ACHIEVING EFFECTIVE MANAGEMENT AND TREATMENT OF DIABETES MELLITUS IN FUTURE PRIMARY CARE

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ACHIEVING EFFECTIVE MANAGEMENT AND TREATMENT OF DIABETES MELLITUS IN FUTURE PRIMARY CARE

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EDITORIAL
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Editorial: Achieving Effective Management and Treatment of Diabetes Mellitus in Future Primary Care

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Editorial on the Research Topic

Achieving Effective Management and Treatment of Diabetes Mellitus in Future Primary Care

Currently, 537 million adults aged 20–79 years have diabetes mellitus (DM) worldwide. It has become one of the fastest-growing health challenges of the 21st century, with a disproportionate burden on low and middle-income countries (1). Considering the significant burden of the disease and its complications, tackling DM at the primary care level becomes imperative. Within the health care system, primary care plays a central role by providing diabetes care in the community for the majority of people with type 2 diabetes (T2D) while forging necessary integrated collaborative care with secondary or tertiary health care providers of multidisciplinary professionals (2). For most people with T2D, primary care physicians are the first point of contact. There is strong evidence worldwide that primary diabetes care can provide cost-effective, comprehensive, and patient-centered management to prevent and treat T2D and its related conditions. For people with type 1 diabetes (T1D), although a specialist diabetes team usually manages them, the involvement of primary care in delivering aspects of care such as monitoring and managing secondary complications is increasing.

The cornerstone of managing T2D is promoting lifestyle interventions that include a healthy diet and regular exercise to attain and maintain healthy body weight. Pharmacological interventions include controlling cardiovascular risk factors such as smoking cessation, blood pressure, and blood cholesterol to personalized and safe targets. Physical exercise plays an essential role as a non-pharmacological and cost-effective treatment, improves insulin sensitivity, a better quality of life (QoL), enhances diabetes treatment efficacy, thus lowering morbidity and mortality in people with T2D. Many types of physical exercise have been studied for their effectiveness in the management of

DM, including low to moderate intensity 'traditional' mind-body exercises such as Tai Chi. According to the systematic review by Qin et al. included in this Research Topic, Tai Chi improved QoL and decreased BMI for people with T2D when compared to either wait-list, no intervention, usual care or sham exercise. Despite its proven benefit, encouraging physical activity among people with (T1D) remains challenging. Undertaking physical exercise needs to be balanced with insulin dosing and food intake to maintain safe blood glucose levels before, during, and after exercise. Participation in a clinical trial on exercise with a multimodal approach which incorporated education support and an interstitial glucose monitoring system improve nocturnal glycemia significantly and reduce insulin use in people with T1D, as reported by McCarthy et al. Self-management skills are essential in fostering lifestyle changes to achieve good metabolic control among people with diabetes. Diabetes self-management education is considered one of the pillars in T2D care. In a randomized controlled trial, van der Velde et al. report that a self-management education program named the "Beyond Good Intentions" (BGI) effectively improved the dietary quality among people with T2D compared to usual care.

T2D and its complications are preventable by ensuring continuous access to prompt and well-organized care, structured patient education, and optimized risk factor control. Several innovative models of care that could enhance T2D management within primary care have been developed and studied. Pay-for-performance (P4P) was introduced as a strategy to improve healthcare quality through financial incentives. Lian et al. provide evidence that implementing a P4P Program to usual care could lower the risk of depression among T2D in Taiwan. In Canada, Hersson-Edery et al. explore the feasibility of a Diabetes Empowerment Group Program (DEGP) to foster patient engagement and empowerment in diabetes self-care and identified seven critical elements: medical visit, continuity of care, group-based dynamics, multi-disciplinarity, clinician facilitation, patient-centered agenda, and a theoretical framework of empowerment The theoretical framework itself comprises of four components: attitude, knowledge, behavior, and relatedness. This goes well with the implementation of shared medical appointments (SMAs) in the management of T2D. SMAs is defined as "consecutive individual medical visits carried out in a supportive group setting of patients of similar medical conditions where all can listen, interact, and learn" (3). Ee et al. report their experience in piloting SMAs in primary care for people with T2DM in Western Sydney, Australia. They found that SMAs, which included a structured education program and mindfulness component, was feasible and acceptable and resulted in lower total cholesterol levels and pain intensity.

T2D is a progressive disease; hence many people with T2D will require insulin therapy during the course of their illness. However, psychological opposition towards insulin use, known as "psychological insulin resistance" (PIR), is frequently found in people with T2DM and healthcare providers (4). The findings of a cross-sectional study by Boels et al. may enhance discussion of this problem as they found that those on insulin therapy have worse vitality, general health, and barriers to activity compared to those receiving oral antihyperglycemic agents only.

In recent years, the armamentarium for the management of hyperglycemia has been strengthened by the introduction of novel therapies, including sodium-glucose cotransporter 2 (SGLT2) inhibitors and Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists. The cardiovascular and kidney protective effects of SGLT2 inhibitors and GLP-1 receptor agonists have now been ascertained, independent of their glucose-lowering properties, and are now recommended as first-line therapies in people with atherosclerotic cardiovascular disease, heart failure, and chronic conditions kidney disease. To add to the evidence, Wei et al., in their meta-analysis of randomized controlled trials, found that SGLT2 inhibitors can remarkably reduce hepatic enzymes, hepatic fat and improve body composition in T2D patients with non-alcoholic fatty liver disease (NAFLD). Thus, providing a new treatment option for this group of patients. Meanwhile, Kim et al. conducted a network meta-analysis to evaluate the effect and safety of adding oral hypoglycemic agents (metformin, SGLT2 inhibitor, or SGLT1/2 co-inhibitor) or injectable GLP-1 RAs to insulin therapy in patients with T1D. They suggest that sotagliflozin and short-acting GLP-1RAs as add-on therapies could have beneficial effects in lowering the HbA1c level, insulin dose, and body weight in patients with T1D.

There is growing evidence suggesting that vitamin D deficiency could play an essential role in T2D pathogenesis (5). Thus, the potential of vitamin D supplementation as part of the management of T2DM to optimize glycemic control and prevent complications were investigated in a randomized controlled trial by Cojic et al. They found that oral daily doses of vitamin D significantly decreased the level of HbA1c after 3 and 6 months of vitamin D supplementation with metformin, compared to the metformin only group. However, the effect of vitamin D on insulin resistant index (calculated as homeostatic model assessment; HOMA-IR), and oxidative stress markers (measured as malondialdehyde levels and Tryglicerides/Thiobarbