0.96-1.11)	0.41
LDL cholesterol (per 10mg/dl)	0.92 (0.89-0.95)	<0.0001	0.93 (0.90-0.96)	<0.0001
HDL cholesterol (per 10mg/dl)	1.20 (1.12-1.30)	<0.0001	1.08 (0.99-1.18)	0.08
Triglycerides (per 10mg/dl)	0.995 (0.99-1.001)	0.11	0.999 (0.99-1.007)	0.87
Glucose (per 10mg/dl)	0.90 (0.85-0.94)	<0.0001	0.91 (0.86-0.96)	0.0001
Uric acid (per 1mg/dl)	0.97 (0.91-1.04)	0.41	1.02 (0.95-1.09)	0.59
Change in body weight (per 1kg loss)	1.02 (0.999-1.04)	0.06	1.06 (1.04-1.08)	<0.0001
Smoking (past) (ref: none)	0.87 (0.67-1.12)	0.28	0.82 (0.62-1.07)	0.14
Smoking (current) (ref: none)	0.87 (0.70-1.08)	0.21	0.83 (0.66-1.05)	0.12
Physical exercise (yes) (ref: no)	0.98 (0.76-1.23)	0.87	0.91 (0.70-1.18)	0.48

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

10.3389/fendo.2022.1019390

TABLE 3 Adjusted odds ratios for type 2 diabetes remission according to BMI category.

	BMI ≥ 25 kg/m^2 (n = 1,101)		BMI < 25 kg/m^2 (n = 802)	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age (per 10years)	0.70 (0.53-0.92)	0.01	0.77 (0.57-1.03)	0.08
Body mass index (per 1kg/m^2)	0.89 (0.85-0.94)	<0.0001	0.80 (0.73-0.88)	<0.0001
Systolic blood pressure (per 10mmHg)	0.99 (0.89-1.10)	0.84	1.08 (0.98-1.20)	0.13
LDL cholesterol (per 10mg/dl)	0.93 (0.89-0.97)	0.002	0.93 (0.89-0.98)	0.002
HDL cholesterol (per 10mg/dl)	1.18 (1.02-1.36)	0.02	1.002 (0.89-1.12)	0.98
Triglycerides (per 10mg/dl)	0.998 (0.99-1.008)	0.70	1.002 (0.99-1.01)	0.65
Glucose (per 10mg/dl)	0.90 (0.83-0.97)	0.005	0.91 (0.84-0.97)	0.004
Uric acid (per 1mg/dl)	1.04 (0.94-1.14)	0.47	1.03 (0.93-1.15)	0.57
Change in body weight (per 1kg loss)	1.09 (1.06-1.12)	<0.0001	0.99 (0.95-1.03)	0.57
Smoking (past) (ref: none)	0.88 (0.60-1.27)	0.49	0.72 (0.48-1.08)	0.11
Smoking (current) (ref: none)	0.95 (0.69-1.32)	0.78	0.68 (0.49-0.97)	0.03
Physical exercise (yes) (ref: no)	0.91 (0.62-1.32)	0.63	0.87 (0.59-1.26)	0.46

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

diabetes remission (14). The strengths of their study were that it involved the Western population in general and used data from their register that included information of 99% of the patients with diabetes in their country. We should consider ethnic differences in diabetes etiology. It has been reported that the BMI cut-off value for incident type 2 diabetes was lower in the Asian population than in the Western population (15). The mean BMI was 35.1 ± 4.5 kg/m^2 in DiRECT, and the median BMI was 30.9 (27.4-35.3) kg/m^2 in the Scottish study; their findings are not applicable to Asian people. Moreover, it might be difficult for participants to achieve a body weight loss of 10 kg in 1 year in a clinical care setting. Therefore, our findings can address the target body weight loss in Japanese in a clinical care setting.

Interestingly, 619 (32.5%) participants achieved type 2 diabetes remission in this study. This rate of remission was higher than that in a Western population (the Scottish study). This might be due to the difference in BMI from the Western population and whether the participants had no new-onset or new-onset diabetes, which could be more prone to remission. A proportion of 42.1% of the participants in our study had a BMI <25.0 kg/m^2 (non-obese). As expected, in these participants, body weight loss was not associated with new-onset type 2 diabetes remission. The findings in participants with a BMI <25.0 kg/m^2 might be due to diminished insulin secretion, which is characteristic of patients with diabetes in Asian countries (16). In the participants with a BMI <25.0 kg/m^2, lipid disorder, increased plasma glucose concentration, and smoking habits might be more important than the change in body weight in new-onset type 2 diabetes remission. A body weight loss in participants with a BMI <25.0 kg/m^2 might be associated with the comorbidity including malignancy, resulting in no improvement of diabetes remission. We found ten patients who have malignancy both in participants with BMI <25 kg/m^2 and with BMI ≥25 kg/m^2. Our results were almost the same when the participants with malignancy were excluded.

It has been proposed that the development of diabetes is triggered by insulin resistance, which eventually leads to the exhaustion of pancreatic β cells (17). Obesity reportedly induces chronic inflammation (18) and insulin resistance (19, 20), which is partly attributed to the dysregulation of adipocytokines such as tumor necrosis factor-α, adiponectin, leptin, and plasminogen activator inhibitor-1 (21, 22). The increased visceral adipose tissue, causing the adipocytes to produce more tumor necrosis factor-α and less adiponectin is associated with weight gain. It has been reported that body weight loss beneficially affects adipocytokines (23). Hence, participants with a BMI ≥25 kg/m^2 and new-onset diabetes needed to lose body weight in the early disease stage to achieve type 2 diabetes remission.

The strengths of our study include its long follow-up period, real-world nature, and consecutive enrolment. However, this study had several limitations. First, in general, the diagnosis is mainly judged by plasma glucose and HbA1c. The diabetes remission is mainly defined as HbA1c below the level of 6.5% and remaining at that level for at least 3 months without continuation of the usual antihyperglycemic medication (24). However, diagnosis and remission of diabetes were judged only by fasting plasma glucose level and use of antihyperglycemic medication, but not HbA1c. Second, change in body composition rather than body weight may be more important for remission (25). However, we have no data about body composition. Thirdly, education on diabetes could have affected the rate of diabetes remission; however, we had no such data. Lastly, our study population was made up of relatively young Japanese men. We have no data in elder participants because our data was derived from cohort of a physical examination program at Panasonic Corporation. Therefore, it is unclear whether our findings are generalizable to women, other ethnic groups and age groups.

In conclusion, our study found that a body weight loss of ≥3.9 kg or ≥5.0% effectively achieved diabetes remission in Japanese men with a BMI ≥25 kg/m^2 and new-onset type 2 diabetes. Therefore, it is important to focus on early body weight loss in participants with a BMI ≥25 kg/m^2 and new-onset diabetes in clinical settings to achieve diabetes remission.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

TM wrote this manuscript. KK, MH, and HM contributed to the discussion. HO analyzed the data. HO and MI collected the data and contributed to the design and discussion. HO and MF edited and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

We thank Kenya Kasahara, Moe Horiuchi, Shinta Yamamoto, Taro Hirozane, Akifumi Shiota, Nozomi Yoshioka, Tomoyuki Matsuyama, Momoko Habu and Yoshitaka Hashimoto for their assistance in this study.

Funding

This study was funded by Osaka foundation for the prevention of cancer and cardiovascular disease.

Conflict of interest

HO received personal fees from Kowa Pharma Co. Ltd; Novo Nordisk Pharma Ltd.; Sumitomo Dainippon Pharma Co. Ltd and Eli Lilly, Japan, outside work. MH received grants from Yamada Bee Farm, AstraZeneca K.K. and Oishi Kenko Inc.; and received personal fees from Eli Lilly, Japan; AstraZeneca K.K.; Daiichi Sankyo Co. Ltd.; Ono Pharma Co. Ltd., Kowa Pharma Co. Ltd.; Mitsubishi Tanabe Pharma Corp., Sanofi K.K., and Sumitomo Dainippon Pharma Co. Ltd., outside the submitted work. MF received grants from Terumo Corp.; Yamada Bee Farm; Kowa Pharma Co. Ltd.; Taiyo Kagaku Co., Ltd; Nippon Boehringer Ingelheim Co. Ltd.; Novo Nordisk Pharma Ltd.; Sanofi K.K.; Kissei Pharma Co. Ltd.; MSD K.K.; Taisho Pharma Co. Ltd.; Abbott Japan Co. Ltd.; Daiichi Sankyo Co. Ltd.; Kyowa Kirin Co. Ltd.; Oishi Kenko Inc.; Sumitomo Dainippon Pharma Co. Ltd.; Eli Lilly, Japan, K.K.; Nippon Chemiphar Co. Ltd.; Astellas Pharma Inc.; Sanwa Kagagu Kenkyusho Co. Ltd.; Tejin Pharma Ltd.; Mitsubishi Tanabe Pharma Corp.; and Johnson & Johnson K.K. Medical Co.; and received personal fees from Kissei Pharma Co., Ltd.; Mitsubishi Tanabe Pharma Corp.; Ono Pharma Co. Ltd.; AstraZeneca K.K.; Novo Nordisk Pharma Ltd.; Kyowa Kirin Co. Ltd.; Astellas Pharma Inc.; Daiichi Sankyo Co. Ltd.; Mochida Pharma Co. Ltd.; Eli Lilly, Japan K.K.; Taisho Pharma Co. Ltd.; Sanwa Kagaku Kenkyusho Co. Ltd.; Medtronic Japan Co. Ltd.; Bayer Yakuhin Ltd.; Teijin Pharma Ltd.; Nipro Corp.; Sanofi K.K.; Nippon Boehringer Ingelheim Co. Ltd.; Arkray Inc.; MSD K.K.; Kowa Pharma Co. Ltd.; Sumitomo Dainippon Pharma Co. Ltd.; and Abbott Japan Co. Ltd., outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Publisher's note

References

1. Doi Y, Ninomiya T, Hata J, Hirakawa Y, Mukai N, Iwase M, et al. Two risk score models for predicting incident type 2 diabetes in Japan. *Diabetes Med* (2012) 29:107–14. doi: 10.1111/j.1464-5491.2011.03376.x

2. Noda M, Kato M, Takahashi Y, Matsushita Y, Mizoue T, Inoue M, et al. Fasting plasma glucose and 5-year incidence of diabetes in the JPHC diabetes study - suggestion for the threshold for impaired fasting glucose among Japanese. *Endocr J* (2010) 57:629–37. doi: 10.1507/endocrj.k10e-010

3. Heianza Y, Arase Y, Hsieh SD, Saito K, Tsuji H, Kodama S, et al. Development of a new scoring system for predicting the 5 year incidence of type 2 diabetes in Japan: the toranomon hospital health management center study 6 (TOPICS 6). *Diabetologia* (2012) 55:3213–23. doi: 10.1007/s00125-012-2712-0

4. Mukai N, Doi Y, Ninomiya T, Hata J, Hirakawa Y, Fukuhara M, et al. Cut-off values of fasting and post-load plasma glucose and HbA1c for predicting type 2 diabetes in community-dwelling Japanese subjects: the hisayama study. *Diabetes Med* (2012) 29:99–106. doi: 10.1111/j.1464-5491.2011.03378.x

5. Heianza Y, Arase Y, Fujihara K, Hsieh SD, Saito K, Tsuji H, et al. Longitudinal trajectories of HbA1c and fasting plasma glucose levels during the development of type 2 diabetes: the toranomon hospital health management center study 7 (TOPICS 7). *Diabetes Care* (2012) 35:1050–2. doi: 10.2337/dc11-1793

6. Nanri A, Nakagawa T, Kuwahara K, Yamamoto S, Honda T, Okazaki H, et al. Development of risk score for predicting 3-year incidence of type 2 diabetes: Japan epidemiology collaboration on occupational health study. *PloS One* (2015) 10:e0142779. doi: 10.1371/journal.pone.0142779

7. Heianza Y, Hara S, Arase Y, Saito K, Fujiwara K, Tsuji H, et al. HbA1c 5·7-6·4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. *Lancet* (2011) 378:147–55. doi: 10.1016/S0140-6736(11)60472-8

8. Saijo Y, Okada H, Hamaguchi M, Habu M, Kurogi K, Murata H, et al. The risk factors for development of type 2 diabetes: Panasonic cohort study 4. *Int J Environ Res Public Health* (2022) 19:571. doi: 10.3390/ijerph19010571

9. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. *Diabetes Res Clin Pract* (2005) 67:152–62. doi: 10.1016/j.diabres.2004.06.010

10. Kawahara T, Takahashi K, Inazu T, Arao T, Kawahara C, Tabata T, et al. Reduced progression to type 2 diabetes from impaired glucose tolerance after a 2-day in-hospital diabetes educational program: the joetsu diabetes prevention trial. *Diabetes Care* (2008) 31:1949–54. doi: 10.2337/dc07-2272

11. Saito T, Watanabe M, Nishida J, Izumi T, Omura M, Takagi T, et al. Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. *Arch Intern Med* (2011) 171:1352–60. doi: 10.1001/archinternmed.2011.275

12. Maskarinec G, Erber E, Grandinetti A, Verheus M, Oum R, Hopping BN, et al. Diabetes incidence based on linkages with health plans: the multiethnic cohort. *Diabetes* (2009) 58:1732–8. doi: 10.2337/db08-1685

13. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* (2018) 391:541–51. doi: 10.1016/S0140-6736(17)33102-1

14. Captieux M, Fleetwood K, Kennon B, Sattar N, Lindsay R, Guthrie B, et al. Epidemiology of type 2 diabetes remission in Scotland in 2019: A cross-sectional

population-based study. *PloS Med* (2021) 18:e1003828. doi: 10.1371/journal.pmed.1003828

15. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. *Diabetes Care* (2011) 34:1741–8. doi: 10.2337/dc10-2300

16. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* (2007) 298:2654–64. doi: 10.1001/jama.298.22.2654

17. Ogihara T, Mirmira RG. An islet in distress: β cell failure in type 2 diabetes. *J Diabetes Investig* (2010) 1:123–33. doi: 10.1111/j.2040-1124.2010.00021.x

18. Tokunaga K, Matsuzawa Y, Kotani K, Keno Y, Kobatake T, Fujioka S, et al. Ideal body weight estimated from the body mass index with the lowest morbidity. *Int J Obes* (1991) 15:1–5.

19. Campbell PJ, Carlson MG. Impact of obesity on insulin action in NIDDM. *Diabetes* (1993) 42:405–10. doi: 10.2337/diab.42.3.405

20. Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G. Relationship between degree of obesity and *in vivo*insulin action in man. *Am J Physiol* (1985) 248:E286–91. doi: 10.1152/ajpendo.1985.248.3.E286

21. Esteve E, Ricart W, Fernández-Real JM. Adipocytokines and insulin resistance: the possible role of lipocalin-2, retinol binding protein-4, and adiponectin. *Diabetes Care* (2009) 32(Suppl 2):S362–7. doi: 10.2337/dc09-S340

22. Lorenzo M, Fernández-Veledo S, Vila-Bedmar R, Garcia-Guerra L, De Alvaro C, Nieto-Vazquez I. Insulin resistance induced by tumor necrosis factor-alpha in myocytes and brown adipocytes. *J Anim Sci* (2008) 86(14):E94–E104. doi: 10.2527/jas.2007-0462

23. Salehi-Abargouei A, Izadi V, Azadbakht L. The effect of low calorie diet on adiponectin concentration: a systematic review and meta-analysis. *Horm Metab Res* (2015) 47:549–55. doi: 10.1055/s-0035-1549878

24. Riddle MC, Cefalu WT, Evans PH, Gerstein HC, Nauck MA, Oh WK, et al. Consensus report: Definition and interpretation of remission in type 2 diabetes. *Diabetes Care* (2021) 44:2438–44. doi: 10.2337/dci21-0034

25. Haines MS, Leong A, Porneala BC, Meigs JB, Miller KK. Association between muscle mass and diabetes prevalence independent of body fat distribution in adults under 50 years old. *Nutr Diabetes*. (2022) 12:29. doi: 10.1038/s41387-022-00204-4

frontiers | Frontiers in Public Health

TYPE Methods
PUBLISHED 30 January 2023
DOI 10.3389/fpubh.2023.1061383

OPEN ACCESS

EDITED BY
Edward Zimbudzi,
Monash University, Australia

REVIEWED BY
Zulfiqarali Abbas,
Muhimbili University of Health and Allied Sciences, Tanzania
Michael Edwin Edmonds,
King's College Hospital NHS Foundation Trust, United Kingdom

*CORRESPONDENCE
Liliana B. Sousa
baptliliana@esenfc.pt

SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Public Health

RECEIVED 04 October 2022
ACCEPTED 06 January 2023
PUBLISHED 30 January 2023

CITATION
Sousa LB, Almeida I, Bernardes RA, Leite TR, Negrão R, Apóstolo J, Salgueiro-Oliveira A and Parreira P (2023) A three step protocol for the development of an innovative footwear (shoe and sensor based insole) to prevent diabetic foot ulceration.
Front. Public Health 11:1061383.
doi: 10.3389/fpubh.2023.1061383

A three step protocol for the development of an innovative footwear (shoe and sensor based insole) to prevent diabetic foot ulceration

Liliana B. Sousa[1]*, Inês Almeida[1], Rafael A. Bernardes[1], Teófilo R. Leite[2], Rui Negrão[1], João Apóstolo[1], Anabela Salgueiro-Oliveira[1] and Pedro Parreira[1]

[1]Health Sciences Research Unit, Nursing (UICISA: E), Nursing School of Coimbra (ESEnfC), Coimbra, Portugal, [2]Indústrias e Comércio de Calçado S. A. (ICC), Sol-Pinheiro, Guimarães, Portugal

Background: The incidence of diabetic foot ulceration (DFU) is increasing worldwide. Therapeutic footwear is usually recommended in clinical practice for preventing foot ulcers in persons with diabetes. The project Science DiabetICC Footwear aims to develop innovative footwear to prevent DFU, specifically a shoe and sensor-based insole, which will allow for monitoring pressure, temperature, and humidity parameters.

Method: This study presents a three-step protocol for the development and evaluation of this therapeutic footwear, specifically: (i) a first observational study will specify the user requirements and contexts of use; (ii) after the design solutions were developed for shoe and insole, the semi-functional prototypes will be evaluated against the initial requirements; (iii) and a pre-clinical study protocol will enable the evaluation of the final functional prototype. The eligible diabetic participants will be involved in each stage of product development. The data will be collected using interviews, clinical evaluation of the foot, 3D foot parameters and plantar pressure evaluation. This three-step protocol was defined according to the national and international legal requirements, ISO norms for medical devices development, and was also reviewed and approved by the Ethics Committee of the Health Sciences Research Unit: Nursing (UICISA: E) of the Nursing School of Coimbra (ESEnfC).

Results: The involvement of end-users (diabetic patients) will enable the definition of user requirements and contexts of use to develop design solutions for the footwear. Those design solutions will be prototyped and evaluated by end-users to achieve the final design for therapeutic footwear. The final functional prototype will be evaluated in pre-clinical studies to ensure that the footwear meets all the requirements to move forward to clinical studies.

Discussion: The three-step study outlined in this protocol will provide the necessary insights during the product development, ensuring this new therapeutic footwear's main functional and ergonomic features for DFU prevention.

KEYWORDS

diabetic foot ulcers (DFUs), prevention, footwear, shoes, sensor-based insoles

1. Introduction

Diabetes mellitus (DM) is considered one of the most impactful non-communicable diseases (NCD) affecting public health at a global level (1). In 2014, according to World Health Organization, almost 422 million adults worldwide were struggling with DM, following the trend registered in the last 36 years (2). In Europe, around 9.1% of the population presents DM diagnosis (3). In this context, the International Diabetes Foundation (4) estimates an increase in the diagnostics of DM by around 52% worldwide and 15% in Europe until 2045. According to the same document, in Portugal, between the age of 20 to 79 years old, DM has an approximate prevalence of 14.2%, which means a ratio of 1:7. According to Liu et al. (1), the worldwide increase in DM has been driven by global aging, economic growth, rapid urbanization, and nutritional transitions worldwide.

Although DM is a commonly referred disorder focused on by researchers and clinicians, the prevalence of undiagnosed cases is still high (5). The untreated DM threatens public health, accelerating comorbidity of micro and macrovascular complications, like neuropathies, retinopathies, deformities, and hampering future preventive measures (6). One of the most severe comorbidities is diabetic foot ulcers (DFU), which are usually associated with the loss of protecting sensibility, foot deformities, and the absence of foot pulses. The DFU is considered a common cause of amputation of inferior limbs (7). In fact, according to the same authors, DFU and amputations, which are consequences of diabetic neuropathy and/or peripheral arterial disease (PAD), are common and represent major causes of morbidity and mortality in people with DM. Early recognition and treatment of signs and symptoms in patients with DM, namely at the feet, is essential to delay or prevent these complications. It follows that appropriate therapeutic footwear and other wearable devices assume an indispensable role when prevention and treatment of DFU are clinical priorities (8–11).

Developing the devices mentioned above, with an application in a specific population with a particular need, receives clear contributions and necessary inputs from its end-user (the person with DM). Recent studies have proven that the efficacy of therapeutic interventions and devices can be improved with patients' and families' involvement in the whole process (12–14). In DM management and DFU prevention, footwear and related wearable devices, like insoles, can be considered medical devices with specific therapeutic or preventive goals. Intelligent devices and new technology has been highlighted to improve illness management and quality of life (15), mainly when patients are involved in their development (16, 17). In this sense, Human-Centred Design (HCD) is one of the most used methods that involve the user in the development process, according to the international directives (18, 19). Those directives were adapted in 2007 in Europe regarding the harmonized human factors and ergonomics standards for the analysis, design, verification and validation of safety-related usability through the medical device development cycle (20). The HCD model can be implemented to define, and design devices based on specific functional requirements and end users' needs (21). This method can predict potential usability errors due to ergonomic features, ensuring essential parameters related to human factors. In conclusion, this model improves safety, satisfaction, effectiveness and efficiency while reducing product recalls and modifications (22–25). In the last few years, the Technology Readiness Level (TRL) was reviewed to consider the technology's readiness for human support, human performance, ease of use, and user satisfaction (26). The Human Readiness Level (HRL) is used as a counterpart of the TRL to identify the level of readiness or maturity of a given technology concerning the use by intended users in the intended operational environment (26, 27). According to the HRL, different types of user research can be used during product development to identify improvement opportunities and minimize human error from the early stages of the design (26, 27).

The project *Science DiabetICC Footwear* aims to develop innovative, customized, and affordable footwear for DFU prevention. This product will have distinctive critical characteristics, such as new materials, better impact absorption, shape adjustment, minor abrasion, and greater recovery after loading. Also, the insole will incorporate sensors for assessing and monitoring essential parameters such as plantar pressure, temperature, and humidity. In this paper, considering HCD principles, we will describe a three-step protocol that will be used to accomplish the initial stages of TRL (levels 1 to 6) and HRL (basic research and development phase and technology demonstration phase) in this device development.

2. Methods

2.1. Study design

This study protocol was developed under the SPIRIT 2013 Guidelines (28), with some adjustments to pre-clinical trials in healthcare simulation research specificities (29, 30). The study employed a three-step protocol following the EU directives (31) implemented in Portugal by the Portuguese National Authority of Medicines and Health Products (INFARMED) (32). According to these recommendations and international standards in this field (18, 19), alongside with the TRL and HRL foundations, the HCD iterative method will be used, ensuring the involvement of the end-users throughout the development process to enhance the device's effectiveness, efficiency, and satisfaction.

In this sense, a three-step protocol supported by a mix-method design of qualitative and quantitative studies was developed and included:

(i) A first observational study will be used to specify the user requirements and contexts of use. Scientific research and preliminary development will occur on paper and in the laboratory (HRL 1 and 2).

(ii) The design solutions for shoe and insole, as well as semi-functional prototypes, will be developed and evaluated against initial requirements. It is expected to achieve a validated proof of concept that addresses human needs, capabilities, limitations, and characteristics (HRL 3 and 4).

(iii) A pre-clinical study protocol will evaluate the final functional prototype of the device (shoe and insole), ensuring that the device meets all the requirements to move forward to clinical studies in real contexts. This phase will demonstrate the fidelity levels of the device in laboratory environments (HRL 5 and 6).

TABLE 1 Eligibility criteria for participants.

	I phase	II phase	III phase
Inclusion			
• Age equal or superior to 18	X	X	X
• Able to communicate in Portuguese	X	X	X
• Collaborative and oriented	X	X	X
• With a diagnosis of Diabetes type 1 or 2	X	X	X
• Informed consent to participate in the study	X	X	X
Exclusion			
• Inability to walk freely without any assistive device	X		X
• Active foot ulcers at the time of assessment			X
• Any type of lower limb amputation			X
• Major foot deformities (e.g., cavus or flat foot, Charcot)			X
• Vascular disease, claudication, retinopathy, nephropathy, and any orthopedic (e.g., fracture) or neurological (e.g., stroke) impairment that could influence gait			X

I. Observational study (user requirements and contexts of use); II. Design solutions evaluation (semi-functional prototypes); III. Pre-clinical study (final functional prototypes).

2.2. Participants' recruitment and sample size

In the study's first phase, a random sample will be extracted from the available database of 919 diabetic patients from a selected primary care organization in Portugal. Slovin's formula is used to calculate the sample size (n) given the population size (N):

$$n = \frac{N}{1+Ne^2} \quad (1)$$

where, n = number of samples, N = total population, and e = margin of error. This formula applies when estimating a population proportion using a confidence coefficient of 95% (33). A random extraction of the 279 diabetic patients will be done from the original database using the Random between function in Microsoft excel. A local family health nurse will contact each selected participant to schedule the assessment according to the eligibility criteria described in Table 1.

Regarding sample size for the usability tests (second and third phases), around 15–25 participants are usually considered to enroll, 15 being the acceptable minimum number according to the regulatory entities of the USA (34). Although these parameters in the EU are not well-established, the U.S. Food and Drug Administration's (FDA) orientation guidelines for medical devices highlight the need to balance the samples' heterogeneity and homogeneity, reflecting the target population as much as possible. According to the standard AAMI/IEC/TIR 62366-2 (19):

$$R = 1-(1-P)^n$$

where, R = cumulative probability of detecting a usability problem; P = probability of a single test showing a usability problem; n = number of participants. According to this, there are residual returns on detecting usability problems when the sample size exceeds 10 for each distinct user group. These participants will be randomly extracted from the database of the participants included in the first phase of the study.

2.3. Materials and equipment

All the procedures in observational and pre-clinical tests will be conducted in a laboratory setting with three main areas previously prepared (i) clinical evaluation of the foot, (ii) evaluation of the participants' shoes, plantar pressure and foot 3D analysis, and (iii) quality of life assessment and interviews. The CRF will include several sections necessary to accomplish the main purposes of each study phase defined in each protocol.

Some instruments and stratification checklists will be used along the three-step study, namely: (i) Portuguese version of the Graffar scale (35) composed by seven items, in order to stratify the socioeconomic level of the participants; (ii) the Portuguese (36) and international (37) classifications will be used to determine the risk level for the development of DFU, both reported by the researcher according to variables like neuropathy, ischaemia, foot deformities, ulcer previous history, amputation, loss of protective sensitivity and peripheral arterial disease; (iii) a questionnaire will be used to evaluate the footwear, which will require a ruler, a tape measure and a scale (38); (iv) EUROHIS QoL 8 (39) will be used to estimate the quality of life of the participants; (v) usability questionnaire with 42 items in a 7-point Likert scale to assess the usefulness, ease of use, ease of learning, satisfaction and intention to use (40).

Specific instruments and materials will be used for the clinical evaluation of the foot, namely: (i) monofilament 10 g of Semmes-Weinstein (41) will be used to assess the sensitivity loss (42); (ii) the 128 Hz tuning fork (43) will be used to assess the vibratory sensitivity; (iii) cotton will be used in the plantar region for the tactile sensation; (iv) the pinprick test will be used to assess the discrimination sensitivity; (v) the reflexion hammer will be used to evaluate the aquilian and rotulian tendons reflexes; (vi) the handheld Doppler device will be used to determine the Ankle-brachial Pressure Index (ABPI) values.

The pedobarographic measurements will be performed with either (i) a platform-based system (EMED; Novel GmbH, Munich, Germany) for dynamic barefoot plantar pressure assessment, with a sampling frequency of 50 Hz and resolution of 2 sensors/cm2 for a network of 2736 sensors; and (ii) an insole-based system (PEDAR X; Novel GmbH, Munich, Germany) for in-shoe plantar pressure evaluation, that comprises flexible 2 mm thick insoles with a matrix of 99 capacitance-based sensors each sampling at 50 Hz placed in the shoes. According to Putti et al. (44), the PEDAR X is one of the most commonly used systems for in-shoe pressure measurement, traducing good repeatability and consistency of measurements. Also, the EMED system is

TABLE 2 Outcomes in each phase of the study.

	I phase	II phase	III phase
Contexts of use	X		
User needs and requirements	X		
Design	X	X	X
Ergonomic and functional features		X	X
Satisfaction and intention to use		X	X
Safety			X
Efficiency and/or effectiveness			X

I. Observational study (user requirements and contexts of use); II. Design solutions evaluation (semi-functional prototypes); III. Pre-clinical study (final functional prototypes).

TABLE 3 Interventions in each phase of the study.

	I phase	II phase	III phase
Demographic data	X	X	X
Clinical data	X	X	X
Clinical evaluation of the foot	X		X
Footwear evaluation	X		X
Plantar pressure assessment	X	X	X
3D foot assessment	X		
Quality of life assessment	X		X
Interview	X	X	X
Usability testing		X	X

I. Observational study (user requirements and contexts of use); II. Design solutions evaluation (semi-functional prototypes); III. Pre-clinical study (final functional prototypes).

among humans' most frequently used clinical tools for barefoot pressure measurement worldwide (45). A 3D scanner (Feetbox 3D; Sidas and Corpus.e) will also be used to determine foot volumetric parameters.

2.4. Outcomes

The main purpose of the first phase will be to explore the concept of the new device for DFU prevention. According to this, the main outcomes will be the definition of the contexts of use, users' needs and requirements, and the footwear design features (Table 2). In phase II, the main outcome will be the definition of the design features of the device and the development of the semi-functional prototypes. Additionally, the main outcomes regarding the evaluation of those prototypes will be related to ergonomic and functional aspects of the footwear, as well as to users' satisfaction and intention to use. These outcomes will also be evaluated in the last phase regarding the functional prototype. Furthermore, the usability testing with the functional prototype will enable the assessment of safety, efficiency and/or effectiveness outcomes (regarding the decreased plantar pressure in critical areas of the foot), ensuring that the medical device accomplishes the needed legal requirements before testing in real settings.

2.5. Procedures

Table 3 explains the interventions in each phase of the study, according to the main purposes defined. All the procedures will be explained to the participants in the three phases, and the consent form will be signed. After the informed consent, data collection will include sociodemographic (e.g., age, gender, education) and clinical variables (depression, physical impairment, smoking or alcohol habits, height, weight, body mass index, prior history of ulceration, angioplasty or vascular surgery), considering important predictive risk factors for diabetic foot ulceration (42, 46, 47). A clinical foot evaluation (phases I and III) will be performed by members of the research team and should include a visual inspection of the foot (skin inspection, foot deformities), vascular (peripheral arterial disease; PAD) and neurological (neuropathy) assessment. Also, in the first phase, a footwear assessment will be performed (as well in phase III), followed by a 3D foot scan. The plantar pressure assessment (in-shoe and barefoot) will be performed in all three phases. The studies will be finished by evaluating the quality of life (phases I and III) and an interview (in all phases, with specific purposes detailed above). Specifically, in phase III, the functional prototypes will be evaluated by their end-users (individuals with diabetes) thorough usability testing. The specific procedures for visual inspection, vascular and neurological evaluation, footwear assessment, 3D scan and plantar pressure evaluation are presented below.

2.5.1. Clinical evaluation of the foot

The foot visual inspection will enable the evaluation of previous lower limb amputations (42, 46), as well as foot deformities (48) that contribute to ulcer development (49). Also, several articular, ungueal and tegumentary deformities will be evaluated, such as erythema, callus formation, deformity, skin integrity, and fungal infections of skin and nails (48).

For vascular assessment, along with pedal pulse palpation, the ABPI is a widely utilized test for diagnosing PAD (50), whose principle is to compare the blood pressure in the lower extremities to central blood pressure. The ABPI will be calculated by measuring the systolic blood pressure with a Doppler on both arms (at the brachial artery) and legs (at posterior tibial and dorsalis pedis arteries), and the higher value is taken for application in the following formula:

$$ABPI = \frac{\textit{higher value (posterior tibial or dorsalis pedis)}}{\textit{higher value (brachial)}}$$

ABPI values are considered: (i) normal between 1.0 and 1.4; (ii) borderline PAD with values between 0.91 and 0.99; (iii) PAD in values below 0.9; (iv) severe PAD in values below 0.4; (v) values above 1.4 suggest calcified rigid and non-compressible arterial walls (51). Also, the temperature will be measured by an infrared thermometer [according to the Houghton et al. conclusions (52)] in both feet as well as overall body temperature, enabling the comparison between the foot and overall temperature, but also the comparison of temperature in the same contralateral anatomical foot regions (14, 52, 53).

The neurological assessment will involve the detection of sensory loss through the 10g monofilament, vibration perception having a tuning fork of 128 Hz, pain sensitivity through the pinprick, kinaesthetic evaluation by cotton, along with the neuropathic

TABLE 4 Risk assessment classifications.

	Category	Ulcer risk	Characteristics
IWGDF (2019)	0	Very low	No LOPS and No PAD
	1	Low	LOPS or PAD
	2	Moderate	LOPS + PAD, or LOPS + Foot deformity, or PAD + Foot deformity
	3	High	LOPS or PAD, and one or more of the following: - history of a foot ulcer - a lower-extremity amputation (minor or major) - end-stage renal disease
DGS (2010)		Low	Absence of risk factors
		Moderate	Presence of neuropathy
		High	Presence of ischemia and/or neuropathy and/or foot deformity, or, history of a healed foot ulcer, or, previous amputation

LOPS, Loss of protective sensation; PAD, Peripheral artery disease.

symptoms and tendon reflexes (aquilian and rotulian) assessment (42, 54). Regarding sensitive evaluation, the most commonly used is the Semmes-Weinstein 10 g monofilament, calibrated as it requires 10 g of force for bending on touching the foot skin. After applying the filament to the patient's hands to demonstrate what the sensation feels like, the filament will be used in five different regions on each foot (hallux, first metatarsal, third metatarsal, fifth metatarsal, and heel), ensuring that the participant cannot see whether or where the examiner applies the filament: apply the filament perpendicular to the skin surface with sufficient force to cause the filament to bend or buckle for nearly 2 s. In each area, the test is repeated three times, with one "mock" application in which the filament is not applied. A protective sensation is present at each site if the patient correctly answers two out of three applications.

After applying the tuning fork to the patient's hands to demonstrate the sensation, the 128 Hz tuning fork test will be used to determine vibration sensation. The participant will be requested to report the vibration perception: apply the tuning fork perpendicularly and with constant pressure at the first toe' dorsum to the nail bed's proximity to the bone prominence. On each toe, the test will be repeated three times, with one "mock" application in which the tuning fork is not vibrating, ensuring that the participant cannot see whether or where the examiner applies the tuning fork. The test is positive if the patient correctly answers at least two out of three applications.

The pinprick-pain stimulus will be performed on the patient's hands first and then twice at the first toe' head (right and left lower limb), ensuring the participant cannot see whether the examiner uses a sharp or dull surface. This test was used for the perception of sharp touch with a toothpick. The patient's pain sensitivity was obtained using this instrument in some regions of the foot (43). The cotton will be used in the right and left lower limbs' plantar area three times, with a "mock" application, to assess the sensory neuropathy detection (42). In both cases, the participants will be asked if they feel the sharp or dull surface of the pinprick and the cotton on the plantar surface.

2.5.2. Risk assessment

To categorize the grade of risk, all the data previously collected will be analyzed to determine the current ulcer risk according to the international (37) and national (36) classification systems (Table 4).

2.5.3. Footwear assessment

To evaluate the footwear characteristics, a specific tool developed by Barton et al. (38) will be applied, which covers the following items: (i) fit of the shoe (length, width, depth); (ii) general features (age of shoe, footwear style, upper and outsole materials, weight, length, weight/length); (iii) general structure (heel and forefoot height, longitudinal profile, last, fixation, forefoot sole flexion point); (iv) motion control properties (density, fixation, heel counter stiffness, midfoot sole sagittal and frontal stability); (v) cushioning (presence, hardness at lateral midsole, medial midsole, and heel sole); (vi) wear patterns (presence, midsole, tread pattern, outsole wear pattern).

2.5.4. Plantar pressure assessment

A quantitative assessment of dynamic foot plantar pressures will be performed, including in-shoe and barefoot examination (55–57). In the barefoot plantar pressure procedure, the participants will be instructed to walk barefoot over the foam runway, with the EMED platform located in the middle of the runway. Participants will be instructed to walk at an average pace and ensure that a minimum of three steps are taken before and after contacting the platform. This three-step protocol may offer consistent results and avoid unnecessary foot loading, especially in individuals with diabetic peripheral neuropathy (56). At least three to five (55) assessments will be required to ensure the reliable evaluation of pressures. Before starting the recording, all participants will be allowed a familiarization period consisting of two practice trials.

For the insole-based PEDAR system, participants will be fitted with the correct insoles for their shoe size (ensuring that the insole will cover the entire plantar surface) and will use their usual footwear. The assessment procedure involves the need to wear a waist belt containing a battery and a wireless Bluetooth, allowing real-time connection and data storage to a laptop computer. The participants will be instructed to walk a distance of ∼15 m before turning and returning to the place where they started. Insole pressure data will be collected during both of these walks, ensuring data for at least 12 steps from each participant, which is the minimum number of steps required to obtain reliable in-shoe pressure data in individuals with peripheral diabetic neuropathy (58). Also, before pressure assessment, a zero-calibration will be performed by unloading each measurement insole, and all participants will be allowed two practice trials before recording.

2.5.5. 3D foot assessment

A 3D scanner (LAVORO) will be used to determine participants' foot volumetric parameters. The main parameters being evaluated are

foot size (EU size), foot length in centimeters (cm), width (cm), ball girth (cm), instep height (cm), heel with (cm), girth calf 15 (cm), girth calf 25 (cm), girth angle floor and gait angle ankle, both in degrees. Participants will be asked to wear a pair of sterilized socks with specific sensors compatible with the platform. Afterwards, they'll assume a static position on the platform's top, with their feet equally distanced and parallel to their shoulders. The platform will smoothly scan the previously mentioned variables, which will be stored in a local computer.

2.5.6. Quality of life assessment

The EUROHIS QoL8 (39) will be used for the quality of life assessment. This is an 8-item index that was developed as an adaptation of the WHOQOL-100 and WHOQOL-Bref (the WHO cross-cultural and generic instruments to assess the quality of life). The EUROHIS QoL8 revealed good internal consistencies across a range of countries. It showed acceptable convergent validity with physical and mental health measures, discriminating well between healthy individuals and those with longstanding conditions such as diabetes (59).

2.5.7. Interview

To complete the study, the participants will be asked to participate in an interview with specific purposes according to the phase of the study. In the first phase (observational study), the interview will characterize the functional and ergonomics aspects of their everyday footwear and identify their difficulties, needs, wellbeing and potential limitations in daily activities related to foot condition and footwear. Also, the interview will identify personal preferences regarding essential characteristics of the footwear that will be developed, such as style, color, fastening system, shape, or materials.

The interview in phase II (regarding the design solutions and semi-functional prototypes) will enable an assessment of the design solutions and determine any necessary modifications to improve the footwear and/or the insole. In phase III, the functional prototype will be evaluated alongside specific usability tests (described above), and an interview will determine potential suggestions for the device improvement.

2.5.8. Usability testing

Usability is "the extent to which a user can use a product to achieve goals with effectiveness, efficiency, and satisfaction in a specific context" (18). Phase II will use the design solutions and semi-functional prototypes in order to evaluate if they meet the initial requirements. Phase III, with the final functional prototype, will ensure that the device meets all the requirements to proceed with clinical studies. In both phase II (semi-functional prototypes) and phase III (functional prototype), along with the interviews, the Usability Questionnaire (40) will be used for the functional prototype evaluation. Specific usability testing will be implemented using the footwear prototype (shoe and insole) in laboratory settings, following the same protocol described for the PEDAR system. The same participant will perform the plantar pressure assessment barefoot, in-shoe (with regular footwear), and with the prototype of the footwear to compare the plantar pressure profiles.

2.6. Data collection, management, and analysis

Study participants' identification numbers (ID) will be used, and all data will be anonymized for subsequent analysis and reports/publications. Individual information to be collected includes demographic (gender, age), academic qualifications (degree), and professional data (clinical experience, work setting) of the nurses eligible to perform the usability tests. The names of the participants on the consent forms will be stored separately in locked cabinets accessible only by named personnel.

Statistical analysis of the collected data will be performed using the Statistical Package for the Social Sciences, version 24 (IBM SPSS Statistics 24; SPSS Inc., Chicago, IL, USA). Means, standard deviations, frequencies, and percentages will be used as descriptive statistics (or median values and interquartile ranges for skewed data). The outcomes in the two groups in each study phase will be examined to detect the effect of group allocation through inferential statistics (Student's *t*-test for independent and paired samples, or non-parametric equivalents, Mann-Whitney U and Wilcoxon tests; X2 test or Fisher's exact test), considering a statistical significance level of 0.05 (two-sided significance level of 5%). For qualitative analysis (interviews), the content analysis technique will be conducted (60) after the transcription of the individual interviews.

2.7. Ethical considerations

The study protocol was reviewed and approved by the Ethics Committee of the Health Sciences Research Unit: Nursing (UICISA: E) of the Nursing School of Coimbra (ESEnfC; Number P631/10-2019) and by the Ethics Committee of the Health Regional Administration (ACeS; Number 70/2020). The pre-clinical stages were defined according to the legal requirements of the European Union (31) and the ISO norms related to ergonomics and usability assessment of medical devices (18, 19, 61–63).

The eligible participants will receive written and oral information about the study. Written informed consent and a non-disclosure agreement (NDA) will be requested. Participants will be assigned an ID number to maintain anonymity and be easier to conciliate all the collated data, which will be used in all data collection instruments (case report form; software for plantar pressure and foot 3D analysis). Personal information will be separated from the main data collection instruments and will not be shared. All the documentation related to the study will be saved in locked cabinets only accessible by the study members. In the same way, the data collected by plantar pressure and 3D software will be obtained and kept in a project computer only accessible by study team members. All collected data will be exclusively for this study, and the confidentiality of participants will always be maintained.

2.8. Dissemination

Due to the absence of specific guidelines for pre-clinical studies with medical devices, upon completion of the several

tests in the three phases, the data obtained will be reported with the necessary adjustments for health care simulation research specificities (29, 30). The data will not be publicly available but accessible from the principal investigator on reasonable request. The research results will be disseminated to open-access, peer-reviewed journals and national and international scientific meetings. Authorship will be considered according to the recommendations of the International Committee of Medical Journal Editors (64) regarding the contributions to the design, conduct, interpretation, and reporting of the pre-clinical data (65).

3. Discussion/conclusion

The development of medical devices has increased over the last years, playing an important role in clinical practice, not only by improving care practices but also by directly influencing patients' wellbeing and quality of life.

The development of a medical device should be an iterative process, where de HCD model plays an essential role in the several stages of product development, according to the international directives that were adapted in Europe since 2007 (18, 19). The involvement of the end-users in product development ensures that the device meets the users' needs and preferences, increases device safety, effectiveness and efficiency, reducing product recalls and modifications (22–25).

This study protocol was developed to provide specifications regarding the end users' involvement in developing footwear and insole to prevent DFU since the definition of users' requirements and contexts of use and evaluation of design solutions and prototypes. Scientific research and preliminary development will be made to verify the clinical need of the end-users (health professionals and diabetic patients), as well as the review the existing medical devices and procedures used to treat or prevent the condition (66). The end-users input regarding their needs and requirements will enable the definition of early design inputs for the development of the initial prototypes. The pre-clinical studies will ensure that the device successfully meets the user needs and requirements, along with the first inputs regarding device validation (feasibility studies), safety and user satisfaction (66).

A detailed description of the activities that will be carried on in each phase was conducted, and effectively will assist both industrial and technological partners in product development and should result in successful and high-quality products.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Author contributions

Conceptualization: LBS and PP. Writing original draft: LBS and IA. Writing review and editing: RAB, RN, AS-O, and PP. Supervision: PP, JA, and TRL. Funding: PP and TRL. All authors have read and agreed to the published version of the manuscript.

Funding

This research was funded by the Research and Technological Development Incentive System (SI I&DT Co-Promotion), with the grant reference POCI-01-0247-FEDER-039784.

Acknowledgments

The authors would like to thank the support of the Health Sciences Research Unit: Nursing (UICISA: E) from the Nursing School of Coimbra (ESEnfC). The authors IA (UIDB/00742/2020) and RAB (UI/BD/151102/2021) thank the Portuguese National Funding Agency for Science, Research and Technology (FCT) for the financial support granted.

Conflict of interest

TRL was employed by the company Indústrias e Comércio de Calçado S.A. (ICC).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Liu J, Ren Z, Qiang H, Wu J, Shen M, Zhang L, et al. Trends in the incidence of diabetes mellitus: results from the Global Burden of Disease Study 2017 and implications for diabetes mellitus prevention. *BMC Public Health*. (2020) 20:9502. doi: 10.1186/s12889-020-09502-x

2. World Health Organization. *Global Report on Diabetes*. Geneve: World Health Organization (2016). p. 345.

3. Danaei G, Fahimi S, Lu Y, Zhou B, Hajifathalian K, Di Cesare M, et al. Effects of diabetes definition on global surveillance of diabetes prevalence and diagnosis: a pooled analysis of 96 population-based studies with 331,288 participants. *Lancet Diab Endocrinol*. (2015) 3:624–37. doi: 10.1016/S2213-8587(15)00129-1

4. International Diabetes Federation 9th ed. (2017). Available online at: www.diabetesatlas.org (accessed March 03, 2022).

5. Manne-Goehler J, Geldsetzer P, Agoudavi K, Andall-Brereton G, Aryal K, Bicaba B, et al. Health system performance for people with diabetes in 28 low- and middle-income countries: a cross-sectional study of nationally representative surveys. *PLoS Med.* (2019) 16:e1002751. doi: 10.1371/journal.pmed.1002751

6. Ferreira MA, Carvalho R. Pé Diabético: doença complexa, abordagem simples. *Revista Portuguesa de Diabetes.* (2013) 8:168–71.

7. Nehring P, Makowski A, Mrozikiewicz-Rakowska B, Sobczyk-Kopcioł A, Płoski R, Karnafel W. Risk factors of diabetic foot of neuropathic origin in patients with type 2 diabetes. *Endokrynol Pol.* (2015) 66:10–4. doi: 10.5603/EP.2015.0003

8. Bus SA, van Deursen RW, Armstrong DG, Lewis JEA, Caravaggi CF, Cavanagh PR. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. *Diabetes Metab Res Rev.* (2016) 32:99–118. doi: 10.1002/dmrr.2702

9. Collings R, Freeman J, Latour JM, Paton J. Footwear and insole design features for offloading the diabetic at risk foot—A systematic review and meta-analyses. *Endocrinol Diab Metabol.* (2020) 11:4. doi: 10.1002/edm2.132

10. Healy A, Naemi R, Chockalingam N. The effectiveness of footwear as an intervention to prevent or to reduce biomechanical risk factors associated with diabetic foot ulceration: a systematic review. *J Diabetes Complications.* (2013) 27:391–400. doi: 10.1016/j.jdiacomp.2013.03.001

11. Heuch L, Streak Gomersall J. Effectiveness of offloading methods in preventing primary diabetic foot ulcers in adults with diabetes. JBI database of systematic reviews and implementation. *Reports.* (2016) 14:236–65. doi: 10.11124/JBISRIR-2016-003013

12. Elberse JE, Pittens CACM, de Cock Buning T, Broerse JEW. Patient involvement in a scientific advisory process: Setting the research agenda for medical products. *Health Policy.* (2012) 107:231–42. doi: 10.1016/j.healthpol.2012.05.014

13. Smith MY, Hammad TA, Metcalf M, Levitan B, Noel R, Wolka AM, et al. Patient engagement at a tipping point - the need for cultural change across patient, sponsor, and regulator stakeholders. *Therap Innovat Regulatory Sci.* (2016) 50:546–53. doi: 10.1177/2168479016662902

14. van Netten JJ, Prijs M, van Baal JG, Liu C, van der Heijden F, Bus SA. Diagnostic values for skin temperature assessment to detect diabetes-related foot complications. *Diabetes Technol Ther.* (2014) 16:714–21. doi: 10.1089/dia.2014.0052

15. Makroum MA, Adda M, Bouzouane A, Ibrahim H. Machine learning and smart devices for diabetes management: systematic review. *Sensors.* (2022) 22:1843. doi: 10.3390/s22051843

16. Shan R, Sarkar S, Martin SS. Digital health technology and mobile devices for the management of diabetes mellitus: state of the art. *Diabetologia.* (2019) 62:877–87. doi: 10.1007/s00125-019-4864-7

17. Sousa AL, Lopes J, Guimarães T, Santos MF. mHealth: monitoring platform for diabetes patients. *Procedia Comput Sci.* (2021) 184:911–6. doi: 10.1016/j.procs.2021.03.113

18. ANSI/AAMI/IEC 62366-1. *Medical Devices Part I—Application of Usability Engineering to Medical Devices.* Geneva: International Electrotechnical Commission (2015).

19. AAMI/IEC/TIR 62366-2. *Medical Devices Part II—Guidance on the Application of Usability Engineering to Medical Devices.* Geneva: Association for the Advancement of Medical Instrumentation (2016).

20. Pelayo S, Marcilly R, Bellandi T. Human factors engineering for medical devices: European regulation and current issues. *Int J Qual Health Care.* (2020) 33(Supplement 1):31–6. doi: 10.1093/intqhc/mzaa103

21. Ciurana J. Designing, prototyping and manufacturing medical devices: an overview. *Int J Comp Integ Manufact.* (2014) 27:901–18. doi: 10.1080/0951192X.2014.934292

22. Borsci S, Uchegbu I, Buckle P, Ni Z, Walne S, Hanna GB. Designing medical technology for resilience: integrating health economics and human factors approaches. *Expert Rev Med Devices.* (2017) 15:15–26. doi: 10.1080/17434440.2018.1418661

23. Harte R, Glynn L, Rodríguez-Molinero A, Baker PM, Scharf T, Quinlan LR, et al. A Human-Centered design methodology to enhance the usability, human factors, and user experience of connected health systems: a three-phase methodology. *JMIR Human Factors.* (2017) 4:e8. doi: 10.2196/humanfactors.5443

24. Martin JL, Murphy E, Crowe JA, Norris BJ. Capturing user requirements in medical device development: the role of ergonomics. *Physiol Meas.* (2006) 27:R49–62. doi: 10.1088/0967-3334/27/8/R01

25. Privitera MB, Evans M, Southee D. Human factors in the design of medical devices–Approaches to meeting international standards in the European Union and USA. *Appl Ergon.* (2017) 59:251–63. doi: 10.1016/j.apergo.2016.08.034

26. Salazar G, Russi-Vigoya MN. Technology readiness level as the foundation of human readiness level. Ergonomics in design. *Quart Human Factors Appl.* (2021) 23:106480462110205. doi: 10.1177/10648046211020527

27. See JE. Human readiness levels explained. Ergonomics in design. *Quart Human Factors Appl.* (2021) 34:106480462110174. doi: 10.1177/10648046211017410

28. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, KrleŽa-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Int Med.* (2013) 158:200. doi: 10.7326/0003-4819-158-3-201302050-00583

29. Cheng A, Kessler D, Mackinnon R, Chang TP, Nadkarni VM, Hunt EA, et al. Reporting guidelines for health care simulation research: extensions to the CONSORT and STROBE statements. *Adv Simulat.* (2016) 1:25. doi: 10.1186/s41077-016-0025-y

30. Sena ES, Currie GL, McCann SK, Macleod MR, Howells DW. Systematic reviews and meta-analysis of preclinical studies: why perform them and how to appraise them critically. *J Cereb Blood Flow Metabol.* (2014) 34:737–42. doi: 10.1038/jcbfm.2014.28

31. European Commission. *Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices*. Brussels: European Commission (2017).

32. Ministério da Saúde. Decreto-Lei n.o 145/2009 de 17 de Junho. *Regras a que devem obedecer a investigação, o fabrico, a comercialização, a entrada em serviço, a vigilância e a publicidade dos dispositivos médicos e respectivos acessórios*. Lisboa: Ministério da Saúde (2009).

33. Tejada JJ, Punzalan RB. On the misuse of Slovin's formula. *Philippine Statist.* (2012) 61:129–36.

34. Wiklund ME, Kendler J, Strochlic AY. *Usability Testing of Medical Devices*. Boca Raton: CRC Press, Taylor & Francis Group (2016). 374 p. doi: 10.1201/b19082

35. Amaro F. *Escala de Graffar*. Costa AMB (ed). Lisboa: Currículos Funcionais (1990).

36. Direção Geral da Saúde. Pé Diabético Programa Nacional de Prevenção e Controlo da Diabetes (PNPCD). Circular Normativa, 05, 1–11. (2010). Available online at: https://www.dgs.pt/programa-nacional-para-a-diabetes/circulares-normas-e-orientacoes.aspx

37. IWGDF. Practical guidelines on the prevention and management of diabetic foot disease. *Int Work Group Diab Foot.* (2019) 36:e3266.

38. Barton CJ, Bonanno D, Menz HB. Development and evaluation of a tool for the assessment of footwear characteristics. *J Foot Ankle Res.* (2009) 2:10. doi: 10.1186/1757-1146-2-10

39. Pereira M, Melo C, Gameiro S, Canavarro MC. Estudos psicométricos da versão em Português Europeu do índice de qualidade de vida EUROHIS-QOL-8. *Laboratório de Psicologia.* (2013) 9:627. doi: 10.14417/lp.627

40. Parreira P, Sousa LB, Marques IA, Santos-Costa P, Cortez S, Carneiro F, et al. Usability assessment of an innovative device in infusion therapy: a mix-method approach study. *Int J Environ Res Public Health.* (2020) 17:8335. doi: 10.3390/ijerph17228335

41. Afolabi BI, Idowu BM, Onigbinde SO. Achilles tendon degeneration on ultrasound in type 2 diabetic patients. *J Ultrasono.* (2020) 20:291–9. doi: 10.15557/JoU.2020.0051

42. Crawford F, Cezard G, Chappell FM, Murray GD, Price JF, Sheikh A, et al. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). *Health Technol Assess.* (2015) 19:1–210. doi: 10.3310/hta19570

43. Paixão JC, de Oliveira FR, Guimarães NS, Machado JAN, de Souza MRCP. Micro-controlled thermal stimulator for detecting fine fiber changes in patients with diabetes mellitus: a diagnostic accuracy study. *Prim Care Diabetes.* (2021) 15:548–53. doi: 10.1016/j.pcd.2021.01.004

44. Putti AB, Arnold GP, Cochrane L, Abboud RJ. The Peda® in-shoe system: repeatability and normal pressure values. *Gait Posture.* (2007) 25:401–5. doi: 10.1016/j.gaitpost.2006.05.010

45. Putti AB, Arnold GP, Cochrane LA, Abboud RJ. Normal pressure values and repeatability of the Emed® ST4 system. *Gait Posture.* (2008) 27:501–5. doi: 10.1016/j.gaitpost.2007.06.009

46. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. *Diabetes Metab Res Rev.* (2012) 28:574–600. doi: 10.1002/dmrr.2319

47. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. *Ann Med.* (2016) 49:106–16. doi: 10.1080/07853890.2016.1231932

48. O'Loughlin A, McIntosh C, Dinneen SF, O'Brien T. Basic concepts to novel therapies: a review of the diabetic foot. *Int J Low Extrem Wounds.* (2010) 9:90–102. doi: 10.1177/1534734610371600

49. Allan J, Munro W, Figgins E. Foot deformities within the diabetic foot and their influence on biomechanics. *Prosth Orthot Int.* (2016) 40:182–92. doi: 10.1177/0309364615592705

50. Brownrigg JRW, Hinchliffe RJ, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: a systematic review. *Diab Metabol Res Rev.* (2016) 32:119–27. doi: 10.1002/dmrr.2703

51. Ankle Brachial Index C, Murray GD, Butcher I, Heald CL, Lee RJ, et al. Ankle Brachial Index combined with Framingham risk score to predict cardiovascular events and mortality. *JAMA.* (2008) 300:197. doi: 10.1001/jama.300.2.197

52. Houghton VJ, Bower VM, Chant DC. Is an increase in skin temperature predictive of neuropathic foot ulceration in people with diabetes? A systematic review and meta-analysis. *J Foot Ankle Res.* (2013) 6:31. doi: 10.1186/1757-1146-6-31

53. Wijlens AM, Holloway S, Bus SA, van Netten JJ. An explorative study on the validity of various definitions of a 22°C temperature threshold as warning signal for impending diabetic foot ulceration. *Int Wound J.* (2017) 14:1346–51. doi: 10.1111/iwj.12811

54. Arad Y, Fonseca V, Peters A, Vinik A. Beyond the monofilament for the insensate diabetic foot: A systematic review of randomized trials to prevent the occurrence

of plantar foot ulcers in patients with diabetes. *Diabetes Care.* (2011) 34:1041–6. doi: 10.2337/dc10-1666

55. Cavanagh PR, Ulbrecht JS. Clinical plantar pressure measurement in diabetes: rationale and methodology. *The Foot.* (1994) 4:123–35. doi: 10.1016/0958-2592(94)90017-5

56. Fernando ME, Crowther RG, Wearing S. "The importance of foot pressure in diabetes". In: Müller B, Wolf S, editors. *Handbook of Human Motion*. Springer International Publishing AG (2018). p. 759-787. doi: 10.1007/978-3-319-14418-4_39

57. Patry J, Belley R, Côté M, Chateau-Degat ML. Plantar pressures, plantar forces, and their influence on the pathogenesis of diabetic foot ulcers. *J Am Podiatr Med Assoc.* (2013) 103:322–32. doi: 10.7547/1030322

58. Arts MLJ, Bus SA. Twelve steps per foot are recommended for valid and reliable in-shoe plantar pressure data in neuropathic diabetic patients wearing custom made footwear. *Clin Biomech.* (2011) 26:880–4. doi: 10.1016/j.clinbiomech.2011.05.001

59. Schmidt S, Mühlan H, Power M. The EUROHIS-QOL 8-item index: psychometric results of a cross-cultural field study. *Eur J Public Health.* (2005) 16:420–8. doi: 10.1093/eurpub/cki155

60. Bardin L. *L'analyse de contenu*. Paris: Quadrige/PU. (2007).

61. International Organization for Standardization. *ISO 14155: Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practices*. Geneva: Author (2011).

62. International Organization for Standardization. *ISO 14971: Medical Devices—Application of Risk Management to Medical Devices*. Geneva: Author (2011).

63. International Organization for Standardization. *ISO 16142-1: Medical Devices—Recognized Essential Principles of Safety and Performance of Medical Devices Part I, General Principles and Additional Specific Essential Principles for All Non-IVD Medical Devices and Guidance on the Selection of Standards*. Geneva: Author (2006).

64. Matheson A. How industry uses the ICMJE guidelines to manipulate authorship and how they should be revised. *PLoS Med.* (2011) 8:e1001072. doi: 10.1371/journal.pmed.1001072

65. Flanagin A. Authorship for research groups. *JAMA*. (2002) 288:3166. doi: 10.1001/jama.288.24.3166

66. Pietzsch JB, Shluzas LA, Paté-Cornell ME, Yock PG, Linehan JH. Stage-gate process for the development of medical devices. *J Med Dev*. (2009) 3:8836. doi: 10.1115/1.3148836

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 07 February 2023
DOI 10.3389/fendo.2023.1056828

OPEN ACCESS

EDITED BY
Hiroshi Okada,
Matsushita Memorial Hospital, Japan

REVIEWED BY
Noriyuki Kitagawa,
Kameoka Municipal Hospital, Japan
WuQiang Fan,
Massachusetts General Hospital,
United States

*CORRESPONDENCE
Xianghai Zhou
xianghai_zhou@bjmu.edu.cn
Linong Ji
prof_jilinong@aliyun.com

SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 29 September 2022
ACCEPTED 23 January 2023
PUBLISHED 07 February 2023

CITATION
Yuan Y, Zhou X, Jia W, Zhou J, Zhang F, Du J and Ji L (2023) The association between self-monitoring of blood glucose and HbA1c in type 2 diabetes. *Front. Endocrinol.* 14:1056828. doi: 10.3389/fendo.2023.1056828

The association between self-monitoring of blood glucose and HbA1c in type 2 diabetes

Yanping Yuan[1], Xianghai Zhou[1*], Weiping Jia[2], Jian Zhou[2], Fan Zhang[3], Jianling Du[4] and Linong Ji[1*]

[1]Department of Endocrinology, Peking University People's Hospital, Beijing, China, [2]Department of Endocrinology & Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Diabetes Institute, Shanghai, China, [3]Department of Endocrinology, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China, [4]Department of Endocrinology and Metabolism, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China

Aims: Fasting capillary blood glucose (FCG) and postprandial capillary blood glucose (PCG) both contribute to HbA1c in diabetes. Due to the collinearity between FCG and PCG, the HbA1c prediction model could not be developed with both FCG and PCG by linear regression. The study aimed to develop an HbA1c prediction model with both FCG and PCG to estimate HbA1c in type 2 diabetes.

Methods: A total of 1,642 patients with type 2 diabetes who had at least three FCG and three PCG measurements in the past 3 months were enrolled in the study. The mean of FCG ($MEAN_{FCG}$) and PCG ($MEAN_{PCG}$) were calculated for each patient. The patients were randomized into exploratory and validation groups. The former was used for developing HbA1c prediction models and the latter for performance evaluation.

Results: The new HbA1c prediction model using ridge regression expressed as HbA1c (%) = $0.320\times MEAN_{FCG}$ (mmol/L) + $0.187\times MEAN_{PCG}$ (mmol/L) + 2.979, R^2 = 0.668. Compared to linear regression models developed with FCG, PCG, fasting plasma glucose (FPG), and 2-hour postprandial plasma glucose (2-h PPG), respectively, the new HbA1c prediction model showed the smallest mean square error, root mean square error, mean absolute error. The concordance correlation coefficient of the new HbA1c prediction model and the linear regression models with $MEAN_{FCG}$, $MEAN_{PCG}$, FPG or 2-h PPG were 0.810,0.773,0.749,0.715,0.672.

Conclusion: We have developed a new HbA1c prediction model with both FCG and PCG, which showed better prediction ability and good agreement.

KEYWORDS

type 2 diabetes, HbA1c, ridge regression, fasting capillary blood glucose, postprandial capillary blood glucose

Introduction

Glycated hemoglobin (HbA1c) is strongly correlated with mean blood glucose levels over 3 months. The American Diabetes Association (ADA) recommends that the goal of HbA1c is <7% in most non-pregnant adults with diabetes, which is directly associated with the reduction of diabetes complications (1). But HbA1c also has limitations in assessing blood glucose control. First, since HbA1c is measured once every 3 months and does not reflect the change in blood glucose promptly, HbA1c was not appropriate for assessing glycemic control in patients with adjusted hypoglycemic agents for less than 3 months. Second, there are marked discrepancies between blood glucose and HbA1c level for patients such as hemoglobin variant, thalassemia, hemolysis, recent blood transfusion and pregnancy (2). For those who are not suitable for HbA1c mentioned above, continuous glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG) provide immediate spot glucose readings in diabetes. CGM is expensive and not available for all type 2 diabetes, while SMBG is undoubtedly a convenient and cost-effective method of blood glucose monitoring that is widely used by patients with diabetes to guide the timely modification of diabetes treatment regimens (3).

Studies on the association between SMBG and HbA1c were limited in patients with type 2 diabetes. The A1c-Derived Average Glucose (ADAG) study provided the correlation between HbA1c and mean blood glucose from CGM and SMBG in patients with type 1 diabetes, type 2 diabetes and nondiabetic, and allowed the calculation of estimated mean blood glucose for a given HbA1c (4). However, the correlation in ADAG was not appropriate for type 2 diabetes with less frequent blood glucose monitoring that was not sufficient to obtain average blood glucose. Compared with premeal glucose or postprandial glucose, the immediate clinical value of mean blood glucose in day-to-day blood glucose monitoring and treatment was limited. Although previous studies have reported the relationship between fasting capillary blood glucose (FCG) or postprandial capillary blood glucose (PCG) with HbA1c (5, 6), there is no doubt that both FCG and PCG contribute to HbA1c levels (5), so the prediction of HbA1c using FCG or PCG alone may be inaccurate. In clinical practice, it can be observed that some patients only reach the FCG target or the PCG target, how to predict the HbA1c levels of these patients individually is unknown for now. Therefore, it is necessary to take both FCG and PCG into account when analyzing the relationship between blood glucose and HbA1c. In the present study, we analyzed the association between FCG, PCG, and HbA1c using data from Chinese patients with type 2 diabetes who had stable diabetes treatment, and thus develop a new HbA1c prediction model based on both FCG and PCG.

Materials and methods

Study population

The multi-center, observational study enrolled patients with type 2 diabetes in endocrinology departments of eight hospitals in China from March 2018 to Jan 2020. The inclusion criteria included the following: 1) Type 2 diabetes aged ≥18 years referred to the endocrinology department; 2) being untreated, or receiving stable antidiabetic treatment including diet, exercise, or hypoglycemic agents for at least 3 months before the study; 3) having at least three FCG and three PCG measurements over a 3-month period before the study. The exclusion criteria included the following: 1) being pregnant or lactated; 2) using drugs that elevate blood glucose such as glucocorticoids, chemotherapy drugs within 3 months; 3) having conditions that may change blood glucose such as infection, myocardial infarction, tumor, inflammation, trauma, hyperthyroidism, hypothyroidism, Cushing's syndrome or acromegaly within 3 months; 4) having a history of severe liver disease or alanine transaminase/aspartate transaminase ≥3 times the normal upper limit; 5) having a history of serious kidney disease or serum creatinine >133 μmol/L; 6) having known hematological disease or hemoglobin <90 g/L; 7) being hypoproteinemia with serum albumin <35g/L; 8) blood transfusion or blood donation within 3 months. The Ethics Committee of the Peking University People's Hospital approved the study protocol. All patients signed informed consent before the interview and data collection. In this study, data were collected from 1737 patients with type 2 diabetes. After excluding 24 patients diagnosed with diabetes for less than 3 months, 5 patients who were found to have hemoglobin variants, 11 patients with hemoglobin <90 g/L, 16 patients with serum creatinine >133 umol/L, 22 patients with serum albumin <35 g/L, 9 patients with alanine transaminase/aspartate transaminase ≥3 times the normal upper limit, and 8 patients with glycated albumin (GA) information missing, data from 1642 patients were used for data analysis. The patients were randomized into an exploratory group including 819 patients and a validation group including 823 patients.

Data collection

Demographic characteristics and medical history of the patients were recorded. Patients' glucose-lowering medications, records of 3 FCGs and 3 to 9 PCGs in SMBG, smoking, and alcohol consumption during the last 3 months before the interview were collected. Body weight and height were measured using a calibrated scale and body mass index (BMI, kg/m^2) was calculated. Blood pressure was measured using a mercury sphygmomanometer.

Laboratory assessments

Venous blood samples were drawn in the morning after an overnight fast. Fasting plasma glucose (FPG), HbA1c, hemoglobin, serum creatinine, albumin, alanine transaminase, aspartate transaminase, total cholesterol, and triglycerides were measured in local laboratories. Patients had breakfast and take their daily hypoglycemic agents. The blood sample was collected 2 hours later to measure 2-hour postprandial plasma glucose (2-h PPG). Glycated hemoglobin HbA1c was tested using ion-exchange high-performance liquid chromatography, capillary electrophoresis, immunoassay, enzymatic assay or boronate affinity chromatography in local laboratories. Local laboratories were required to perform 10 samples comparison quarterly with the Department of Laboratory Medicine, Zhongshan Hospital, Fudan University, which is an HbA1c

Secondary Referral Laboratory certificated by the National Glycohemoglobin Standardization Program (NGSP) (7). At 1 year, all local laboratories achieved a deviation of ≤6% in at least 38 of 40 HbA1c results. Serum and whole blood specimens were stored at -80° C and transported to the central laboratory at Peking University People's Hospital for GA and hemoglobin electrophoresis. GA was measured by enzymatic methods (Lucica GA-L, Japan). Hemoglobin electrophoresis was performed to screen the Hb variant using the method of capillary electrophoresis (Minicap Flex Piercing, Sebia, France).

Definition

FCG referred to the capillary blood glucose before breakfast of a day. PCG referred to the capillary blood glucose 2 hours after breakfast, lunch or dinner. The mean of FCG ($MEAN_{FCG}$) and PCG ($MEAN_{PCG}$) were calculated for each patient. The $MEAN_{PCG}$ was the mean PCG of each patient after three meals. The mean PCG of breakfast ($MEAN_{PCGB}$), lunch ($MEAN_{PCGL}$) and dinner ($MEAN_{PCGD}$) were also calculated for each patient.

Criteria for the diagnosis of type 2 diabetes and definition of HbA1c goal achievement of <7% were based on American Diabetes Association ADA (2022) guidelines (1). FCG control target range was 80-130 mg/dL (4.4-7.2 mmol/L) according to ADA guideline and 80-126 mg/dL (4.4-7.0 mmol/L) according to the Chinese Diabetes Society (CDS) (8). The target of PCG control was <180mg/dL (10.0 mmol/L) according to the ADA and CDS guidelines. Medical history of type 2 diabetes was also an auxiliary criterion for the diagnosis of type 2 diabetes. Hypoglycemia was defined as the patient's SMBG recorded blood glucose or plasma glucose concentration <3.9 mmol/L, as well as self-reported hypoglycemic symptoms.

Statistical analysis

Data analysis was performed using SPSS software (version 23.0; IBM Corp., Armonk, New York, USA). Continuous variables were presented as mean ± standard deviation or median (interquartile range). Categorical variables were expressed as number (percentage).

The patients were randomized into exploratory and validation groups by SPSS software. HbA1c prediction models were developed in the exploratory group and validated in the validation group. The correlation coefficient between $MEAN_{FCG}$ and $MEAN_{PCG}$ was 0.827 (P <0.001). Correlation coefficient >0.8 was considered collinearity (9). Due to the collinearity between $MEAN_{FCG}$ and $MEAN_{PCG}$, the ridge regression model was used to develop a new HbA1c prediction model using both $MEAN_{FCG}$ and $MEAN_{PCG}$ to predict HbA1c. Ridge parameter k (lambda) was introduced to the regression equation to make the estimated value of the regression coefficient essentially stable. The trend of ridge trace became stable with the optimal ridge parameter k (10). The optimal value of ridge parameter k was selected by the machine learning method with cross-validation using Python 3.8. Simple linear regression models were developed to predict HbA1c with $MEAN_{FCG}$, $MEAN_{PCG}$, FPG, and 2-h PPG, respectively. The difference in performance between the new HbA1c prediction model and simple linear regression models was assessed by mean square error (MSE), root mean square error (RMSE), mean absolute error (MAE), and coefficient of determination (R^2) in the validation group. The MSE, RMSE, MAE was calculated by

$$MSE = \frac{1}{m}\sum_{i=1}^{m}(X_i - Y_i)^2,\ RMSE = \sqrt{\frac{1}{m}\sum_{i=1}^{m}(X_i - Y_i)^2},\ MAE = \frac{1}{m}\sum_{i=1}^{m}|X_i - Y_i|$$

respectively. X_i represents the predicted HbA1c, Y_i represents the actual measured HbA1c, m means the sum of participants. The smaller MSE, RMSE, and MAE demonstrated the better accuracy of the prediction model (11).

Bland–Altman plots and concordance correlation coefficient (CCC) were used to evaluate the agreement between actual HbA1c and predicted HbA1c in the validation group. The CCC >0.80 suggested a strong agreement between actual and predicted values. Receiver operating characteristic (ROC) curves were used to assess the sensitivity and specificity of the new HbA1c prediction model and simple linear regression models to detect patients with HbA1c <7% using MedCalc version 20.0. The areas under the ROC curves (AUC) of HbA1c prediction models were calculated and compared using the DeLong test. All *P*-values were two-tailed and *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

There were 1642 patients with a mean age of 59.3 ± 11.0 years in the study. Males accounted for 61.9%. The median duration of type 2 diabetes was 7.9 years. Patients had an average $MEAN_{FCG}$ of 8.29 ± 2.64 mmol/L, average $MEAN_{PCG}$ of 11.55 ± 3.73 mmol/L, and mean HbA1c of 7.80 ± 1.86%. The mean number of daily glucose tests was 7.51 ± 2.08. The percentage of patients experiencing hypoglycemia was 11.1% within 3 months. The clinical characteristics of the patients were not statistically different between the exploratory group and the validation group (Table 1). The mean number of daily glucose tests was not significantly different between those on non-insulin-treated and insulin-treated patients in the exploratory group (7.49 ± 2.06 vs 7.45 ± 2.00, *P*=0.784), but the mean number of daily glucose tests in non-insulin-treated patients was more than those in insulin treatment in the validation group (7.68 ± 2.20 vs 7.28 ± 1.95, *P*=0.011).

HbA1c prediction models and their performance

In the exploratory group, the trend of ridge trace became stable when ridge parameter k was 0.03 (Figure 1). The new HbA1c prediction model expressed as HbA1c (%) = 0.320×$MEAN_{FCG}$ (mmol/L) + 0.187×$MEAN_{PCG}$ (mmol/L) + 2.979 when k = 0.03. The four simple linear regression models of HbA1c based on $MEAN_{FCG}$, $MEAN_{PCG}$, FPG, or 2-h PPG expressed as HbA1c (%) = 0.554×$MEAN_{FCG}$ (mmol/L) +3.218, HbA1c (%) = 0.376×$MEAN_{PCG}$ (mmol/L) +3.434, HbA1c (%) = 0.417×FPG (mmol/L) +4.251 and HbA1c (%) = 0.256×(2-h PPG)

10.3389/fendo.2023.1056828

TABLE 1 Characteristics of 1642 patients with type 2 diabetes.

Variable	Total population	Exploratory group	Validation group
Subjects, n	1642	819	823
Male, n (%)	1017 (61.9)	507 (61.9)	510 (62.0)
Smoking†, n (%)	389 (23.7)	188 (23.0)	201 (24.4)
Drinking†, n (%)	241 (14.7)	116 (14.2)	125 (15.2)
Age, years	59.3 ± 11.0	59.2 ± 11.2	59.4 ± 10.7
Duration of diabetes, years	7.9 (2.6, 14.3)	8.0 (2.6, 14.5)	7.7 (2.5, 14.0)
BMI, kg/m^2	25.45 ± 3.46	25.47 ± 3.48	25.42 ± 3.43
SBP, mmHg	132.81 ± 17.19	132.39 ± 16.85	133.23 ± 17.51
DBP, mmHg	79.86 ± 10.27	79.56 ± 10.12	80.16 ± 10.41
Total cholesterol, mmol/L	4.48 ± 1.27	4.49 ± 1.18	4.48 ± 1.36
Triglyceride, mmol/L	1.53 (1.08, 2.26)	1.59 (1.12, 2.33)	1.46 (1.05, 2.16)
FPG, mmol/L	8.57 ± 3.25	8.54 ± 3.24	8.60 ± 3.25
2-h PPG, mmol/L	12.86 ± 5.12	12.86 ± 5.23	12.84 ± 5.00
HbA1c, %	7.80 ± 1.86	7.82 ± 1.87	7.79 ± 1.85
GA, %	20.89 ± 6.37	20.83 ± 6.24	20.95 ± 6.51
$MEAN_{FCG}$, mmol/L	8.29 ± 2.64	8.30 ± 2.66	8.28 ± 2.62
$MEAN_{PCG}$, mmol/L	11.55 ± 3.73	11.66 ± 3.85	11.44 ± 3.61
Number of daily glucose tests	7.51 ± 2.08	7.47 ± 2.04	7.54 ± 2.13
Diabetes treatment, n (%)			
OAD	1175 (71.6)	596 (72.8)	579 (70.4)
One OAD	550 (46.8)	292 (49.0)	258 (44.6)
Two OADs	468 (39.8)	219 (36.7)	249 (43.0)
≥Three OADs	157 (13.4)	85 (14.3)	72 (12.4)
Insulin, n (%)	585 (35.6)	305 (37.2)	280 (34.0)
Hypoglycemia*†, n (%)	191 (11.6)	95 (11.6)	96 (11.7)

Data are shown as mean ± standard deviation, median (interquartile range), or n (%).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2-h PPG, 2-hour postprandial plasma glucose; HbA1c, glycated hemoglobin; GA, glycated albumin; $MEAN_{FCG}$, average fasting capillary glucose (FCG) for each patient; $MEAN_{PCG}$, average postprandial capillary glucose (PCG) for each patient; OAD, oral anti-hyperglycemic drug.
* Hypoglycemia was defined as the patient's SMBG recorded blood glucose or plasma glucose concentration < 3.9mmol/L, as well as self-reported hypoglycemia symptom.
† within 3 months before the study.

(mmol/L) +4.527, respectively. The R^2 of the new HbA1c prediction model and the linear regression model with $MEAN_{FCG}$, $MEAN_{PCG}$, FPG or 2-h PPG was 0.668, 0.622, 0.599, 0.523 and 0.511, respectively, indicating that the predictors of the new HbA1c prediction model were more strongly correlated with HbA1c compared with the other linear regression models (Table 2). In addition, the ridge regression model of HbA1c based on both FPG and 2-h PPG expressed as HbA1c (%) = 0.248×FPG (mmol/L) + 0.144×(2-h PPG) (mmol/L) + 3.844 when k = 0.02, R^2 = 0.639. Sensitivity analysis of PCG was performed. In patients who had PCG of three meals (N=417), the R^2 of linear regression model of HbA1c based on $MEAN_{PCGB}$, $MEAN_{PCGL}$ and $MEAN_{PCGD}$ was 0.556, 0.504 and 0.506, respectively. And R^2 of the linear regression model of 2-h PPG and HbA1c in 417 patients was 0.496.

In the validation group, the new HbA1c prediction model yielded the smallest value of MSE, RMSE, and MAE compared with four simple linear regression models with $MEAN_{FCG}$, $MEAN_{PCG}$, FPG, or 2-h PPG in the validation group (Table 2). The Bland-Altman plot showed that the mean difference (95% limits of agreement) was 0.03 (-1.97,2.02) between actual HbA1c and predicted HbA1c with the new prediction model (Figure 2). The mean difference of four simple linear regression models by $MEAN_{FCG}$, $MEAN_{PCG}$, FPG, or 2-h PPG was also close to zero, with -0.01(-2.21,2.18), 0.06(-2.19,2.30), -0.04 (-2.44,2.36), -0.02(-2.55,2.50), respectively. Most of the differences between actual HbA1c and predicted HbA1c in different prediction models were within 95% limits of agreement. Of the new HbA1c prediction model and simple linear regression models, only the CCC of the new HbA1c prediction model was greater than 0.80, indicating that the predicted HbA1c with the new HbA1c prediction model had a stronger agreement with actual HbA1c (Table 2). After removing patients who experienced hypoglycemia, the HbA1c prediction

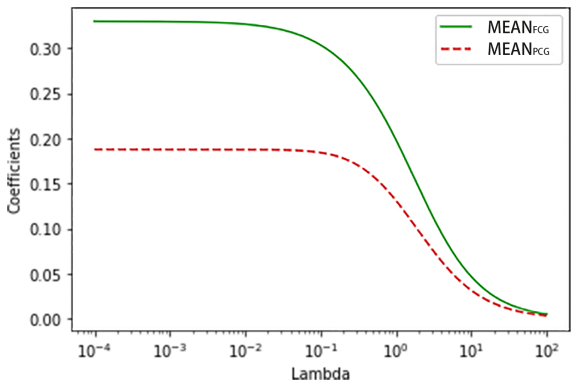


FIGURE 1
The ridge trace of the ridge regression model for predicting HbA1c with MEAN$_{FCG}$ and MEAN$_{PCG}$.

models showed similar performance (the results were not shown here).

The ability of HbA1c prediction models to detect patients with HbA1c <7%

In the validation group, the new HbA1c prediction model for predicting HbA1c with MEAN$_{FCG}$ and MEAN$_{PCG}$ showed strong predictive ability to detect patients who had HbA1c <7% with AUC of 0.895 (95% CI: 0.872, 0.915), which was higher than simple linear regression models with MEAN$_{PCG}$ [0.860 (0.835, 0.883), P <0.0001], FPG [0.863 (0.838, 0.886), P=0.011] or 2-h PPG [0.850 (0.824, 0.874), P=0.001]. But the new HbA1c prediction model did not show better predictive ability compared to the simple linear regression model with MEAN$_{FCG}$ [0.884 (0.860, 0.905), P=0.107] (Figure 3).

Consistency of actual and predicted HbA1c grouped with FCG and PCG control targets

Patients were grouped with MEAN$_{FCG}$ ≤7.2 and >7.2 mmol/L, MEAN$_{PCG}$ <10.0 and ≥10.0 mmol/L, respectively. More than 80% of patients had the consistency of actual and predicted HbA1c for both <7% and both ≥7% in patients with both MEAN$_{FCG}$ and MEAN$_{PCG}$ within/outside the control target range (Table 3). In patients who had MEAN$_{FCG}$ within the control target range and MEAN$_{PCG}$ ≥10.0 mmol/L, a proportion of 35.1% patients had actual HbA1c <7% but predicted HbA1c ≥7%. And two of these patients with actual HbA1c <7% but predicted HbA1c ≥7% had experienced hypoglycemia, one of them was given insulin treatment and the other one was given insulin secretagogues, compared with no one had experienced hypoglycemia in both actual and predicted HbA1c <7%. In patients who had MEAN$_{FCG}$ >7.2 mmol/L and MEAN$_{PCG}$ within the control target range, patients with actual HbA1c <7% but predicted HbA1c ≥7% accounted for 20.6%. Only one patient with insulin use had experienced hypoglycemia compared with no one who had experienced hypoglycemia in both actual and predicted HbA1c <7%.

Similar results were found when patients were grouped with MEAN$_{FCG}$ ≤7.0 and >7.0 mmol/L, MEAN$_{PCG}$ <10.0 and ≥10.0 mmol/L, respectively.

Discussion

Our study analyzed the correlation of MEAN$_{FCG}$ and MEAN$_{PCG}$ with HbA1c using ridge regression and developed a new model for predicting HbA1c by combining MEAN$_{FCG}$ and MEAN$_{PCG}$. The new HbA1c prediction model predicted HbA1c with better performance than the HbA1c prediction model using MEAN$_{FCG}$, MEAN$_{PCG}$, FPG, or 2-h PPG alone. The new HbA1c prediction model had a better predictive ability to detect patients who had HbA1c <7% than simple linear model with MEAN$_{PCG}$, FPG, or 2-h PPG, but was similar to the simple linear model with MEAN$_{FCG}$.

To our knowledge, our study was the first to use a ridge regression model to establish a model using FCG and PCG together to predict HbA1c in patients with type 2 diabetes. This new HbA1c prediction model was appropriate for patients who were not suitable for HbA1c measurement after adjusting hypoglycemic treatment for less than 3 months, especially when patients only reached FCG or PCG target. Individualized predicted HbA1c with SMBG results was used to determine whether the hypoglycemic treatment should be adjusted to promote HbA1c to reach the goal quickly. When the patient's actual HbA1c was inconsistent with the predicted HbA1c, the cause should be actively sought, such as frequent hypoglycemia, anemia,

TABLE 2 The comparison of ridge regression model and simple linear regression model for HbA1c.

Model	Variable	R^2	MSE	RMSE	MAE	Mean difference	95%LoA	PA, %	CCC
Ridge regression	MEAN$_{FCG}$, MEAN$_{PCG}$	0.668	1.038	1.019	0.742	0.03	(-1.97,2.02)	93.68	0.810 (0.787, 0.830)
Linear regression	MEAN$_{FCG}$	0.622	1.253	1.120	0.826	-0.01	(-2.21,2.18)	93.92	0.773 (0.746, 0.797)
	MEAN$_{PCG}$	0.599	1.318	1.148	0.852	0.06	(-2.19,2.30)	93.20	0.749 (0.721, 0.775)
	FPG	0.523	1.498	1.224	0.912	-0.04	(-2.44,2.36)	93.92	0.715 (0.683, 0.744)
	2-h PPG	0.511	1.659	1.288	0.959	-0.02	(-2.55,2.50)	95.02	0.672 (0.637, 0.703)

R^2, coefficient of determination; MSE, mean square error; RMSE, root mean square error; MAE, mean absolute error; 95% limits of agreement, 95% LoA; PA, percentage of agreement; CCC, concordance correlation coefficient.

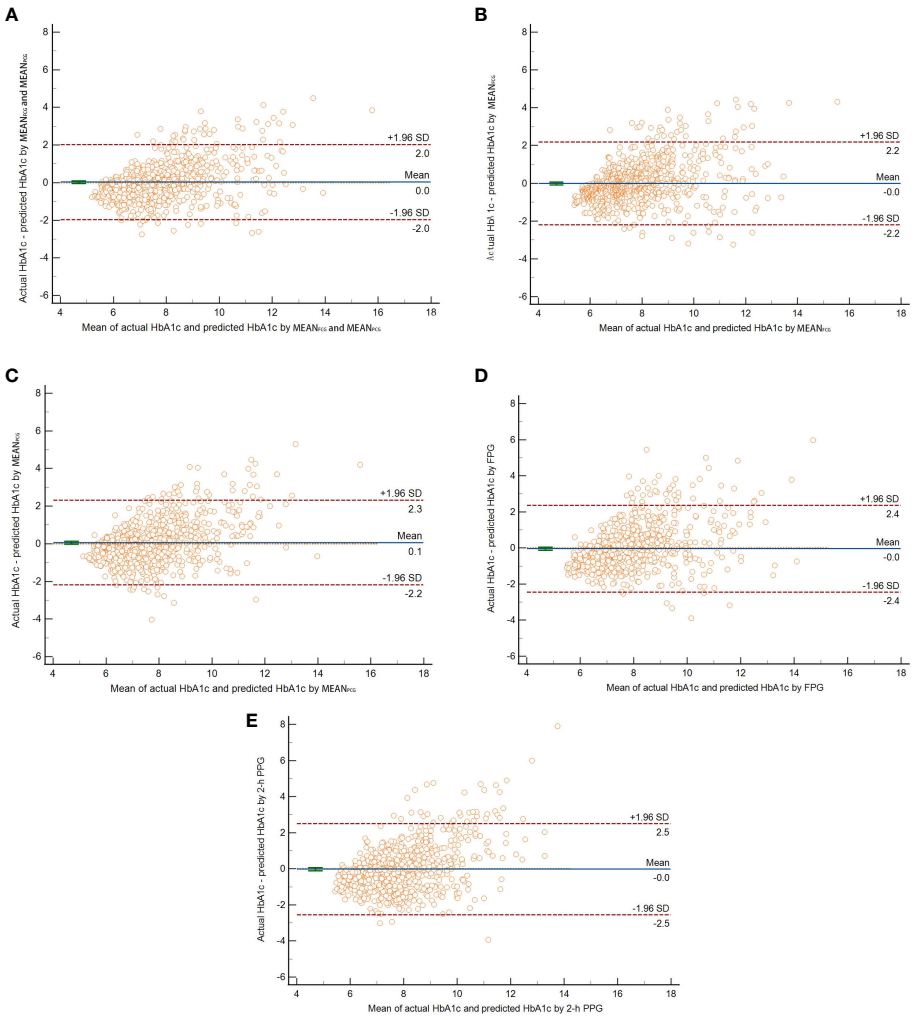


FIGURE 2
The Bland-Altman plot of actual HbA1c and predicted HbA1c by ridge regression with both $MEAN_{FCG}$ and $MEAN_{PCG}$ **(A)**, linear regression with $MEAN_{FCG}$ **(B)**, $MEAN_{PCG}$ **(C)**, FPG **(D)**, or 2-h PPG **(E)** respectively. The horizontal solid line in the middle indicated the mean difference between actual HbA1c and predicted HbA1c. The upper and lower horizontal dotted lines indicated the 95% limits of agreement.

hemolysis, pregnancy, hemoglobinopathy, etc. In these patients, the new HbA1c prediction model might be applied to evaluate long-term glycemic control.

Our study showed that FCG had a stronger predictive performance for HbA1c than FPG alone, which was similar to the results of a previous study (5). When comparing PCG after three meals and 2-h PPG, it seems that PCG after breakfast was better than that after lunch, after dinner, and 2-h PPG, indicating that PCG after breakfast was more important than other meals, and superior to intravenous blood glucose after breakfast. This suggested that patients should pay more attention to PCG after breakfast in the PCG after three meals. Moreover, the R^2 of the model developed using both FPG and 2-h PPG was lower than that of the new HbA1c prediction model using both $MEAN_{FCG}$ and $MEAN_{PCG}$, indicating that SMBG at home was better than single intravenous blood glucose measurement in hospital when predicting HbA1c. A possible explanation was that FPG and 2-h PPG had day-to-day variability (12–14), so that the average blood glucose level over a period of time was a more accurate reflection of HbA1c levels than a single plasma glucose test.

Compared with the new prediction model, simple linear model with FCG showed comparable ability to identify patients with HbA1c <7%, but the simple linear model with PCG showed worse ability. It indicated that FCG had a higher value than PCG in determining whether patients had achieved an HbA1c goal of <7%. This was consistent with previous reports that premeal blood glucose was more closely related to HbA1c than postmeal blood glucose (15). In patients without monitoring PCG, FCG alone can be used to identify whether a patient is meeting the HbA1c goal using the simple linear model with FCG.

There was a discrepancy between the actual HbA1c and predicted HbA1c by the new HbA1c prediction model in this study. In patients who had only FCG within control target range, about 1/3 of patients with actual HbA1c <7.0% had predicted HbA1c ≥7%. Compared to patients with actual and predicted HbA1c <7.0%, we found that more patients had experience hypoglycemia in those with actual HbA1c <7.0% and predicted HbA1c ≥7%. The possible explanation was that these patients had a higher risk of hypoglycemia, which lead to the actual HbA1c reaching the goal. At this time, the actual HbA1c might

10.3389/fendo.2023.1056828

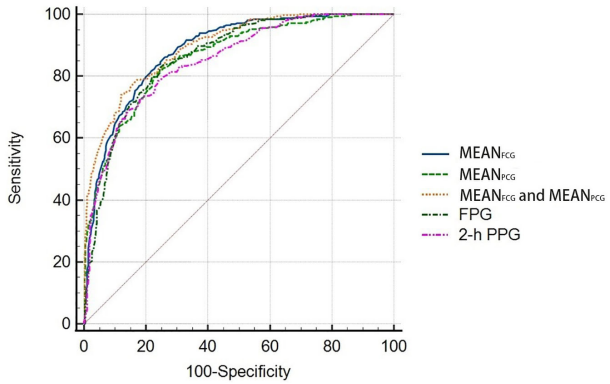


FIGURE 3
Receiver operating characteristic (ROC) curves for the HbA1c prediction models to detect patients with HbA1c <7%.

be inaccurate, suggesting that clinicians should not reduce blood glucose excessively to further increase the risk of hypoglycemia in this case. For those who had only PCG within control target range, 1/4 of the patients with actual HbA1c <7% had predicted HbA1c ≥7%. Limited by the number of people with hypoglycemia occurrence, it was difficult to speculate whether these people had an increased risk of hypoglycemia.

Studies have found that blood glucose testing number correlated with HbA1c attainment in insulin-treated patients (16, 17). In our study, although the frequency of blood glucose was different in insulin-treated patients, the average blood glucose was finally included in the model for HbA1c prediction. In addition, there was no difference in the number of blood glucose tests between the insulin-treated and non-insulin-treated patients in the model-established group, which could avoid the interference to the prediction model caused by the increased number of tests in insulin-treated patients. Although more glucose tests were observed in non-insulin-treated patients than insulin-treated patients in the validation group, studies showed that SMBG frequency was not associated with glycemic control in non-insulin-treated patients (18, 19).

The strength of this study was that it was a multicenter study, and only required type 2 diabetes with insulin-treated and non-insulin-treated to have at least three FCG and three PCG measurements, indicating that this study had good extrapolation in type 2 diabetes. Several limitations exist in the current study. First, SMBG measurements were performed by the patient's glucose-monitoring devices. Improper operation during blood glucose measurement, expiration of the test strip, and failure to calibrate might affect the accuracy and precision of the glucose readings. Second, the SMBG values were collected from four points including fasting and after three meals for several days over 3 months, some higher or lower values might be missed. But each point

TABLE 3 Actual and predicted HbA1c grouped with FCG and PCG control targets.

Group	actual <7% predicted <7%	actual <7% predicted ≥7%	actual ≥7% predicted <7%	actual ≥7% predicted ≥7%
ADA guideline				
$MEAN_{FCG}$ ≤ 7.2mmol/L				
$MEAN_{PCG}$ <10.0mmol/L	192 (79.7)	9 (3.7)	35 (14.5)	5 (2.1)
$MEAN_{PCG}$ ≥10.0mmol/L	6 (6.4)	33 (35.1)	9 (9.6)	46 (48.9)
$MEAN_{FCG}$ >7.2mmol/L				
$MEAN_{PCG}$ <10.0mmol/L	7 (9.6)	15 (20.6)	6 (8.2)	45 (61.6)
$MEAN_{PCG}$ ≥10.0mmol/L	0	49 (11.8)	0	366 (88.2)
CDS guideline				
$MEAN_{FCG}$ ≤ 7.0mmol/L				
$MEAN_{PCG}$ <10.0mmol/L	190 (84.4)	31.2	31 (13.8)	1 (0.4)
$MEAN_{PCG}$ ≥10.0mmol/L	6 (8.7)	22 (31.2)	9 (13.0)	32 (46.4)
$MEAN_{FCG}$ >7.0mmol/L				
$MEAN_{PCG}$ <10.0mmol/L	9 (10.1)	21 (23.6)	10 (11.2)	49 (55.1)
$MEAN_{PCG}$ ≥10.0mmol/L	0	60 (13.6)	0	380 (86.4)

Data are shown as n (%).

glucose value had at least 3 measurements for each patient with stable hypoglycemic treatment, which avoid a snapshot of glucose variability and reduce the impact of intra-individual differences. Third, validation of the new HbA1c prediction model was performed internally, and further validation of the model in external populations will be required in the future. Fourth, the efficacy and safety of this new HbA1c prediction model remained to be investigated, and we are conducting clinical trials to evaluate its efficacy and safety in patients with type 2 diabetes who have just been adjusted for hypoglycemic treatment.

In conclusion, we have established the association between FCG, PCG and HbA1c and developed a new HbA1c prediction model based on both FCG and PCG. The new HbA1c prediction model provided an available and convenient way to convert real-time SMBG readings to HbA1c. Applying the new HbA1c prediction model might help to make the most of SMBG information and promote HbA1c to reach the goal quickly in patients with type 2 diabetes.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Peking University People's Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XZ designed this study. YY drafted the initial manuscript. XZ and LJ revised the manuscript. XZ, WJ, JZ, FZ, JD were responsible for collecting and managing the data of their hospital. All authors contributed to the article and approved the submitted version.

Funding

This work is supported by the grant 2016YFC1305600, 2016YFC1305603 from the Major Chronic Non-communicable Disease Prevention and Control Research, National Key R&D Program of China.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. American Diabetes Association Professional Practice Committee. 6. glycemic targets: Standards of medical care in diabetes-2022. *Diabetes Care* (2022) 45:S83–96. doi: 10.2337/dc22-S006

2. American Diabetes Association Professional Practice Committee. 2. classification and diagnosis of diabetes: Standards of medical care in diabetes-2022. *Diabetes Care* (2022) 45:S17–38. doi: 10.2337/dc22-S002

3. American Diabetes Association Professional Practice Committee. 7. diabetes technology: Standards of medical care in diabetes-2022. *Diabetes Care* (2022) 45:S97–S112. doi: 10.2337/dc22-S007

4. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, et al. Translating the A1C assay into estimated average glucose values. *Diabetes Care* (2008) 31:1473–8. doi: 10.2337/dc08-0545

5. Monami M, Lamanna C, Lambertucci L, Longo R, Cocca C, Addante F, et al. Fasting and post-prandial glycemia and their correlation with glycated hemoglobin in type 2 diabetes. *J Endocrinol Invest* (2006) 29:619–24. doi: 10.1007/BF03344161

6. Chubb SAP, Van Minnen K, Davis WA, Bruce DG, Davis TME. The relationship between self-monitoring of blood glucose results and glycated haemoglobin in type 2 diabetes: the fremantle diabetes study. *Diabetes Res Clin Pract* (2011) 94:371–6. doi: 10.1016/j.diabres.2011.07.038

7. NGSP Home. Available at: http://www.ngsp.org/ (Accessed Feb 8, 2022).

8. Chinese Diabetes Society (CDS). Guideline for the prevention and treatment of type 2 diabetes in China (2020 edition). *Chinese J Diabetes* (2021) 13(4):317–411. doi: 10.3760/cma.j.cn115791-20210221-00095

9. Vatcheva KP, Lee M, McCormick JB, Rahbar MH. Multicollinearity in regression analyses conducted in epidemiologic studies. *Epidemiol Sunnyvale Calif* (2016) 6:227. doi: 10.4172/2161-1165.1000227

10. Hoerl AE, Kennard RW. Ridge regression: Biased estimation for nonorthogonal problems. *Technometrics* (1970) 12:55–67. doi: 10.1080/00401706.1970.10488634

11. Chicco D, Warrens MJ, Jurman G. The coefficient of determination r-squared is more informative than SMAPE, MAE, MAPE, MSE and RMSE in regression analysis evaluation. *PeerJ Comput Sci* (2021) 7:e623. doi: 10.7717/peerj-cs.623

12. Ollerton RL, Playle R, Ahmed K, Dunstan FD, Luzio SD, Owens DR. Day-to-day variability of fasting plasma glucose in newly diagnosed type 2 diabetic subjects. *Diabetes Care* (1999) 22:394–8. doi: 10.2337/diacare.22.3.394

13. DeVries JH, Bailey TS, Bhargava A, Gerety G, Gumprecht J, Heller S, et al. Day-to-day fasting self-monitored blood glucose variability is associated with risk of hypoglycaemia in insulin-treated patients with type 1 and type 2 diabetes: A *post hoc* analysis of the SWITCH trials. *Diabetes Obes Metab* (2019) 21:622–30. doi: 10.1111/dom.13565

14. Sacks DB. A1C versus glucose testing: a comparison. *Diabetes Care* (2011) 34:518–23. doi: 10.2337/dc10-1546

15. Fan W, Zheng H, Wei N, Nathan DM. Estimating HbA1c from timed self-monitored blood glucose values. *Diabetes Res Clin Pract* (2018) 141:56–61. doi: 10.1016/j.diabres.2018.04.023

16. Elgart JF, González L, Prestes M, Rucci E, Gagliardino JJ. Frequency of self-monitoring blood glucose and attainment of HbA1c target values. *Acta Diabetol* (2016) 53:57–62. doi: 10.1007/s00592-015-0745-9

17. Weinstock RS, Braffett BH, McGuigan P, Larkin ME, Grover NB, Walders-Abramson N, et al. Self-monitoring of blood glucose in youth-onset type 2 diabetes: Results from the TODAY study. *Diabetes Care* (2019) 42:903–9. doi: 10.2337/dc18-1854

18. Davis WA, Bruce DG, Davis TME. Is self-monitoring of blood glucose appropriate for all type 2 diabetic patients? the fremantle diabetes study. *Diabetes Care* (2006) 29:1764–70. doi: 10.2337/dc06-0268

19. Young LA, Buse JB, Weaver MA, Vu MB, Mitchell CM, Blakeney T, et al. Glucose self-monitoring in non-Insulin-Treated patients with type 2 diabetes in primary care settings: A randomized trial. *JAMA Intern Med* (2017) 177:920–9. doi: 10.1001/jamainternmed.2017.1233

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 24 February 2023
DOI 10.3389/fpubh.2023.1000162

OPEN ACCESS

EDITED BY
Martha M. Funnell,
University of Michigan, United States

REVIEWED BY
Linda Siminerio,
University of Pittsburgh, United States
Kevin Joiner,
School of Nursing, University of Michigan, United States

*CORRESPONDENCE
Fabio A. Almeida
✉ fabio.almeida@unmc.edu;
✉ almeida.fabio@live.com

SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Public Health

RECEIVED 21 July 2022
ACCEPTED 08 February 2023
PUBLISHED 24 February 2023

CITATION
Almeida FA, You W, Brito FA, Alves TF, Goessl C, Wall SS, Seidel RW, Davy BM, Greenawald MH, Hill JL and Estabrooks PA (2023) A randomized controlled trial to test the effectiveness of two technology-enhanced diabetes prevention programs in primary care: The DiaBEAT-it study. *Front. Public Health* 11:1000162. doi: 10.3389/fpubh.2023.1000162

A randomized controlled trial to test the effectiveness of two technology-enhanced diabetes prevention programs in primary care: The DiaBEAT-it study

Fabio A. Almeida[1]*, Wen You[2], Fabiana A. Brito[1], Thais F. Alves[1], Cody Goessl[3], Sarah S. Wall[4], Richard W. Seidel[5], Brenda M. Davy[4], Mark H. Greenawald[6], Jennie L. Hill[7] and Paul A. Estabrooks[8]

[1]Department of Health Promotion, University of Nebraska Medical Center, Omaha, NE, United States, [2]Department of Public Health Sciences, University of Virginia, Charlottesville, VA, United States, [3]Center for Clinical Epidemiology and Population Health, Marshfield Clinic Research Institute, Marshfield, WI, United States, [4]Department of Human Nutrition, Foods and Exercise, Virginia Tech, Blacksburg, VA, United States, [5]Department of Psychiatry, Carilion Clinic, Roanoke, VA, United States, [6]Department of Family and Community Medicine, Carilion Clinic, Roanoke, VA, United States, [7]Department of Populational Health Sciences, University of Utah, Salt Lake City, UT, United States, [8]Department of Health and Kinesiology, University of Utah, Salt Lake City, UT, United States

Objective: To evaluate the effectiveness of two technology-enhanced interventions for diabetes prevention among adults at risk for developing diabetes in a primary care setting.

Methods: The DiaBEAT-it study employed a hybrid 2-group preference (Choice) and 3-group randomized controlled (RCT) design. This paper presents weight related primary outcomes of the RCT arm. Patients from Southwest Virginia were identified through the Carilion Clinic electronic health records. Eligible participants (18 and older, BMI $\geq$ 25, no Type 2 Diabetes) were randomized to either Choice ($n = 264$) or RCT ($n = 334$). RCT individuals were further randomized to one of three groups: (1) a 2-h small group class to help patients develop a personal action plan to prevent diabetes (SC, $n = 117$); (2) a 2-h small group class plus automated telephone calls using an interactive voice response system (IVR) to help participants initiate weight loss through a healthful diet and regular physical activity (Class/IVR, $n = 110$); or (3) a DVD with same content as the class plus the same IVR calls over a period of 12 months (DVD/IVR, $n = 107$).

Results: Of the 334 participants that were randomized, 232 (69%) had study measured weights at 6 months, 221 (66%) at 12 months, and 208 (62%) at 18 months. Class/IVR participants were less likely to complete weight measures than SC or DVD/IVR. Intention to treat analyses, controlling for gender, race, age and baseline BMI, showed that DVD/IVR and Class/IVR led to reductions in BMI at 6 (DVD/IVR −0.94, $p < 0.001$; Class/IVR −0.70, $p < 0.01$), 12 (DVD/IVR −0.88, $p < 0.001$; Class/IVR-0.82, $p < 0.001$) and 18 (DVD/IVR −0.78, $p < 0.001$; Class/IVR −0.58, $p < 0.01$) months. All three groups showed a significant number of participants losing at least 5% of their body weight at 12 months (DVD/IVR 26.87%; Class/IVR 21.62%; SC 16.85%). When comparing groups, DVD/IVR were significantly more likely to decrease BMI at 6 months ($p < 0.05$) and maintain the reduction at 18 months ($p < 0.05$) when compared to SC. There were no differences between the other groups.

Conclusions: The DiaBEAT-it interventions show promise in responding to the need for scalable, effective methods to manage obesity and prevent diabetes in primary care settings that do not over burden primary care clinics and providers.

Registration: https://clinicaltrials.gov/ct2/show/NCT02162901, identifier: NCT02162901.

KEYWORDS

diabetes prevention, DVD, IVR, behavior change, weight loss, primary care

1. Introduction

The Centers for Disease Control and Prevention (CDC) estimates that there are 34.2 million (10.5%) Americans with diabetes, in addition to the 88 million (34.5% of the population) with prediabetes in the United States, and strongly recommends healthcare approaches to prevent diabetes (1). Approximately 5–10% of individuals with prediabetes develop type 2 diabetes (T2D) yearly with an American Diabetes Association (ADA) (2) expert panel estimating that up to 70% of individuals with prediabetes will eventually progress to diabetes, further highlighting the importance of intervening (3). Finally, due to the continued growth of the obesity epidemic, the burden of prediabetes and diabetes are expected to continue to rise (4). As there is no known treatment available to cure diabetes and self-management for those with diabetes remains a challenge, the importance of prevention is paramount (5).

The Diabetes Prevention Program (DPP) was seminal in demonstrating that a modest weight loss achieved through diet and exercise was superior to medication in delaying the onset of T2D (6). The DPP program found that 30 min of physical activity per day 5 times a week coupled with a 5–10% weight loss resulted in a 58% reduction in the incidence of diabetes (6). Following on the success of the DPP, researchers have sought to determine the effectiveness of the DPP in more typical community and clinical settings (7–9). However, barriers to large-scale implementation of these adaptations still exist, where information on primary prevention and management of T2D is still limited (10). Recent studies (11, 12) have shown the lack of availability of these programs in underserved areas, with lifestyle coaches reporting lack of space, administrative support, sufficient allocation of their own time for the program, overall costs, and difficulty scheduling as barriers to broad dissemination of these programs (13). On the other hand, participants have reported distance, work schedules, lack of transportation and childcare needs as remaining issues that prevent them from fully engaging in these in-person group adaptations of the DPP (14–16).

To address these barriers, several interventions have used technology to successfully adapt and deliver the DPP. Several systematic reviews have shown that technology-based resources can optimize diabetes prevention intervention to achieve clinically significant weight loss (17). A review by Levine et al. (18) found that technology-assisted weight loss interventions that included some form of human coaching were successful in helping individuals lose weight in primary care settings. Another review (19) of technology-mediated diabetes prevention interventions found that these types of programs can result in a clinically significant amount of weight loss in patients with prediabetes. This review included studies that used a variety of technologies including DVDs, e-videos, web-based resources, videoconferencing, telephone calls, interactive voice response, text messages, e-counseling, email, and online group forums with a variety of Supplementary material (e.g., Physical Activity and Nutrition workbooks, log books, and in person group DPP). Joiner et al. (20) found similar results further supporting the effectiveness of technology-based interventions in helping individuals at risk for developing diabetes to lose clinically significant amounts of weight. However, questions remain regarding the effectiveness of eHealth interventions within primary care settings and in promoting weight loss maintenance or weight gain prevention (18, 21–23).

The original diaBEAT-it study (24) was a pragmatic clinical trial employing a hybrid preference/randomized control trial (RCT). The study focused primarily on the individual-level factors of reach, effectiveness, maintenance, and cost (24) but each active intervention was designed for broad dissemination and scalability within and across healthcare and, potentially, public health systems. The overarching goal of the study was to determine the effectiveness and maintenance of effects of two technology-enhanced interventions relative to standard care (SC) in reducing body weight within the context of a traditional RCT, while concurrently determining the relative reach of these two interventions within the context of a two-group preference design where participants had the option to choose which intervention they would like to participate in (Choice). The diaBEAT-it study has been fully described elsewhere (24). The purpose of the present paper is to evaluate the effectiveness of the two technology-enhanced interventions in supporting patients to reduce their body mass index (BMI) over an 18-month period relative to a minimal standard care intervention. We hypothesized that compared to minimal standard care, each intervention would result in greater mean reduction in BMI over 18 months.

2. Design and methods

Patients at risk for developing diabetes were randomly assigned (2-1) by the project manager to either an RCT or Choice study arm using a blocked (groups of 4) randomization table stratified by sex created by the study statistician. Patients in the RCT arm

were further randomized (1-1-1) to one of three groups: (1) a 2-h small group class designed to help patients develop a personal action plan to prevent diabetes (SC) (25); (2) a 2-h small group class plus automated telephone calls using an interactive voice response system (IVR) to help participants initiate weight loss *via* the promotion of a healthful diet and regular physical activity, and maintain their behavior changes over a period of 12 months (Class/IVR); or (3) a DVD with same content as the class plus the same IVR calls over a period of 12 months (DVD/IVR).

This paper presents weight related outcomes associated with the randomized control trial arm of the DiaBEAT-it study (24). We powered our study to detect statistically significant body weight changes at 6 and 12 months in Class/IVR and DVD/IVR when compared with the SC group within the RCT design. Sample size was determined by using the average weight loss and standard deviations found in our previous studies (25–27) for the 6-month effect and averages from the literature (28, 29) for the 12-month effect. As such, assuming a correlation of 0.5 between repeated measures, we estimated that a sample size of 78 participants per group would give us a 90% power to detect a minimum detectable difference in change in weight of 2.3 lbs. at 6 months and 2.7 lbs. at 12 months. The goal for enrollment was 120 participants per group to achieve a sample size of 78 after an estimated 35% attrition at 18 months. The trial design and methods have been described in detail elsewhere (24). Supplementary Figure 1 provides the CONSORT information for the RCT study arm. This study and protocol were approved by the Carilion Clinic Institutional Review Board and was registered at clinicaltrials.gov (NCT02162901).

2.1. Participant eligibility and recruitment

Potential participants were initially identified through a Carilion Clinic electronic health records (EHR) query of primary care patients between January 2014 and August 2015 (24). EHR eligibility included patients that over the previous 12 months were 18 years of age and older, BMI $\geq$ 25, had ICD-9 codes for prediabetes, glucose intolerance, metabolic syndrome, and/or obesity while excluding those with ICD-9 codes indicating diagnosed diabetes, congestive heart failure, and coronary artery disease. A list of patients meeting initial eligibility criteria were sent to their physicians for final approval. All approved patients were recruited *via* a physician letter providing general information about the study and went through telephone screening for final eligibility determination. During the phone screening, a research assistant reiterated key points of the letter, answered any questions, and determined diabetes risk and study eligibility. Diabetes risk was determined using the Diabetes Risk Calculator (DRC) (30). Individuals with a score of 5 or higher are considered to be in particularly greater risk and were the target for recruitment.

Individuals were eligible if they were 18 years of age or older with a BMI of at least 25 kg/m^2 (BMI $>$ 22 for Asian), spoke English, were not pregnant or planning to become pregnant in the following 18 months, were not diagnosed with T2D, congestive heart failure, or coronary artery disease, had no contraindication for physical activity (PA) or weight loss, had access to a phone, and had a DRC test score indicative of high risk for developing T2D (Score of 5 or higher). Eligibility was broadly defined to allow for most typical primary care patients to be eligible to participate in the study.

Prior to the baseline visit, the project manager created sealed opaque envelopes with group assignment information according to the blocked (groups of 4) randomization table stratified by gender created by the study statistician to blind research staff to intervention assignment. Informed consent procedures were initiated during the screening telephone call with participants receiving the informed consent *via* mail prior to their initial visit so they could prepare for the first study visit. These procedures were completed at the time of the first study visit with participants (1) receiving information on the risks and benefits of participating on the trial, (2) being given the opportunity to ask questions, clarifications, and raise any concerns, and (3) being informed of the interventions of interest and their rights as a research subject. All assessments took place after full consent was given by study participants. Once all assessments were completed, a research assistant randomized participants in the RCT study arm to one of the three study groups using the previously created envelopes. Participants randomized to SC received information about the class and a workbook. Those randomized to the Class/IVR group received a workbook and were assisted by a research assistant in signing into an IVR account to select days and times best for their calls and setup a security PIN. Research assistants also helped participants in completing an initial test of the system to familiarize themselves with the IVR calls. Participants randomized to the DVD/IVR group received a workbook, a DVD and a brief instruction on how to use the TV to navigate the DVD in addition to the IVR system setup. Finally, all randomized participants received $25.00 as a thank you for their time in completing the baseline assessments.

2.2. Interventions

2.2.1. Standard care

Participants in the SC comparison group took part in a 2-h small group session class (25) taught by two trained Carilion Clinic employees (Certified Diabetes Educators and Registered Dietitians). This class has been offered for the past 6 years and although they are available to all Carilion Clinic patients, for the purpose of the project, separate classes to each intervention group were offered. As such, both groups attended project specific classes for their given study group (SC or Class/IVR). The content, format, and individuals teaching these classes did not differ from the currently taught classes. Participants in the SC group received no additional intervention contact after the initial class. They were contacted 6, 12, and 18 months following their class date for follow-up assessments. During the class participants were encouraged to develop their own personal action plan to preventing T2D by setting a goal of losing 10% of their current weight over 12 months and to be physically active for 60 min, 5 days per week. The personal action plan also included a listing of motivational reasons to

prevent diabetes, personal goals for weight management, physical activity, and healthful eating, identifying barriers, strategies to overcome barriers, and upholding accountability for these goals through a commitment to enlist friends and/or family members in the change process (25). Class instructors provided detailed information on current recommendations for physical activity and healthy eating (*MyPlate* guidelines) and gave a workbook covering all 22 session topics following a similar curriculum as developed by the original DPP. The class is fully described elsewhere (24).

2.2.2. Class/IVR group

Participants in this group attended the 2-h class described above, received a workbook, completed a "Live" counseling call (31), and received 22 tailored IVR calls over a period of 12 months with the final 6 months focusing on maintenance and relapse prevention based on DPP's after Core program. This intervention was designed to help participants initiate moderate weight loss through physical activity and healthful eating and maintain these behavior changes. All participants developed a personal action plan with the goal of losing 10% of their current weight in 12 months and being physically active for 60 min a day, 5 days per week. Workbook content topics focused on achieving a balanced diet through the reduction of fat and caloric intake plus adding regular physical activity to enhance initial weight loss and prevent weight regain. Additionally, we used the 5 A's model to assist participants in setting physical activity and healthful eating goals necessary for weight loss and maintenance (32). One week after class completion, participants received a telephone call lasting 45–60 min to reinforce learning objectives and provide further clarifications (31). Research assistants delivered this call using teach-to-goal and teach-back strategies to allow participants to describe key intervention concepts (i.e., MyPlate guidelines, types, and length of physical activity) using their own words and provide additional rounds of education until the participant demonstrated a firm understanding of the information. For those participants that did not attend the initial 2-h class, the research assistants provided the full content of the class and assisted them in creating their personal action plan. One week after the live telephone call the participants began receiving IVR support calls. There were 22 IVR calls lasting between 15 and 30 min with 8 weekly calls, followed by 8 biweekly calls and 6 monthly calls focusing on maintenance and relapse prevention. Participants were required to complete one call before moving on to the next call, as such, it was not possible to skip IVR calls and content. For those participants that did not complete an IVR call, reminder contacts using telephone, text, and email were used for up to 2 weeks to try and get participants back on track. Each IVR call included an assessment of current weight, PA, and dietary behaviors, feedback on goal progression, content related to the session topic (i.e., Move Those Muscles, Being Active: A Way of Life, Healthy Eating With MyPlate, Be A Fat Detective), teach to goal reinforcement of key messages, and a homework assignment. New action plans were created every month (Calls 4, 8, 12, and 16) through Call 16 and then on every call during the maintenance and relapse prevention phase. This included updating goals, identifying new barriers, selecting strategies to resolve barriers, and goal setting-feedback loops.

2.2.3. DVD/IVR group

This group was identical to the Class/IVR group but was initiated with a DVD that replicated the class content. The DVD included the following segments: (1) What is pre-diabetes? (2) What are the risk factors for diabetes? (3) Developing your DiaBEAT-it action plan, (4) Goal setting for physical activity and healthy eating, (5) putting together a toolbox of resources, and (6) making a commitment to change. The DVD was about 60 min in duration with several planned pauses to allow for completion of activities. This replicated the 5 A's approach that guided the class and included the completion of an action plan page in the accompanying workbook. Finally, the DVD included an appendix with additional free-of-charge, online nutrition and physical activity informational videos. Participants received their live counseling call within 7 days of being given the DVD. Similar to the Class/IVR group, those participants that reported not watching the DVD the research assistants provided full information and guided them through developing their personal action plan during the "Live" call. The IVR structure and content was the same as described above.

2.3. Outcome measures

Trained research assistants unaware of group assignment collected data at baseline, 6, 12, and 18 months. The primary outcome was change in BMI from baseline to 18 months. Secondary outcomes included percentage of participants achieving weight loss goals of 5% or more, changes in percent weight reduction as well as maintenance of those changes at 12 and 18 months. Height was assessed in stocking feet with a calibrated stadiometer with a fixed vertical backboard and adjustable headboard. Weight was assessed with the calibrated Health-O-Meter 2101KL digital stand-on scale (www.homscales.com). Body Mass Index was calculated in kg/m^2. Demographic characteristics were collected using a computer-based questionnaire (https://surveymethods.com/). Research assistants were available on site to answer any questions and help participants with potential computer/survey issues. All assessments took place at a research facility.

2.4. Statistical analysis

Statistical analysis included descriptive statistics for age, sex, race, ethnicity, education, income, health literacy, employment, health insurance, Diabetes Risk Calculator (DRC), and weight status. Chi-square and independent *t*-tests were conducted to determine if any of the groups differed on baseline characteristics (Supplementary Table 1). Data were examined for the presence of outliers, violations of normality (for those continuous variables) and missing data. No violations of normality were detected. Between group differences in changes in BMI and other weight

outcomes were prespecified using intention-to-treat (ITT) analysis. To simultaneously account for individual effects regardless of the condition, we employed a linear mixed effect model to a multi-treatment framework (33) for the treatment effect analysis (34). To be specific, two group dummies are in the model along with assessment time dummies and their interactions. This model allows us to control error non-independence of over time assessment within the same individual and heteroskedasticity caused by between individual heterogeneity, and a-priori-determined covariates that are influencing factors of outcome-specific production. The goal was to make more robust inferences about the treatment effect of main outcomes of interest: for example, the effect of Class/IVR and DVD/IVR in reducing BMI over 18 months when compared to SC group. For those participants with missing outcome measurements, we replaced the missing data with their baseline value following the Baseline Carried Forward approach.

Additionally, we conducted analysis based on participants completing at least 4 sessions (i.e., meeting NDPP threshold for recognition standards) (35), at least 6 months (i.e., core intervention effects), and the full 12 months (i.e., post-core effects). For the purposes of these analyses, class and "Live-Call" completion were calculated based on attendance, DVD was based on participant self-report, and IVR call completion was based on the voice files for the lesson of the week being played (24). Further, for the dichotomous outcome measures (i.e., achieve 5% weight loss goal), we treated those models as linear probability models in order to retain the straight-forward treatment effect interpretation of the results by applying generalized linear models in the analysis. Means and standard deviations for all primary and secondary outcomes at baseline, 6, 12, and 18 months are also presented. All statistical analyses were conducted in Stata v16 and the 5% significance level was used.

3. Results

3.1. Participant enrollment and characteristics

Supplementary Figure 1 presents participant enrollment and retention at 6, 12, and 18 months. A total of 3,115 were identified as potentially eligible to join the study. Of those, 1,712 (55%) were reached by phone with 689 completing screening questions and 427 scheduling an initial study visit to determine full eligibility. A total of 358 patients were eligible to participate in the study with 334 (93%) completing full baseline assessments and being randomized (SC = 117, Class/IVR = 110, DVD/IVR = 107). The mean age of participants was 52.3 (±12.1) years with a mean BMI of 37.2 (±7.3) kg/m^2 (Supplementary Table 1). At baseline, 68.1% of participants were female, 76.8% were non-Hispanic white, 20.0% were Non-Hispanic black, 25.8% had high school or lower education, and 55.8% were employed full time (Supplementary Table 1). Intervention groups (Class/IVR and DVD/IVR) participants were less likely to be retired (P = 0.036), had higher average diabetes risk scores (P = 0.019) and higher average BMI (P = 0.004) when compared with SC participants (Supplementary Table 1). Of the 334 participants that were randomized, 232 (69%) had study measured weights at 6 months, 221 (66%) at 12 months, and 208 (62%) at 18 months. Class/IVR participants were less likely to complete weight measures than SC or DVD/IVR (Supplementary Figure 1).

3.2. Weight loss

Supplementary Table 2 reports estimated mean changes in BMI and weight over an 18-month period. A total of eight participants (SC = 1, Class/IVR = 6, DVD/IVR = 1) were eliminated from full analysis due to becoming pregnant during trial (Supplementary Figure 1). ITT results show that at month 6, the mean ± SE change in BMI from baseline in DVD/IVR was significant with −0.94 ± 0.21 (P = 0.022 vs. SC; P = 0.450 vs. Class/IVR), significant in Class/IVR with −0.70 ± 0.24 (P = 0.206 vs. SC), and non-significant in SC with −0.33 ± 0.17. At month 12, the mean ± SE change in BMI from baseline in DVD/IVR was significant with −0.88 ± 0.20 (P = 0.058 vs. SC; P = 0.853 vs. Class/IVR), significant in Class/IVR with −0.82 ± 0.25 (P = 0.141 vs. SC), and non-significant in SC with −0.36 ± 0.19. At month 18, the mean ± SE change in BMI from baseline in DVD/IVR was significant with −0.78 ± 0.22 (P = 0.030 vs. SC; P = 0.550 vs. Class/IVR), significant in Class/IVR with −0.58 ± 0.23 (P = 0.160 vs. SC), and non-significant in SC with −0.18 ± 0.17.

At month 6, mean percent weight loss ± SE change from baseline was significant in all three conditions (DVD/IVR: −2.77 ± 0.48; Class/IVR: −1.42 ± 0.46; SC: −1.40 ± 0.42) with DVD/IVR significantly losing more weight than Class/IVR (P = 0.046) and SC (P = 0.031) (Supplementary Table 2). At month 12, the mean percent weight loss ± SE change remained significant in all three conditions (DVD/IVR: −2.56 ± 0.50; Class/IVR: −1.80 ± 0.50; SC: −1.47 ± 0.44) with no between group differences (Supplementary Table 2). At month 18, the mean percent weight loss ± SE change remained significant in all three conditions (DVD/IVR: −2.18 ± 0.54; Class/IVR: −1.27 ± 0.48; SC: −1.11 ± 0.44) with no between group differences (Supplementary Table 2). Finally, results show positive time effects for DVD/IVR (6M: 25.84%, 12M: 26.87%, 18M: 20.69%), Class/IVR (6M: 18.59%, 12M: 21.62%, 18M: 18.59%), and SC (6M: 15.94%, 12M: 16.85%, 18M: 16.85%) participants achieving 5% weight loss across all three timepoints with no treatment effect found across groups (Supplementary Table 2).

3.3. Intervention participation rates: CDC recognition standards

On average participants in the DVD/IVR group completed 15.5 (±8.6) sessions compared to 14.1 (±8.3) for Class/IVR. Approximately, 86.3% of participants in the intervention groups (DVD/IVR: 86.6%; Class/IVR: 86%) met the CDC threshold of completing at least 4 sessions with 48.4% (DVD/IVR: 52.6%; Class/IVR: 44%) staying in the program for at least 6 months, and 29.5% (DVD/IVR: 37.1%; Class/IVR: 21.5%) completing every session during the 12-month program. Average percent weight loss at 12 months for those meeting the CDC threshold were 3.24%

(DVD/IVR) and 2.74% (Class/IVR) with 35.74% (DVD/IVR) and 33.44% (Class/IVR) achieving a 5% weight loss.

3.3.1. Adverse events

During the trial, 40 adverse events (AE) were reported; 6 were classified as serious adverse events (SAE). The majority were associated with immune system disorders (allergic reactions–21). Additional categories included cardiac disorders (1), musculoskeletal disorders (3), general disorders (1), infections (1), injury or procedure complications (3), neoplasms benign, malignant and unspecified (1), nervous systems disorders (1), respiratory disorders (1), and vascular disorders (2). Twenty-one AEs were determined to be related to the study and 3 had insufficient information to make a determination. The 21 related AEs were all associated with a skin irritation as result of the application of the accelerometer used in the study. One SAE also associated with the application of the accelerometer led to a severe reaction and hospitalization. Overall events were equally balanced between groups, with 13 in SC, 11 in Class/IVR, and 14 in DVD/IVR.

4. Discussion and conclusion

The randomized control trial arm of our study demonstrated that two technology-enhanced diabetes prevention programs both led to modest reductions in body weight over an 18-month period. Most importantly, the DVD/IVR group showed significant reductions in BMI when compared to the SC group confirming our original hypothesis. However, there were no significant differences between Class/IVR and SC groups. Participants in the DVD/IVR group lost a mean 2.79 kg over 12 months with 26.9% of participants losing 5% or more of initial body weight in ITT analyses. These numbers improve for both technology-enhanced groups as the number of sessions attended increased.

Our results support the findings of several recent reviews on technology mediated DPPs (19, 20), eHealth obesity interventions (23), weight loss interventions in primary care (18, 36), and self-help weight loss interventions (22). Joiner et al. (20) found an estimated mean percent weight loss from baseline to 15 months to be −3.98% across the 22 studies included in the review. This magnitude of effect varied from −3.32% for stand-alone eHealth interventions to −4.49% for interventions with behavioral support given by a counselor remotely to −4.65% for interventions with behavioral support given by a counselor in-person.

When investigating the effects of eHealth obesity interventions, Hutchesson et al. (23) found that eHealth interventions demonstrated significantly greater weight loss (kg) than control groups (−2.70), or minimal intervention comparisons (−1.40). This review of 84 studies also showed significant weight loss for web-based interventions that incorporated non-eHealth components (−3.70); mobile interventions (−2.40) and web-based interventions delivered only using eHealth technologies (−2.21). Levine et al. (18) found 12 interventions that achieved weight loss (range: 0.08 kg −5.4 kg) compared to controls, 5–45% of patients losing at least 5% of baseline weight with trial duration and attrition ranging from 3 to 36 months and 6–80%, respectively. On another review (36) of 15 RCTs focusing on weight loss in primary care settings, the authors showed pooled results from meta-analysis indicating a mean weight loss of −1.36 kg at 12 months, and −1.23 kg at 24 months. Hartmann-Boyce et al. (22) found similar results in their meta-analysis of 23 studies of self-help interventions for weight loss in overweight and obese adults. They found that intervention participants lost significantly more weight than controls at 6 months (−1.85 kg) with no significant effect at 12 months (−0.76). They also showed that programs using some form of interactivity appeared to be more effective than controls at 6 months (−0.94 kg).

Taken altogether, our results support existing evidence on the effectiveness of technology mediated DPPs (19, 20), eHealth interventions for weight loss (18, 23, 36), and weight loss interventions in primary care settings (18, 36). Our intent-to-treat weight loss magnitude across all three conditions at 6 (SC: −1.52, Class/IVR: −1.70, DVD/IVR: −3.04), 12 (SC: −1.56, Class/IVR: −2.04, DVD/IVR: −2.79), and 18 months (SC: −1.15, Class/IVR: −1.46, DVD/IVR: −2.55) were well within the range found in these reviews (−0.08 to −3.76). Most importantly, our study presents results at 18 months with significant reductions in BMI, which represents a significant addition to current literature on the weight loss maintenance effect of technology enhanced interventions delivered within a primary care setting (18, 23, 36). Additionally, our attrition rates (31–38%) and percent of individuals achieving at least 5% weight loss in all study groups across all timepoints (ITT: 15.94–26.87%) are well within the range found by Levine et al. (18) when investigating technology-assisted weight loss interventions in primary care.

Additionally, while not the original purpose of this study, results from this trial seem to indicate that both the DVD/IVR and the Class/IVR groups could meet CDC recognition standards (35) minus the "Live" health coaching requirement. Most importantly, our CDC threshold results indicate similar results to the latest NDPP evaluation (37). We found that on average participants completed 15.5 sessions in DVD/IVR and 14.1 in Class/IVR (NDPP: 14) with 86.3% of participants in the intervention groups (NDPP: 86.6%) meeting the CDC threshold of completing at least 4 sessions, 48.4% (NDPP: 48.3%) staying in the program for at least 6 months, and 29.5% (NDPP: 10.4%) attending at least the full 12-month program. Average weight lost at 12 months for DVD/IVR participants meeting the CDC threshold was 3.24% compared to 2.74% for Class/IVR (NDPP: 3.6%) with 35.74% of DVD/IVR participants and 33.44% of Class/IVR (NDPP: 35.5%) achieving 5% weight loss goal.

These are important findings when considering that several barriers to large scale implementation remain for technology enhanced DPPs (19, 20) and weight loss interventions in primary care settings (18, 23, 36). In fact, recent studies (11, 12) have shown that the NDPP as currently delivered and its technology-based options are not able to reach a large proportion of the American population. These studies have shown a lack of availability of these programs in underserved areas (11, 12) where primary care is overburdened and under resourced, and when these programs are offered, they fail to attract a large and representative sample of the target population (12). Further, the spotty access to internet services and reliance on data plans presents a barrier to engagement in traditional eHealth programs requiring Internet connection

(38). The use of smart automated telephone calls to deliver DPP content shows promise in addressing these issues. The IVR system addresses barriers at multiple implementation levels. At the organizational, setting level the IVR system reduces the need for space, staff time, overall costs, and scheduling barriers. At the organizational, staff-level the IVR system reduces staff burden of delivering NDPP, and difficulty on scheduling participants, and allows staff to spend more time building relationships with participants to improve overall engagement. At the individual level, the IVR system addresses issues of distance, lack of transportation, work schedules, unreliable access to the Internet, and childcare needs. This is particularly important for primary care settings in underserved communities where there is a lack of resources, (i.e., medically underserved areas, space, competing demands, and expertise) and geographic segregation makes it difficult to deliver the NDPP or weight loss programs (13–16).

The present trial is not without limitations. First, study participants in the DVD/IVR group presented significantly higher BMI with a higher proportion being at Class III Obesity status at baseline. While we used randomization procedures, we did not stratify by BMI status. Nevertheless, we accounted for these initial differences by using baseline BMI values as control variable in our models. Second, we had an overall high attrition rate. As such, our results must be seen with caution as up to 38% of our participants did not complete follow-up assessments. These numbers were particularly higher among Class/IVR participants reaching 50% at 18 months. Nonetheless, we used Intent-to-treat analysis to include all participants with a baseline value in our models. When comparing with other studies, we also see similar attrition rates for weight loss programs in primary care (18). Future studies should continue to investigate factors influencing participant engagement and retention in weight loss interventions delivered in primary care settings. Finally, our trial lasted only 18 months and did not include glycemic control (e.g., HbA_1) or event based (e.g., T2D incidence) outcomes. Thus, long-term effects of the three groups await further investigation.

In closing, our findings show that a technology-enhanced diabetes prevention program was effective in reducing BMI at 6 months and maintaining these results at 12 and 18 months in a group of primary care patients at risk for developing T2D. The DiaBEAT-it interventions respond to the need for scalable, effective methods to manage obesity and prevent diabetes in primary care settings that do not over burden primary care clinics and providers. Further, the CDC requires the inclusion of a lifestyle coach in any in-person or technology-based program as one of the standards for recognition in its National Diabetes Prevention Program (35). Consideration of expanded program criteria to include fully-automated systems and or the possibility of engaging clinical staff as engagement agents instead of lifestyle coaches, may reduce the burden placed on many resource strapped primary care clinics and improve the potential for adoption and sustainability of DPP adaptations. Effective automated technologies such as DiaBEAT-it represent one of these strategies with the potential to serving a large, representative and geographically distant population, while decreasing the need for organizational resources and reliance on Internet availability.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Carilion Clinic Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FA, WY, RS, BD, MG, JH, and PE contributed to the conception of the protocol and study design. FA, WY, FB, TA, CG, and SW were involved with the data collection and analysis. All authors were involved in writing the paper and had final approval of the submitted manuscript.

Funding

This research was funded by the National Institute of Health and a National Institute of Digestive Diabetes and Kidney Disorders R018 Award—The Reach and Effectiveness of a Technology-Enhanced Diabetes Prevention Program (5R18DK091811, FA, PI). None of the funders had a role in the design, conduct, or analysis of this study.

Acknowledgments

The authors would like to acknowledge the entire DiaBEAT-it! research team who have been vital in the support and work of this project, including Kate Jones, Nicky Young, Ashley Merritt, Kimberlee Pardo, Cynthia Karllson, Peter Moreau, Rochelle Brown, Jessica Ladage, Jessica Mays, Felipe Marta, Camilia Squarcini, Nick Bilbro, Katie Brajdic, and Visva Patel.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of

their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1000162/full#supplementary-material

References

1. Centers for Disease Control and Prevention. *Estimates of Diabetes and Its Burden in the United States. National Diabetes Statistics Report*. Atlanta, GA: US Department of Health and Human Services (2020).

2. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for developing diabetes. *Lancet*. (2012) 379:11. doi: 10.1016/S0140-6736(12)60283-9

3. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care*. (2007) 30:753–9. doi: 10.2337/dc07-9920

4. Centers for Disease Control and Prevention. *Adult Obesity Facts*. Atlanta, GA: US Department of Health and Human Services (2020).

5. Centers for Disease Control and Prevention. *Prediabetes - Your Chance to Prevent Type 2 Diabetes*. Atlanta, GA: US Department of Health and Human Services (2020).

6. Knowler WC, Barrett-Connor E, Fowler SE. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. (2002) 346:393–403. doi: 10.1056/NEJMoa012512

7. Ali MK, Echouffo-Tcheugui J, Williamson DF. How effective were lifestyle interventions in real-world settings that were modeled on the Diabetes Prevention Program? *Health Aff*. (2012) 31:67–75. doi: 10.1377/hlthaff.2011.1009

8. Whittemore R. A systematic review of the translational research on the Diabetes Prevention Program. *Transl Behav Med*. (2011) 1:480–91. doi: 10.1007/s13142-011-0062-y

9. Dunkley AJ, Bodicoat DH, Greaves CJ, Russell C, Yates T, Davies MJ, et al. Diabetes prevention in the real world: effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes and of the impact of adherence to guideline recommendations: a systematic review and meta-analysis. *Diabetes Care*. (2014) 37:922–33. doi: 10.2337/dc13-2195

10. Dugani SB, Mielke MM, Vella A. Burden and management of type 2 diabetes in rural United States. *Diabetes Metab Res Rev*. (2020) 37:e3410. doi: 10.1002/dmrr.3410

11. Ariel-Donges AH, Gordon EL, Dixon BN, Eastman AJ, Bauman V, Ross KM, et al. Rural/urban disparities in access to the National Diabetes Prevention Program. *Transl Behav Med*. (2020) 10:1554–8. doi: 10.1093/tbm/ibz098

12. Ali MK, Bullard KM, Imperatore G, Benoit SR, Rolka DB, Albright AL, et al. Reach and use of diabetes prevention services in the United States, 2016–2017. *JAMA Netw Open*. (2019) 2:e193160. doi: 10.1001/jamanetworkopen.2019.3160

13. Halley MC, Petersen J, Nasrallah C, Szwerinski N, Romanelli R, Azar KM. Barriers and facilitators to real-world implementation of the diabetes prevention program in large healthcare systems: lifestyle coach perspectives. *J Gen Intern Med*. (2020) 35:8. doi: 10.1007/s11606-020-05744-y

14. Venditti EM, Wylie-Rosett J, Delahanty LM, Mele L, Hoskin MA, Edelstein SL. Short and long-term lifestyle coaching approaches used to address diverse participant barriers to weight loss and physical activity adherence. *Int J Behav Nutr Phys Act*. (2014) 11:16. doi: 10.1186/1479-5868-11-16

15. Laws RA, Fanaian M, Jayasinghe UW, McKenzie S, Passey M, Davies GP, et al. Factors influencing participation in a vascular disease prevention lifestyle program among participants in a cluster randomized trial. *BMC Health Serv Res*. (2013) 13:12. doi: 10.1186/1472-6963-13-201

16. Ackermann RT. Working with the YMCA to implement the Diabetes Prevention Program. *Am J Prev Med*. (2013) 44(Suppl. 4):S352–6. doi: 10.1016/j.amepre.2012.12.010

17. Rhoon LV, Byrne M, Morrissey E, Murphy J, McSharry J. A systematic review of the behaviour change techniques and digital features in technologydriven type 2 diabetes prevention interventions. *Digital Health*. (2020) 6:26. doi: 10.1177/2055207620914427

18. Levine DM, Savarimuthu S, Squires A, Nicholson J, Jay M. Technology-assisted weight loss interventions in primary care: a systematic review. *J Gen Intern Med*. (2015) 30:107–17. doi: 10.1007/s11606-014-2987-6

19. Bian RR, Piatt GA, Sen A, Plegue MA, De Michele ML, Hafez D, et al. The effect of technology-mediated diabetes prevention interventions on weight: a meta-analysis. *J Med Internet Res*. (2017) 19:e76. doi: 10.2196/jmir.4709

20. Joiner KL, Nam S, Whittemore R. Lifestyle interventions based on the diabetes prevention program delivered *via* ehealth: a systematic review and metaanalysis. *Prev Med*. (2017) 100:13. doi: 10.1016/j.ypmed.2017.04.033

21. Block G, Azar KM, Romanelli RJ, Block TJ, Hopkins D, Carpenter HA, et al. Diabetes prevention and weight loss with a fully automated behavioral intervention by Email, Web, and Mobile Phone: a randomized controlled trial among persons with prediabetes. *J Med Internet Res*. (2015) 17:e240. doi: 10.2196/jmir.4897

22. Hartmann-Boyce J, Jebb SA, Fletcher BR, Aveyard P. Self-help for weight loss in overweight and obese adults: systematic review and meta-analysis. *Am J Public Health*. (2015) 105:e43–57. doi: 10.2105/AJPH.2014.302389

23. Hutchesson MJ, Rollo ME, Krukowski R, Ells L, Harvey J, Morgan PJ, et al. eHealth interventions for the prevention and treatment of overweight and obesity in adults: a systematic review with meta-analysis. *Obes Rev*. (2015) 16:376–92. doi: 10.1111/obr.12268

24. Almeida FA, Pardo KA, Seidel RW, Davy BM, You W, Wall SS, et al. Design and methods of "fthodsA, Seid a hybrid preference/randomized control trial design using the RE-AIM framework. *Contemp Clin Trials*. (2014) 38:383–96. doi: 10.1016/j.cct.2014.06.010

25. Almeida FA, Shetterly S, Smith-Ray RL, Estabrooks PA. Reach and effectiveness of a weight loss intervention in patients with prediabetes in Colorado. *Prev Chronic Dis*. (2010) 7:A103.

26. Smith-Ray RL, Almeida FA, Bajaj J, Foland S, Gilson M, Heikkinen S, et al. Translating efficacious behavioral principles for diabetes prevention into practice. *Health Promot Pract*. (2009) 10:58–66. doi: 10.1177/1524839906293397

27. Estabrooks PA, Smith-Ray RL. Piloting a behavioral intervention delivered through interactive voice response telephone messages to promote weight loss in a pre-diabetic population. *Patient Educ Couns*. (2008) 72:34–41. doi: 10.1016/j.pec.2008.01.007

28. Harvey-Berino J, Pintauro S, Buzzell P, Gold EC. Effect of internet support on the long-term maintenance of weight loss. *Obes Res*. (2004) 12:320–9. doi: 10.1038/oby.2004.40

29. Perri MG, Limacher MC, Durning PE, Janicke DM, Lutes LD, Bobroff LB, et al. Treatment of obesity in underserved rural settings (TOURS): a randomized trial of extended-care programs for weight management. *Arch Intern Med*. (2008) 168:7. doi: 10.1001/archinte.168.21.2347

30. Heikes KE, Eddy DM, Arondekar B, Schlessinger L. Diabetes risk calculator: a simple tool for detecting undiagnosed diabetes and pre-diabetes Diabetes. *Care*. (2008) 31:1040–5. doi: 10.2337/dc07-1150

31. Goessl C, Estabrooks P, You W, Britigan D, DeAlba A, Almeida F. Effectiveness of DVD vs. group-initiated diabetes prevention on information uptake for high & low health literacy participants. *Patient Educ Couns*. (2019) 102:968–75. doi: 10.1016/j.pec.2018.12.026

32. Estabrooks PA, Glasgow RE, Dzewaltowski DA. Physical activity promotion through primary care. *JAMA*. (2003) 289:2913–6. doi: 10.1001/jama.289.22.2913

33. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. (1982) 38:963–74. doi: 10.2307/2529876

34. Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data*. New York, NY: Springer (2000).

35. Centers for Disease Control and Prevention. *Diabetes Prevention Recognition Program: Standards and Operating Procedures*. Atlanta, GA: US Department of Health and Human Services (2021).

36. Booth HP, Prevost TA, Wright AJ, Gulliford MC. Effectiveness of behavioural weight loss interventions delivered in a primary care setting: a systematic review and meta-analysis. *Family Practice*. (2014) 31:10. doi: 10.1093/fampra/cmu064

37. Ely EK, Gruss SM, Luman ET, Gregg EW, Ali MK, Nhim K, et al. A national effort to prevent type 2 diabetes: participant-level evaluation of CDC's national diabetes prevention program. *Diabetes Care*. (2017) 40:10. doi: 10.2337/dc16-2099

38. Perrin A. *Digital Gap Between Rural and Nonrural America Persists*. Washington, DC: Pew Research Center (2019).

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 27 June 2023
DOI 10.3389/fendo.2023.1111565

OPEN ACCESS

EDITED BY
Hiroshi Okada,
Matsushita Memorial Hospital, Japan

REVIEWED BY
Huiying Zhang,
Harbin Medical University, China
Xiaoxia Wei,
Chinese Academy of Medical Sciences and Peking Union Medical College, China
Kyuyong Cho,
Hokkaido University, Japan

*CORRESPONDENCE
Guanhua Fan
fangh@stu.edu.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 29 November 2022
ACCEPTED 16 May 2023
PUBLISHED 27 June 2023

CITATION
Lin M, Chen T and Fan G (2023) Current status and influential factors associated with adherence to self-monitoring of blood glucose with type 2 diabetes mellitus patients in grassroots communities: a cross-sectional survey based on information-motivation-behavior skills model in China. *Front. Endocrinol.* 14:1111565. doi: 10.3389/fendo.2023.1111565

Current status and influential factors associated with adherence to self-monitoring of blood glucose with type 2 diabetes mellitus patients in grassroots communities: a cross-sectional survey based on information-motivation-behavior skills model in China

Manxin Lin[1,2†], Tingting Chen[1,2†] and Guanhua Fan[2,3*†]

[1]School of Public Health, Shantou University, Shantou, China, [2]Shantou University Medical College, Shantou, China, [3]Health Management Center of Outpatient Department, Cancer hospital of Shantou University Medical College, Shantou, China

Objective: Self-monitoring of blood glucose (SMBG) plays a vital role in the maintenance of blood glucose with type 2 diabetes mellitus(T2DM) and pre-diabetes patients. The study was intended to describe the current status of SMBG with T2DM and pre-diabetes patients in grassroots communities, explore the relationship between SMBG frequency and blood glucose level and apply information-motivation-behavior(IMB) model to analyze the potential influencing factors of SMBG compliance based on electronic questionnaires.

Methods: A cross-sectional study was conducted with 1388 T2DM and pre-diabetes patients who completed electronic questionnaires composed of demographics and IMB model content. Chi-square test, Mann-Whitney U test and multivariable logistic regression model analysis were utilized to explore deeply causes of SMBG compliance.

Results: The results of this study showed that among 1388 T2DM patients, only 26.2% (363/1388) patients reached SMBG standard, indicating low compliance with SMBG. Given that SMBG is one of the individual predictors of type 2 risk in prediabetes patients, this result suggests that the SMBG compliance rate needs to be improved. Patients with fixed occupation (OR=1.989, P=0.035), BMI in normal range (OR=1.336, P=0.049), smoking habit(OR=1.492, P=0.019), understanding SMBG frequency (OR=1.825, P<0.001), understanding control goal of blood glucose (OR=1.414, P<0.001), knowing all the functions of the blood glucose meter (OR=1.923, P<0.001), buying a blood glucose meter/test paper conveniently(OR=2.329, P=0.047), taking supplementary measurement when forgetting blood glucose test(OR=2.044, P=0.005), rotating all the fingers when measuring blood glucose (OR=1.616, P<0.001) and less pain at the

needling site(OR=2.114, P<0.001)were independently promoting factors of adherence to SMBG. However, the lack of accessibility and convenience of blood glucose meter or heavy financial burden were blocking factors of adherence to SMBG. Moreover, there were still bottlenecks such as lack of health care knowledge and needle pricking pain.

Conclusion: This study verified the practicability of applying IMB model to SMBG with T2DM and pre-diabetes patients. Adherence to SMBG still remained to improved, and putting more emphasis in improvement of individual information, motivation and behavioral skills with patients might be beneficial to maintain better adherence to SMBG in long-term routine of diabetes self-management.

KEYWORDS

type 2 diabetes mellitus (T2DM), pre-diabetes, self-monitoring of blood glucose (SMBG), adherence, influencing factors, IMB model

1 Introduction

In recent years, the incidence and prevalence rate of DM has increasing worldwide, with its protracted courses and high mortality rate, which has placed a heavy burden on health of the global population. Under the background of primary care, community is the "front line" and "main battlefield" of diabetes management. Diabetes management in grass-roots communities is one of the most effective means to delay the progress of diabetes and reduce the risk of diabetes complications (1). At present, there are many deficiencies in diabetes management in domestic diabetes communities, such as inconsistent standards, low operating efficiency, floating form and so on (2, 3). The keys to integrate respective advantages, improve patients' cognition of diabetes, reduce patients' economic burden as much as possible and maximize the convenience and accessibility of community health resources at the grass-roots level is to exert the synergy of self-monitoring in the comprehensive management of diabetes. Tilting the diabetes management mode to the community, taking the self-monitoring of diabetics in the daily community environment as a breakthrough, and digging out a replicable self-monitoring mode for diabetics in the community will give new significance to the community management of diabetes in the post-epidemic era. Admittedly, grass-roots communities shoulder the heavy responsibility of diabetes management.

According to the latest data from the International Diabetes Federation, an estimated 537 million adults aged 20-79 were living with diabetes in 2021, accounting for 10.5 percent of the global population. China has about 140 million diabetics (about 26% of the world's total). T2DM was the most common type of diabetes(90% of all diabetics), whose prevalence rate has increasing year by year and the epidemic trend has not yet reached the plateau. In addition, pre-diabetes was regarded as a key window period, which was a sign or watershed to reverse diabetes (4, 5). Around 5%-10% of pre-diabetes turned into diabetes each year. In 2003, American Diabetes Association (ADA) proposed that a critical threshold for diagnosing of pre-diabetes impaired fasting blood glucose (IFG) should be reduced from 6.1 mmol/L to 5.6 mmol/L. It is estimated that the scale of people with IFG in China will increase to exceed to 470 million and more and more people have become a huge reserve army for diabetes (6). Move the strategic pass of diabetes management forward could make more patients be managed at an early stage, in order to reduce diabetes complications.

Diabetes is a typical lifestyle disease, and its prevention and control needs comprehensive strategy of "Five Carriages of Diabetes Treatment"(FCDT), which is composed of drug treatment, blood glucose monitoring, diet control, exercise control and health education. Single continuously intensive drug treatment was no longer the priority strategy (7). Among them, blood glucose monitoring played a vital role in controlling blood glucose and inhibiting complications. As an effective tool for diabetes management, SMBG could help patients better understand their own conditions and then making corresponding drug and behavior adjustments. On the other hand, it could also provide more diagnosis and treatment basis for clinicians, so that the disease conditions of diabetics could be better controlled (8–10).

Many studies turned out that there was a yawning gap between recommended SMBG frequency and the actual application, which were affected by many factors (11). Studies in China, the United States, Europe and worldwide have revealed several factors that affect patients' compliance with SMBG, including occupation, economic status, living habits, hobbies, SMBG related cognition, SMBG related behaviors, accessibility and so on. Additionally, a series of studies exhibited that the practicability and maturity of IMB model have been verified on T2DM. Integrating analysis of various influencing furtherly was beneficial to provide a clearer explanation of ultimate causes and feasible goals of SMBG behaviors (12, 13). Research have shown that the increase of diabetes knowledge (information) was associated to the significantly reduced glycosylated hemoglobin level, which contributed to the self-management of diabetes (14–16). High motivation level improved T2DM patients SMBG compliance

(17). And good behavioral skills were essential to enhance SMBG compliance which was key to reach the best blood glucose level (18, 19). Nevertheless, most studies neglected the influence from patients in pre-diabetes stage, as well as failed to fully explore the relationship between IMB model and SMBG of T2DM patients, which was exactly the gap that our study intended to fill with.

In a nutshell, the study selected T2DM and pre-diabetes patients in China grassroots communities as research objects, explored status of SMBG based on the IMB framework and analyzed the influencing factors of adherence to SMBG, deeply explaining the maintenance mechanism and providing a new sight of SMBG with T2DM and pre-diabetes patients.

2 Objects and methods

2.1 Research design and data collection process

2.1.1 Research design and participants

The subjects of the study were diabetic patients with different clinical stages available to the investigator's unit (Shantou community). The data collection method of convenience sampling was adopted in this study, and quality control was strictly implemented in the process to ensure good quality of data provided by diabetes patients in grassroots communities participating in this study.

During the study, relevant questionnaires were filled in after obtaining the consent of community patients. Inclusion criteria were: ① Patients with prediabetes and T2DM meeting WHO diagnostic criteria. ② The patient is over 18 years old and has certain understanding and communication skills. ③ The patient had a daily community residence and a relatively stable living state. ④ I have been followed up in the outpatient clinic for diabetes evaluation, and basically know my own diabetes clinical stage. ⑤All the interviewed patients voluntarily participated in this study with informed consent. Exclusion criteria: ① suffering from serious organic disease; ② Patients with severe complications. As shown in Figure 1.

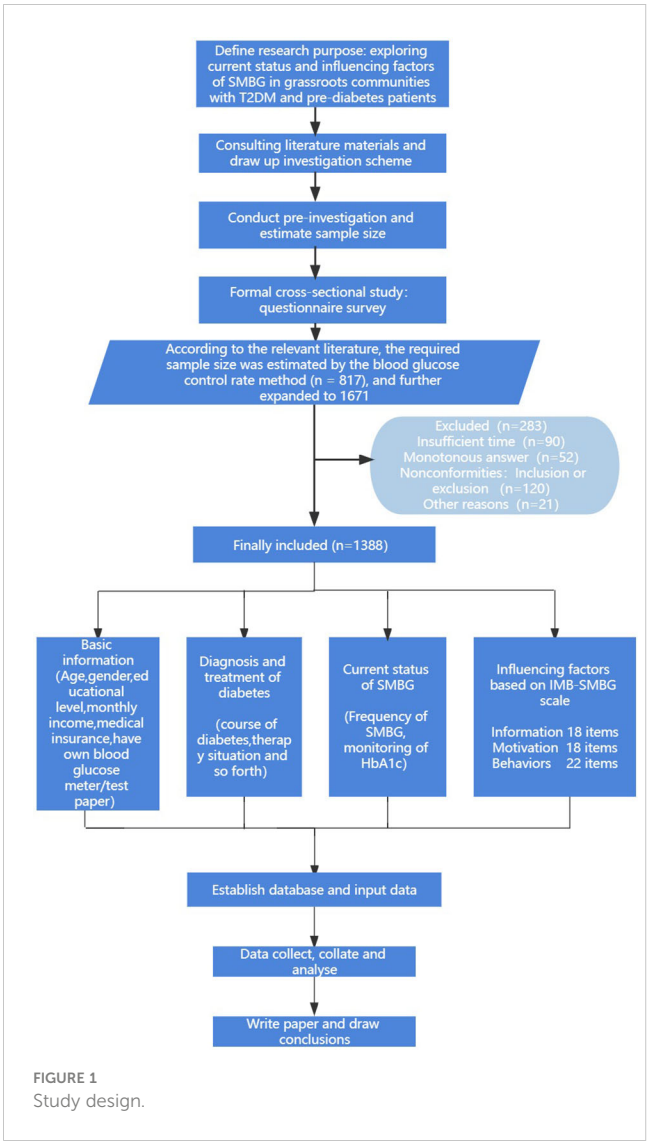


FIGURE 1
Study design.

2.1.2 SMBG criteria for grouping

According to the standards of China's guidelines for the prevention and treatment of type 2 diabetes mellitus (2020 edition) (part I), the patients treated with insulin were divided into groups (18). Since patients requiring insulin therapy have different requirements for SMBG frequency than non-insulin therapy patients, we used insulin therapy and non-insulin therapy as the basis for grouping. At the same time, patients were further grouped based on self-reported HbA1c values. As a first step, screening should be performed in patients treated with insulin, when HbA1c is in the normal range, the frequency of SMBG should be 4 or more times per day. If the HbA1c value is not within the normal range, the SMBG frequency should be 7 or more times per day. Next, in patients not receiving insulin, the frequency of SMBG should be 6 or more times per week when HbA1c is within the normal range. If the HbA1c value is not within the normal range, the SMBG frequency should be 4 or more times per day. Finally, all patients with SMBG reaching the required monitoring frequency were included in the SMBG standard group. Patients whose monitoring frequency did not meet the requirements were included in the SMBG sub-standard group. As shown in Table 1.

2.2 Methods

2.2.1 Research indicators and tools

The IMB-SMBG scale (21) was used for quantitative statistics, and the IMB-SMBG scale was translated into the Chinese version. The Chinese version of the IMB-SMBG questionnaire consisted of three subscales: SMBG information, motivation and behavioral skills. This questionnaire has a total of 58 items, including 18 items in information part, 18 items in motivation part and 22 items in behavior part. This is a five-level Likert scale with five responses: "strongly agree", "agree", "neutral", "disagree" and "strongly disagree". The score of each item ranges from 1 to 5. The

TABLE 1 SMBG grouping standard.

	HbA1c normal value	HbA1c abnormal value
Insulin therapy	≥4 times/day	≥7 times/day
Non insulin therapy	≥6 times/week	≥4 times/day

The normal range of glycated hemoglobin in patients with type 2 diabetes is 4.4% ~ 7.0%, and that in patients with pre-diabetes is less than or equal to 6.1% (20).

compliance degree of blood glucose self-monitoring of each patient will be the total score of the sum of the scores obtained from the answers to each question. The total score of this part represents the compliance degree of blood glucose self-monitoring of the patient, and the higher score represents the better diabetes self-management. The Cronbach's α coefficient of the questionnaire internal consistency test was 0.965, and the Cronbach's α coefficients of information, motivation and behavior were 0.695, 0.932 and 0.965, respectively. Construct validity KMO=0.967, Bartlett's spherical test $\chi 2$ = 15299.427, P<0.000.

2.2.2 Sample size

Based on a review of previous literature (22–24), we found that the reported glycemic control rate (HbA1c<7%, 58mmol/mol) in Chinese patients with T2DM varied from 31.78% to 39.7%. Assume that the glycemic control rate is 35%, α is 0.05, and the allowable error of sampling is 0.06. We calculate the required sample size of 1002, which would allow for a non-response rate of 20%, and calculate the required sample size of 1253. In order to further improve the robustness of the research conclusions, we further expanded the sample size. We received 1,671 total questionnaires and excluded 283 invalid questionnaires (such as taking too short time to fill in the questionnaire or giving a single answer), and finally included 1388 sample sizes.

2.2.3 Data collection

The Chinese version of IBM-SMBG scale was input into the electronic questionnaire, and patients filled in the questionnaire by scanning the QR code of "Questionnaire Star Platform". The purpose and significance of the survey and the method of filling out the questionnaire were explained to the patients through subheadings. All the questionnaires were checked and screened by professionals after they were collected. Records of the patient's general condition (age, gender, educational level, income, type of medical insurance and have glucose meter/blood sugar test paper, etc.), the situation of diagnosis and treatment of diabetes (course, treatment, etc.), SMBG status (including frequency of SMBG, outpatient measuring blood sugar, glycosylated hemoglobin HbA1c) monitoring and potential influence factors of SMBG.

2.2.4 Statistical analysis

The collected data were analyzed and processed by SPSS25.0. The background data and scale scores were statistically described to present demographic and other characteristics. The measurement data of non-normal distribution was expressed by M(P50), and Mann-Whitney U test was used for comparison between the two groups. The data were expressed in relative number (%), and comparison between the two groups was performed by chi-square test. Multivariate Logistic regression was used to analyze the potential influencing factors of SMBG in T2DM patients. The test level α=0.05, P < 0.05 was considered statistically significant.

3 Results

3.1 Basic information

A total of 1671 questionnaires were distributed and collected. Excluding the invalid questionnaires such as incomplete filling and short filling time, there were 1388 questionnaires were valid, and the recovery rate was 83.1%(1388/1671). Among them, there were 986 males (71.0%) and 402 females (29.0%). 72% were T2DM patients and 28% were pre-diabetes patients. In China, the number of pre-diabetes patients with low fasting blood glucose and high postprandial blood glucose was huge, hence we included pre-diabetes patients in communities. Moreover, patients who were in pre-diabetes stage could inhibit developing into T2DM by changing their dietary habits and increasing physical exercise. Thus, it was of great value for diabetics to strengthen the adherence to SMBG. Specifically, based on the IMB model composed of the information, motivation and behavior three parts, the score range of the SMBG up-to-standard group were 32-67 (M = 53), 29-86 (M = 61) and 31-110 (M = 73) respectively, while the score range of the SMBG not-up-to-standard group were 31-68 (M = 47), 22-86 (M = 50) and 22-88 (M = 59) respectively, with differences statistically significant (P < 0.001). As shown in Table 2.

3.2 Bivariate analysis of potential influencing factors of SMBG

There were 363 cases (26.2%) in SMBG up-to-standard group and 1025 cases (73.8%) in SMBG not-up-to-standard group in study. Patients with different occupational status had distinct SMBG compliance, and the difference was significant(P<0.001). The study results exhibited that unmarried patients had lower adherence to SMBG than married, divorced or widowed T2DM patients, and the difference was statistically significant (P<0.005). As Pereira MG (25) studied, better family coping and higher level of positive support in patient evaluation predict would insist SMBG more after four months of intervention, thus patients with families meant better blood glucose monitoring. As for the course of diabetes, the SMBG compliance of diabetic patients in distinct course of diabetes was different(P<0.001). Besides, compared with patients who lacked basic knowledge of diabetes as well as not formed a scientific method of blood glucose control in the diagnosis period (less than half a year after diagnosis of diabetes) and exploration

10.3389/fendo.2023.1111565

TABLE 2 Bivariate analysis of potential influencing factors of SMBG.

	SMBG adherence (n=363)	SMBG non-adherence (n=1025)	χ^2/Z value	P value
Age [n (%)]				
Under 18 years old	5 (20.8)	19 (79.2)	1.873	0.866
18-30 years old	144 (26.9)	391 (73.1)		
31-45 years old	127 (24.8)	386 (75.2)		
46-60 years old	73 (28.3)	185 (71.7)		
61-75 years old	12 (25.0)	36 (75.0)		
Over 76 years old	2 (20.0)	8 (80.0)		
Gender [n (%)]				
Male	258 (26.1)	728 (73.9)	0	1
Female	105 (26.2)	297 (73.8)		
Type of diabetes [n (%)]				
Pre-diabetes	115 (29.6)	273 (70.4)	3.389	0.067
T2DM	248 (24.8)	752 (75.2)		
Education level [n (%)]				
Primary school and below	8 (19.0)	34 (81.0)	5.834	0.120
Middle school/technical secondary school	98 (28.7)	243 (71.3)		
Colleges	169 (27.6)	443 (72.4)		
Bachelor degree or above	88 (22.4)	305 (77.6)		
Occupation [n (%)]				
Worker	107 (21.8)	384 (78.2)	19.684	0.001**
Farmer	130 (26.7)	357 (73.3)		
Freelancer	107 (34.6)	202 (65.4)		
Retired/unemployed	10 (16.4)	51 (83.6)		
cadre	9 (22.5)	31 (77.5)		
Medical fee payment method [n (%)]				
Urban medical insurance	78 (22.6)	267 (77.4)	10.610	0.600
Employee medical insurance	120 (25.2)	357 (74.8)		
Rural cooperative medical insurance	118 (27.3)	315 (72.7)		
Government/business subsidy	28 (40.6)	41 (59.4)		
Diabetes special clinic	14 (29.8)	33 (70.2)		
Self-payment	5 (29.4)	12 (70.6)		
Marital status [n (%)]				
Single	75 (20.3)	294 (79.7)	10.751	0.005**
Married	270 (27.8)	700 (72.2)		
Divorced/widowed	18 (36.7)	31 (63.3)		
Duration of diabetes [n (%)]				
<1 year	42 (18.8)	182 (81.3)	24.133	0.000***
1-5 years	169 (23.6)	548 (76.4)		

(Continued)

TABLE 2 Continued

	SMBG adherence (n=363)	SMBG non-adherence (n=1025)	χ^2/Z value	P value
6-10 years	119 (33.3)	238 (66.7)		
11-20 years	31 (37.8)	51 (62.2)		
>20 years	2 (25.0)	6 (75.0)		
Taking oral drugs to control blood glucose [n (%)]				
Yes	218 (25.9)	625 (74.1)	0.95	0.755
No	145 (26.6)	400 (73.4)		
Average monthly income [n (%)]				
<3000	26 (17.2)	125 (82.8)	14.169	0.007**
3000-6000	124 (24.5)	383 (75.5)		
6000-9000	144 (27.4)	382 (72.6)		
9000-12000	57 (35.0)	106 (65.0)		
>12000	12 (29.3)	29 (70.7)		
Smoking [n (%)]				
Yes	228 (28.4)	574 (71.6)	5.096	0.026*
No	135 (23.0)	451 (77.0)		
Drinking [n (%)]				
Yes	262 (27.8)	679 (72.2)	4.321	0.043*
No	101 (22.6)	346 (77.4)		
BMI [n (%)]				
BMI <18.5	51 (24.2)	160 (75.8)	3.061	0.382
18.5≤ BMI <24.0	226 (27.7)	590 (72.3)		
24.0≤ BMI <28.0	60 (22.7)	204 (77.3)		
BMI ≥28.0	26 (26.8)	71 (73.2)		
With diabetic family history [n (%)]				
Yes	173 (27.8)	450 (72.2)	1.529	0.220
No	190 (24.8)	575 (75.2)		
Diabetes-related complications [n (%)]				
Yes	190 (24.9)	573 (75.1)	1.373	0.244
No	173 (27.7)	452 (72.3)		
Outpatient frequency per year [n (%)]				
0-2	107 (21.7)	386 (78.3)	16.966	0.000***
3-5	219 (27.1)	588 (72.9)		
≥6	37 (42.0)	51 (58.0)		
Frequency of hospitalizations per year [n (%)]				
<1	94 (24.7)	286 (75.3)	2.544	0.280
1-2	237 (26.0)	673 (74.0)		
>3	32 (32.7)	66 (67.3)		

(Continued)

TABLE 2 Continued

	SMBG adherence (n=363)	SMBG non-adherence (n=1025)	χ^2/Z value	P value
Knowing HbA1c [n (%)]				
Yes	198 (23.7)	638 (76.3)	6.633	0.011*
No	165 (29.9)	387 (70.1)		
Having own blood glucose meter [n (%)]				
Yes	288 (25.7)	831 (74.3)	0.516	0.487
No	75 (27.9)	194 (72.1)		
Knowing the frequency of SMBG [n (%)]				
Yes	79 (33.5)	157 (66.5)	7.893	0.006**
No	284 (24.7)	868 (75.3)		
IMB-SMBG scale (information)	53 (32,67)	47 (31,68)	-14.775	0.000***
IMB-SMBG scale (motivation)	61 (29,86)	50 (22,86)	-16.430	0.000***
IMB-SMBG scale (behavior)	73 (31,110)	59 (22,88)	-17.037	0.000***

SMBG, Self-monitoring of blood glucose; BMI, Body mass index.
*P<0.05; **P<.01; ***P<0.001.

period (six months to two years after diagnosis of diabetes), most patients in the stable period of diabetes (more than two years after diagnosis) had better compliance of SMBG. The SMBG compliance rate in patients with various average monthly income was different (P<0.007); patients with smoking and drinking habits had higher SMBG compliance rate, and difference was statistically significant (P<0.05); Adherence to SMBG of patients with distinct outpatient frequency per year was different. Patients who went to diabetes clinic more than 6 times a year had better compliance of SMBG, and difference was statistically significant (P<0.001). No statistically significant differences in adherence to SMBG, age, gender, type of diabetes, education level, type of medical insurance, taking oral drugs to control blood glucose, BMI, family history of diabetes, having diabetes-related complications, frequency of hospitalizations per year, having own blood glucose meter were found (P>0.05, as shown in Table 2).

3.3 Multivariate logistic regression analysis of potential influencing factors of SMBG

Whether SMBG meets the standard (yes =1, no =0) is taken as the dependent variable, and factors with statistical significance in the above univariate analysis results are taken as independent variables. As shown in Table 3. The results of multivariate Logistic regression analysis revealed that occupational type, BMI, smoking habit, whether knowing frequency of SMBG, whether you feel pain at the prick site, whether knowing all the functions of blood glucose meter, whether buying test paper conveniently, whether understanding self-glycemic control goals, whether taking supplementary measurement when forgetting blood glucose test and whether rotating all the fingers when measuring blood glucose were potential influencing factors of SMBG.(P<0.05, as shown in Table 4). The compliance of SMBG with T2DM patients in normal BMI range was higher than that in patients without in normal BMI range (OR=1.336, P<0.049). Types of occupation could also affect SMBG compliance (OR=1.989, P<0.035), and patients with fixed occupation had higher compliance of SMBG than that with freelancers. In addition, the compliance of T2DM patients who knew frequency of SMBG was higher than that of those who knew it less (OR=1.825, P<0.001); T2DM patients who had their glucose control goal had higher adherence to SMBG(OR=1.414, P<0.001), and knowing all the functions of blood glucose meter was beneficial to improve compliance of SMBG(OR=1.923, P<0.001).Therefore, mastering SMBG skills could enhance the understanding of blood glucose monitoring, meanwhile, improving the operability of SMBG could promote adherence to SMBG.

3.4 ROC curve analysis based on IMB-SMBG score

Receiver operating characteristics curve (ROC) analysis was aimed at evaluating prediction potential of IMB model. AUC represented the area under ROC curve, which indicated prediction accuracy. Its value was between 0 and 1, and the larger value was within the higher the accuracy. In the ROC curve, the best diagnostic cut-off point of SMBG compliance was when Youden index was the largest and the coincidence sensitivity was relatively high. In this study, SMBG compliance and non-compliance were taken as state variables of ROC, and the value of state variable was set as 1. The test variables were the total score of the scale and the scores of three sub-items (information, motivation and behavioral skills), respectively. The ROC curve analysis was carried out, and the relevant results were shown in Figure 2. The critical value of total IMB-SMBG score on adherence to SMBG was 136.5 points and AUC was 0.814.(95%CI=0.786～0.841, P<0.001); the critical

TABLE 3 Assignment of multivariate logistic regression analysis of potential influencing factors of SMBG with T2DM and pre-diabetes patients.

Variable	Value
Gender	Male=1;Female=0
Age	>45 years old=1;≤45 years old=0
Type of diabetes	T2DM patients=1;Pre-diabetes patients=0
Educational level	Bachelor degree or above=1; Blow bachelor degree=0
Occupation	Fixed occupation=1;Freelancer=0
BMI	In normal range=1; out of normal range=0
Whether smoking	Yes=1;No=0
Whether drinking	Yes=1;No=0
Whether knowing the frequency of SMBG	Yes=1;No=0
Whether feeling pain at the needling site	Yes=1;No=0
Whether knowing all the functions of the blood glucose meter	Yes=1;No=0
Whether buying a blood glucose meter/test paper conveniently	Yes=1;No=0
Whether understanding self-glycemic control goals	Yes=1;No=0
Whether taking supplementary measurement when forgetting blood glucose test	Yes=1;No=0
Whether rotating all the fingers when measuring blood glucose	Yes=1;No=0

TABLE 4 Multivariate logistic regression analysis of potential influencing factors of SMBG with T2DM and pre-diabetes patients.

Factors	β	SD	Wald	P Value	OR (95%CI)
Gender	-0.167	0.172	0.937	0.333	0.847 (0.604～1.186)
Age	0.06	0.176	0.001	0.971	1.006 (0.713～1.420)
Educational level	-0.656	0.469	1.955	0.162	0.519 (0.207～1.301)
Occupation	0.688	0.327	4.421	0.035*	1.989 (1.048～3.777)
BMI	0.290	0.147	3.874	0.049*	1.336 (1.001～1.784)
Whether smoking	0.400	0.170	5.542	0.019*	1.492 (1.069～2.081)
Whether drinking	-0.197	0.180	1.191	0.275	0.821 (0.577～1.170)
Whether knowing the frequency of SMBG	-0.602	0.178	11.371	0.001**	1.825 (1.287～2.589)
Whether feeling pain at the needling site	0.748	0.176	18.032	0.000***	2.114 (1.496～2.986)
Whether knowing all the functions of the blood glucose meter	0.654	0.172	14.526	0.000***	1.923 (1.374～2.691)
Whether buying a blood glucose meter/test paper conveniently	0.845	0.166	25.794	0.047*	2.329 (1.681～3.227)
Whether understanding self-glycemic control goals	0.346	0.174	3.954	0.000***	1.414 (1.005～1.989)
Whether taking supplementary measurement when forgetting blood glucose test	0.715	0.167	18.324	0.005**	2.044 (1.473～2.835)
Whether rotating all the fingers when measuring blood glucose	0.480	0.171	7.913	0.000***	1.616 (1.157～2.258)

*P<0.05; **P<0.01; ***P<0.001.

value of subscale on information was 49.5 points, and AUC was 0.760 (95%CI=0.732~0.789, P<0.001); the critical value of subscale on motivation was 57.5points, and AUC was 0.790 (95% CI=0.762~0.817, P<0.001); the critical value of subscale on behaviors was 69.5points, and AUC was 0.800 (95% CI=0.773 ~ 0.828, P<0.001).

The results turned out that subscales on information, motivation and behavior skills all had high diagnostic value for SMBG compliance (AUC>0.7). For T2DM and pre-diabetes patients, the diagnostic accuracy of IMB-SMBG on behaviors was the highest, and the best diagnostic cut-off point was 69.5 points. Overall, the ROC curve showed superb prediction ability of IMB-

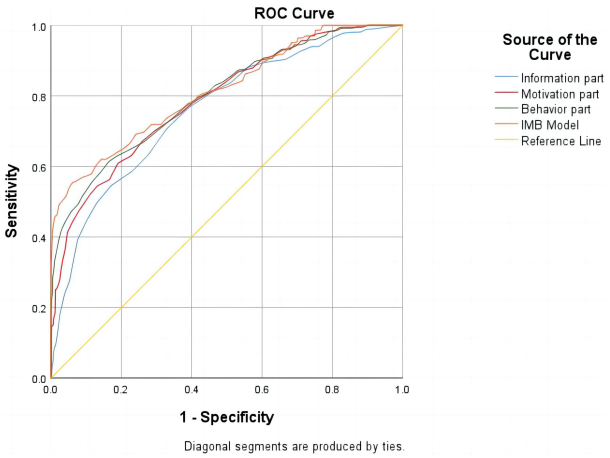


FIGURE 2
ROC curve of cumulative state on behavioral elements required for SMBG compliance with T2DM and pre-diabetes patients.

SMBG (AUC = 0.814, 95%CI=0.786-0.841), which was beneficial to evaluate the potential of the final multivariate logistic regression model. When the total score of the three parts of the equivalence table is greater than or equal to 136.5 points, the blood glucose monitoring is up to standard. Specifically in the sub-items, it indicates that the intensity of patients' daily information needs to be ≥49.5 points, the intensity of motivation needs to be ≥57.5 points, and the intensity of behavioral achievement needs to be ≥69.5 points. If a patient achieves these scores in SMBG, it indicates that the intensity requirements of information, motivation and practical behavior required by the patient to achieve the goal of daily blood glucose monitoring can promote the achievement of the goal of blood glucose monitoring. In addition, improving patients' understanding and learning of diabetes knowledge, motivating them to take action, persuading them to believe and form good habits, and teaching them relevant behavioral skills can effectively promote the improvement of SMBG compliance to a certain extent.

4 Discussion

4.1 Status and problems of SMBG in T2DM patients

Results of this study showed that among 1388 patients with T2DM, only 26.2% (363/1388) patients reached SMBG standard. Given that SMBG is one of the individual predictors of type 2 risk in prediabetic patients, this result suggests low SMBG compliance. The results showed that patients with normal BMI had better SMBG compliance than those with abnormal BMI (OR=1.336, P<0.049). In T2DM patients, the rate of blood glucose monitoring in regular occupation was higher than that in non-regular occupation (OR=1.989, P<0.035). In terms of SMBG cognition, there is a significant difference between knowing SMBG frequency (P<0.001) and knowing SMBG's sugar control goal (P<0.001). In terms of SMBG behavior, there are statistically significant differences in whether you feel pain at the acupuncture site (P<0.000), whether you can make up blood sugar test (P<0.005) and whether you can rotate your fingers during self-test (P<0.001). In terms of the feasibility of SMBG, there are statistically significant differences between whether it is convenient to buy a blood glucose meter/blood glucose test paper (P<0.047) and whether you know how to use all functions of the blood glucose meter (P<0.001).

4.2 Analysis of potential influencing factors and corresponding measures

4.2.1 Accessibility and convenience of blood glucose meter/test paper

This study showed that T2DM patients who did not have convenient access to glucose meters or blood glucose test strips had worse SMBG compliance than those who did (P<0.047). The reason is that many T2DM patients cannot afford a blood glucose meter due to economic reasons (26). Although there are a variety of self-monitoring equipment and supplies for blood glucose in China, the price of blood glucose meter and blood glucose test paper is a certain pressure for patients with poor economic affordability, which leads to a low compliance of SMBG in some T2DM patients. From the perspective of objective factors, it is found that the lack of blood glucose meter is one of the obstacles of SMBG in diabetic patients (27). While patients with blood glucose meters tend to have higher frequency SMBG, because having blood testing equipment can makes it easy for patients to perform SMBG (28). Therefore, it would be remiss to ignore the economic impact and the accessibility and convenience of blood glucose meter/test paper, and the income of SMBG should be balanced with its cost. In this regard, we suggest that according to the characteristics of patients' economic status and age, and refer to the suggestions of medical staff or patients' families, help diabetic patients choose an economical blood glucose meter and teach them to use technology and some skills. For the manufacturers of glucose meters, we suggest that they develop new technologies to reduce the cost of blood glucose meters, ease the purchase pressure of diabetic patients, improve the accessibility of blood glucose meters, and encourage patients to perform regular SMBG.

4.2.2 Cognition about SMBG

This study found that T2DM patients with good understanding of SMBG had better compliance with SMBG than those with poor understanding, that is, patients who knew the frequency of SMBG and clear glucose control goals had better compliance with SMBG, and the difference was statistically significant (P<0.001). The reason may be the misunderstanding of SMBG. Some patients think that blood glucose monitoring should be done by medical staff. They have monitored their blood glucose in hospital, but there is no need to monitor their blood glucose at home. Some patients think that SMBG is not helpful to control their own condition, so they don't need to monitor their blood sugar when they feel good. Some patients are afraid that their blood glucose monitoring technology is not in place, and inaccurate blood glucose monitoring and

incomplete disinfection will lead to infection and other misperceptions, resulting in poor compliance with SMBG (9). Studies have shown that T2DM patients have poor knowledge of SMBG (29), 54.09% of them do not know the frequency of SMBG, 95.08% of them do not know the correct time of SMBG, 67.62% of them do not know the goal of fasting blood glucose control, and 95.08% of them don't know the goal of postprandial blood glucose control. Therefore, T2DM patients need to set a SMBG glucose control target, because goal setting has a certain positive effect on improving the short-term compliance of patients with SMBG (30), and it is also beneficial for patients to know about the positive aspects and potential negative aspects of SMBG, so as to further enhance the cognition of the positive aspects (31).

Postprandial blood glucose is also an important indicator of blood glucose control, but most T2DM patients only monitor fasting blood glucose, and do not know the significance of postprandial blood glucose, which is also the content of individualized diabetes education. Therefore, it is an important measure to develop individualized and targeted education and nursing program of diabetes blood glucose management to increase patients' knowledge of blood glucose monitoring and compliance. In this regard, we suggest that medical staff should carry out more systematic, comprehensive and targeted SMBG guidance and education for patients according to the guidelines, so as to enhance their knowledge and belief of SMBG, improve their compliance of SMBG, and enable diabetic patients to actively and effectively conduct SMBG.

4.2.3 Receive SMBG-related education

However, effective self-management requires frequent and high-level educational investment and continuous support. This study found that patients who actively know about medical health knowledge, such as T2DM patients who know about SMBG frequency and know how to use all functions of blood glucose meter ($P<0.001$), have better compliance with SMBG, which is consistent with previous research conclusions. In previous studies (32, 33), it was found that receiving blood glucose monitoring education can significantly improve SMBG compliance, and patients who have received diabetes education had better control of blood glucose level and glycosylated hemoglobin (34). T2DM patients who know how to use the blood glucose meter have better compliance with SMBG. The reason may be that patients who know how to use blood glucose meter pay more attention to their blood glucose level, so they will actively learn and understand some SMBG-related skills and knowledge to achieve the purpose of SMBG. The time point of SMBG and the goal of SMBG for T2DM patients vary from person to person, and are closely related to the age, course of disease, complications and drug use of patients. Diabetes education plays a very important role in the treatment of diabetes, which is related to the control of blood glucose and the prevention of complications. Therefore, in community diabetes patients, when the perfect disease management system is not well implemented, it is especially important for patients to actively learn and understand the knowledge of diabetes-related diseases to improve SMBG compliance.

Therefore, we suggest that T2DM patients establish a correct SMBG concept and receive SMBG-related education. First of all, the operation of SMBG is easy to learn, and it is not limited by time and place. Its measurement results can better reflect the blood glucose level of diabetic patients. For hospitalized patients, different forms of health education can be provided in the hospital, such as propaganda boards, brochures, small lectures, peer education (the missionary can effectively improve the effect of diabetes education and management by conducting the education as peers), etc. Secondly, for community patients, through community lecture halls, publicity materials, TV or pamphlets, the frequency, time and significance of SMBG and the correct operation method of blood glucose monitor are explained and demonstrated, so that T2DM patients can form a correct concept of SMBG. In addition, strengthening the education and management of patients' SMBG and improving the level of patients' SMBG are also inseparable from the education and management of medical staff. Medical staff should increase the number of SMBG drill teaching for patients, and focus on the misunderstandings that are easy to occur in SMBG during the drill (35).

4.2.4 Relevant behaviors of SMBG

This study found that patients with T2DM who experienced needle pain had lower adherence to SMBG than patients who did not experience pain ($P<0.001$). The reason is that SMBG is a traumatic operation, and pricking the finger for sampling may induce certain negative effects. The pain related to finger pricking is probably the main reason why patients resist the use of SMBG, which makes them bored or even refuse to use SMBG. At the same time, there will be some consequences: such as scar formation and calluses; Loss of sensitivity, resulting in cognitive impairment (36). For acupuncture pain, we suggest to teach T2DM patients some techniques to relieve pain, such as telling patients to soak their hands in warm water before taking blood, choosing the angle of needle insertion according to the thickness of skin, choosing the right blood collection needle, and changing the blood collection needle every time. Through the application of new technology, the pain caused by needle pricking can be reduced. The use of SMBG gloves can reduce puncture infection, relieve the pain of diabetic patients during needle pricking, and improve the compliance of blood glucose monitoring. For example, the Scanning Glucose Monitoring FGM system, which consists of a flexible probe sensor, monitor, and related software, detects glucose concentrations in tissue with a flexible probe inserted under the skin. Finger blood calibration is not required during patient testing, which is minimally invasive, painless and easy to operate. Only scanning can obtain immediate glucose values and provide 14-day Ambulatory glucose Profile (AGP) (37). Through clinical application, it has been proved that it can effectively improve patients' SMBG behavior, reduce the probability of hypoglycemia, and help patients reach the standard of SMBG frequency.

4.2.5 Economic pressure

In a survey (38) of elderly diabetic patients, it was found that 89.5% of T2DM patients were reluctant to have their blood glucose monitored for economic reasons. At present, China's blood glucose test paper has not been included in the scope of medical insurance

reimbursement, which needs to be borne by patients themselves (39, 40). The direct cost of blood glucose monitoring is not high. The lowest price of a household blood glucose meter is less than that of 100 yuan, and the prices of blood collection needles and test paper are not high. The average monthly price is estimated to be as low as that of 30 yuan. However, due to daily consumption, it will still cause obvious economic burden to patients' psychology. And because diabetes is a chronic lifelong disease, SMBG needs to be maintained for life. Blood glucose meter, blood glucose test paper and monitoring needle are expensive, and they are not covered by the reimbursement of urban medical insurance and rural cooperative medical insurance, which brings huge economic pressure to diabetic patients. Therefore, some families with poor economic status are reluctant to carry out SMBG in order to save medical expenses (41).

Therefore, on the one hand, medical staff need to strengthen patient health education, and inform patients that with the help of SMBG, medical staff can timely adjust the treatment plan according to the blood glucose control of T2DM patients, so that the blood glucose of patients can reach the standard, the occurrence of complications can be reduced, the additional medical expenses can be reduced, and patients can accept it voluntarily. On the other hand, we suggest that the medical insurance bureau can include test paper and needles in the scope of reimbursement, and limit a certain amount of reimbursement, thus alleviating the financial burden of diabetic patients.

Finally, the state or society should pay attention to diabetic patients and give psychological and spiritual support, so as to improve SMBG compliance of diabetic patients.

5 Conclusion

According to the analysis of this study, diabetes cognition, self-efficacy, glucose meter operation and monitoring cost of blood glucose meter are the potential influencing factors of SMBG in T2DM patients. Among them, understanding the frequency of SMBG and having a clear goal of sugar control were the promoting predictors of SMBG. In this study, the frequency of SMBG monitoring in T2DM patients still needs to be improved. Currently, there are still bottlenecks such as lack of disease health care knowledge and needle pain. In addition, the lack of accessibility and convenience of blood glucose meter and the heavy economic burden in T2DM patients are one of the barriers to the low frequency of SMBG monitoring, which further affects the effect of blood glucose control (42). In addition, forgetting to take a blood glucose test leads to a follow-up blood glucose test, and a 10-finger rotation during blood glucose test leads to higher SMBG compliance.

The low level of disease cognition can directly affect SMBG compliance of T2DM patients, and the lack of attention to blood glucose control makes it easy to ignore the exhortations of medical staff (43). Self-efficacy is reflected in patients' confidence in adhering to blood glucose monitoring. Lack of self-efficacy makes it difficult for patients to believe that they can adhere to blood glucose monitoring for a long time, and it is easy to interrupt monitoring or reduce monitoring frequency (44). The operation of blood glucose meter is an important instrument for monitoring blood glucose level. Patients are unfamiliar with the operation of blood glucose meter, resulting in complex understanding of blood glucose monitoring and resistance. Social support is very important for patients' SMBG. Some studies have shown that patients with better social support can better monitor their blood glucose under the supervision of others. Based on the above situation, hospitals should establish a long-term management mechanism for blood glucose monitoring, strengthen patients' cognition of T2DM patients, and increase the importance of blood glucose monitoring. Strengthen individualized nursing intervention to improve patients' self-efficacy; Guide patients to use blood glucose meters correctly and select appropriate blood glucose meters according to patients' condition and economic conditions; Strengthen communication with patients' families, and instruct them to actively supervise patients' blood glucose monitoring.

6 Limitations and prospects

6.1 Limitations

This study is a cross-sectional study and could not find the relationship between SMBG and T2DM complications. A large-sample prospective cohort study should be conducted to explore the long-term benefits of SMBG on T2DM complications. There are many factors affecting SMBG, such as the comprehensive health status of patients and the degree of support from family members, which are not all included. Data collection was self-reported, so the data may be affected, such as memory bias. In addition, some patients may not truthfully answer the privacy questions in daily life, such as income. Due to some elderly people over 60 years old who didn't use smart phones might not be surveyed in the questionnaire filled out by online platform, the majority of respondents were between 18 and 60 years old. This study did not include a glycemic index to assess glycemic control, such as fasting glucose values. And future research may focus on the relationship between SMBG compliance and glycemic control.

6.2 Novelty and prospect

Diabetes is a chronic lifelong disease that cannot be cured. It is impossible for patients to be treated in the hospital from the time of diagnosis of diabetes, and most of the time is self-management outside the hospital. Therefore, SMBG plays an important role in the blood glucose control of T2DM patients. With the development and popularization of blood glucose monitoring technology, SMBG has become the main form of blood glucose monitoring for diabetic patients. Standardized SMBG can make patients know whether their blood glucose is controlled at a good level, and provide effective basis for consulting doctors or timely adjustment of treatment plans.

The main advantage of this study lies in the cross-sectional design, which evaluates a series of variables, including gender, age, occupation, BMI, marital status, course of disease, pain, knowledge

of SMBG frequency and glucose control goals, as well as basic demographic characteristics and living habits. This is helpful for us to explore the specific and highly detailed status of the quality of individual self-glucose monitoring in community T2DM population, and its relationship with individual information cognition, motivation and behavior.

The IMB model used in this study has practical value and extension in explaining SMBG of T2DM patients in Chinese communities. While behavior change is a continuous process, IMB model emphasizes that information, motivation and behavior skills are indispensable to complete behavior change. On the other hand, the research on SMBG compliance of diabetic patients based on IMB model can help patients improve their understanding of the disease, enhance their motivation for behavior change, and thus establish good self-management behavior habits of diabetes. This study makes up the gap between motivation and behavior shaping of T2DM patients' health management behavior, provides new ideas for improving SMBG of diabetic patients, and provides direction and reference for improving self-management ability of diabetic patients, reducing or delaying the occurrence and development of complications. In addition, in future research, it would be beneficial to explore the differences in attention, application, and sophistication of SMBG devices among Type 2 diabetes populations in different regions of the world.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Shantou University Medical College. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. The protocol was approved approved by The Ethics Committee of Shantou University Medical College (Code: SUMC-2021–064).

Author contributions

ML undertook the literature reviews, data analysis, completion of statistical tables, research process, completion of result and discussion analysis. TC undertook data analysis, research process, completion of discussion and conclusion. GF was in charge of the conception design, undertook the design of the study framework and survey questionnaire, completed statistical tables and result analysis, took responsibility for the integrity of the data and the accuracy of the data and revised the entire manuscript. GF also wrote in the research process and interpreted the results, ultimately modified the manuscript. All authors read and approved the final manuscript.

Funding

General program of Guangdong Natural Science Foundation (2022A1515012192), Medical research fund project of Guangdong Province(A2021500, A2022535), Shantou science and technology plan's medical and health category project (190716185262435, SFK (2019) No. 106-10). Philosophy and Social Sciences Planning Foundation Discipline Co-construction Project of Guangdong Province of 2022(GD22XXW10), Undergraduate teaching quality and teaching reform project of Guangdong Province in 2022(Yue Gao Jiao Han[2023]4-581). Clinical Teaching Base Teaching Reform Research Project of Guangdong Province in 2021(2021JD062).

Acknowledgments

We thank all the respondents participated in this study for their cooperation and contribution.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Tang C, Han C, Wang G, Liu J, Zheng W, Xu Q, et al. Cross-sectional study and reference to British QOF management mode and control mode of diabetes in communities of Shanghai. *China Gen Pract* (2014) 19:2255–8. doi: 10. 3969/j.issn.1007-9572.2014.19. 021

2. Ji S, Zeng H, Wang H, He G, Guo J. Community management model on diabetes: a literature review. *J Nurs Sci* (2017) 32(05):101–4. doi: 10.3870/j.issn.1001-4152.2017.05.101

3. Wang J, Liu Y, Li L. Diabetes management in China:Types and reflections. *Chin Gen Pract* (2021) 24(24):3019–25. doi: 10.12114/j.issn.1007-9572.2021.00.551

4. China Diabetes report 2000 - 2045, in: *Diabetes report 2000 - 2045*. Available at: https://www.diabetesatlas.org/data/en/country/42/cn (Accessed 2022).

5. Diabetes Atlas. Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* (2022) 183:109119. doi: 10.1016/j.diabres.2021.109119

6. Tuso P. Prediabetes and lifestyle modification: time to prevent a preventable disease. *Perm. J* (2014) 18:88–93. doi: 10.7812/TPP/14-002

7. Gossain VV, Aldasouqi S. The challenge of undiagnosed pre-diabetes, diabetes and associated cardiovascular disease. *Int J Diabetes Mellit* (2010) 2:43–6. doi: 10.1016/j.ijdm.2009.10.004

8. Diabetes Branch of Chinese Medical Association. Guidelines for prevention and treatment of type 2 diabetes in China (2017 edition). *Chin J Pract Internal Med* (2018) 38:292–344. doi: 10.19538/j.nk2018040108

9. Xiong Z, Yuan L, Ye Z, Ni X, Yang J, Liu M, et al. Current situation and influencing factors of self-monitoring of blood glucose in type 2 diabetic patients in Sichuan Province. *Chin J Evidence-Based Med* (2013) 13:5. doi: 10.7507/1672-2531.20130049

10. Guo T, Zhang J, Li Y, Li J, Xie Y. Status and influencing factors of self-monitoring blood glucose in patients with type 2 diabetes mellitus. *Clin Meta-analysis* (2017) 32:317–22. doi: 10.3969/j.issn.1004-583X.2017.04.011

11. Polonsky WH, Fisher L, Schikman CH, Hinnen DA, Parkin CG, Jelsovsky Z, et al. Structured self-monitoring of blood glucose significantly reduces A_1C levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the structured testing program study. *Diabetes Care* (2011) 34:262–7. doi: 10.2337/dc10-1732

12. Chen Q, Wang H, Wang Y, Wang Z, Zhao D, Cai Y. Exploring effects of self-management on glycemic control using a modified information-motivation-behavioral skills model in type 2 diabetes mel litus patients in shanghai, China: a cross-sectional study. *J Diabetes* (2018) 10:734–43. doi: 10.1111/1753-0407.12655

13. Yao X, Zhang L, Du J, Gao L. Effect of information-Motivation-Behavioral model based on protection motivation theory on the psychological resilience and quality of life of patients with type 2 DM. *Psychiatr Q* (2021) 92:49–62. doi: 10.1007/s11126-020-09783-w

14. Bains SS, Egede LE. Associations between health literacy, diabetes knowledge, self-care behaviors, and glycemic control in a low income population with type 2 diabetes. *Diabetes Technol Ther* (2011) 13:335–41. doi: 10.1089/dia.2010.0160

15. Al-Qazaz HK, Sulaiman SA, Hassali MA, Shafie AA, Sundram S, Al-Nuri R, et al. Diabetes knowledge, medication adherence and glycemic control among patients with type 2 diabetes. *Int J Clin Pharm* (2011) 33:1028–35. doi: 10.1007/s11096-011-9582-2

16. Berikai P, Meyer PM, Kazlauskaite R, Savoy B, Kozik K, Fogelfeld L. Gain in patients' knowledge of diabetes management targets is associated with better glycemic control. *Diabetes Care* (2007) 30:1587. doi: 10.2337/dc06-2026

17. Shigaki C, Kruse RL, Mehr D, SheldonKM, GeB, MooreC, et al. Motivation and diabetes self-management. *ChronicIIn* (2010) 0603:202–14. doi: 10.1177/1742395310375630

18. Reyes J, Tripp-Reimer T, Parker E, Muller B, Laroche H. Factors influencing diabetes self-management among medically underserved patients with type II diabetes. *Global Qual Nurs Res* (2017) 4:1–13. doi: 10.1177/2333393617713097

19. Deakin T, Mcshane CE, Cade JE, Williams RD. Group based training for self-management strategies in people with type 2 diabetes mellitus. *Cochrane Database Syst Rev* (2005) 18:CD003417. doi: 10.1002/14651858.CD003417.pub2

20. Diabetes Branch of Chinese Medical Association. Guidelines for the prevention and treatment of type 2 diabetes in China (2020 edition) (Part I). *Chin J Pract Internal Med* (2021) 41:668–95. doi: 10.19538/j.nk2021080106

21. Gao J, Wang J, Zhu Y, Yu J. Validation of an information-motivation-behavioral skills model of self-care among Chinese adults with type 2 diabetes. *BMC Public Health* (2013) 13:100. doi: 10.1186/1471-2458-13-100

22. Chen R, Ji L, Chen L, Chen L, Cai D, Feng B, et al. Glycemic control rate of T2DM outpatients in china:a multi-center survey. *Med Sci Moni* (2015) 21:1440–6. doi: 10.12659/MSM.892246

23. Zhang SL, Chen ZC, Yan L, Chen LH, Cheng H, Ji LN. Determinants forinadequate glycaemic control in Chinese patients with mild-to-moderate type 2 diabetes on oral antidiabetic drugs al one. *Chin Med J (Engl)* (2011) 124:2461–8. doi: 10.3760/cma.j.issn.0366-6999.2011.16.012

24. Ji LN, Lu JM, Guo XH, Yang W, Weng J, Jia W, et al. Glycemic control among patients in China withtype 2 diabetes mellitus receiving oral drugs or injectables. *BMC Public Health* (2013) 13:602. doi: 10.1186/1471-2458-13-602

25. Pereira MG, Pedras S, Ferreira G, Machado J. Family and couPle variables regarding adherence in type 2 diabetes patients in the initial stages of the disease. *J Marital Fam Ther* (2019) 45:134–48. doi: 10.1111/jmft.12281

26. Yuan L, Guo X, Xiong Z, Lou Q, Shen L, Zhao F, et al. Self-monitoring of blood glucose in type 2 diabetic patients in China: current status and influential factors. *Chin Med J* (2014) 127:201–7. doi: 10.3760/cma.j.issn.0366-6999.20131776

27. Chen M, Yun Q, Lin H, Liu S, Liu Y, Shi Y, et al. Factors related to diabetes self-management among patients with type 2 diabetes: a Chinese cross-sectional survey based on self-determination theory and social support theory. *Patient Prefer Adherence* (2022) 16:925–36. doi: 10.2147/PPA.S335363

28. Wang X, Luo J, Qi L, Long Q, Guo J, Wang H. Adherence to self-monitoring of blood glucose in Chinese patients with type 2 diabetes: current status and influential factors based on electronic questionnaires. *Patient Prefer Adherence* (2019) 13:1269. doi: 10.2147/PPA.S211668

29. Qi Y, Feng W. Cause analysis and nursing countermeasures of self-monitoring of blood glucose in diabetic patients. *Electronic J Pract Clin Nurs* (2017) 16:44–5. doi: 10.3969/j.issn.2096-2479.2017.16.034

30. Patton SR. Adherence to glycemic monitoring in diabetes. *J Diabetes Sci Technol* (2015) 9(3):1–8. doi: 10.1177/1932296814567709

31. Hortensius J, Marijke CK, Wierenga WS, Kleefstra N, Bilo HJ, van der Bijl JaaP J. Perspectives of patients with type 1 or insulin-treated type 2 diabetes on self-monitoring of blood glucose: a qualitative study. *BMC Public Health* (2012) 12(1):1–11. doi: 10.1186/1471-2458-12-167

32. Ouyang X, Hu Y, Ouyang Q. Study on the related factors influencing the compliance of blood glucose monitoring in patients with type 2 diabetes mellitus. *China Med Sci* (2019) 09:190–2.

33. Al-Keilani M, Almomani B, Al-Sawalha N, Shhabat B. Self-monitoring of blood glucose among patients with diabetes in Jordan: Perception, adherence, and influential factors. *Diabetes Res Clin Pract* (2017) 126. doi: 10.1016/j.diabres.2017.01.005

34. Li Y, Zhang H, Gao L, Tian H, Yuan A. Analysis of the current situation of blood sugar control and related factors in elderly patients with type 2 diabetes. *China Chronic Dis Prev Control* (2014) 22:318–21. doi: 10.16386/j.cjpccd.issn.1004-6194.2014.03.036

35. Huang J, Chen J, Liu X, Dai W, Cao Y. Current situation and countermeasures of self-monitoring of blood glucose in elderly patients with type 2 diabetes mellitus. *Anhui Med Sci* (2019) 40:950–2. doi: 10.3969 /j. issn. 1000-0399.2019.08.031

36. Heinemann L. Finger pricking and pain: a never ending story. *J Diabetes Sci Technol* (2008) 2:5. doi: 10.1177/193229680800200526

37. Han Y, Sun Z, Li X, Wu Y, Shen Y, et al. Application of self blood glucose monitoring gloves for patients with type 2 diabetes mellitus in community. *Nurs Res* (2017) 31:329–31. doi: 10.3969/j.issn.1009-6493.2017.03.021

38. Jiang Y, Lin J, Chen Z. A cross-sectional survey of self-monitoring compliance of patients with type 2 diabetes mellitus. *Guide China Med* (2019) 17:93–4. doi: 10.15912/j.cnki.gocm.2019.10.064

39. Luo J. Investigation on self-monitoring of blood glucose in elderly diabetic patients in Yizhou, Guangxi. *Internal Med* (2016) 11:640–1. doi: 10.16121/j.cnki.cn45-1347/r.2016.04.48

40. Wu J, Wu R, Cheng K, Gao Y, Yuan X, lv W. Influencing factors of the self-monitoring of blood glucose in patients with type 2 diabetes mellitus: qualitative research. *Nurs J Chin PLA* (2018) 35:30–3. doi: 10.3969/j.issn.1008-9993.2018.18.006

41. Xiao B, Wu C, Tang L. The compliance with self-blood glucose monitoring in patient with type 2 diabetes mellitus. *Chin J Prev Med* (2020) 21:943–6. doi: 10.16506/j.1009-6639.2020.08.022

42. Babenko AY, Mosikian AA, Lebedev DL, Khrabrova EA, Shlyakhto EV. Mental state, psychoemotional status, quality of life and treatment compliance in patients with type 2 diabetes mellitus. *J Comp effectiveness Res* (2019) 8:2. doi: 10.2217/cer-2018-0105

43. Ji L, Su Q, Feng B, Shan Z, Hu R, Xing X, et al. Glycemic control and self-monitoring of blood glucose in Chinese patients with type 2 diabetes on insulin: baseline results from the COMPASS study. *Diabetes Res Clin Pract* (2016) 112:82–7. doi: 10.1016/j.diabres.2015.08.005

44. Li Y, Wang Q, He L, Ouyang S. The effective of follow up of self blood glucose monitoring in patients with diabetes mellitus. *Sichuan Med J* (2015) 36:1320–1. doi: 10.16252/j.cnki. issn1004-0501-2015.09.033

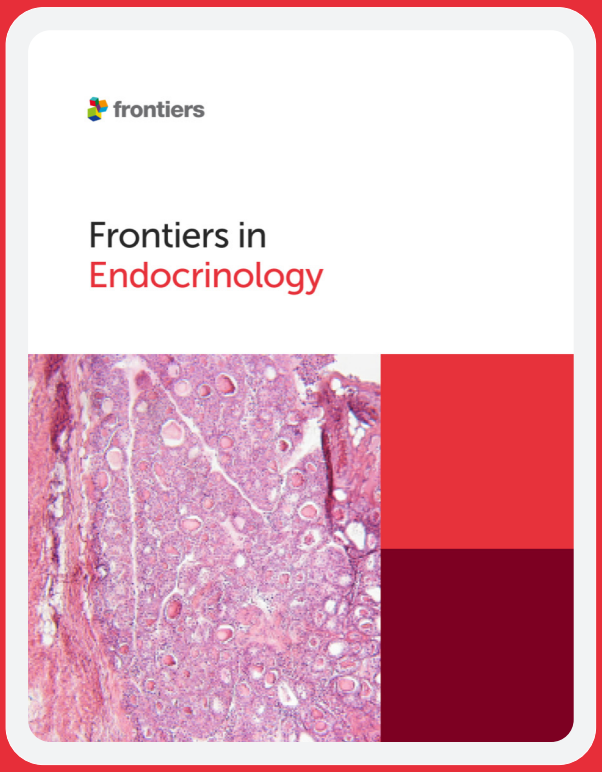
Frontiers in Endocrinology

Explores the endocrine system to find new therapies for key health issues

The second most-cited endocrinology and metabolism journal, which advances our understanding of the endocrine system. It uncovers new therapies for prevalent health issues such as obesity, diabetes, reproduction, and aging.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact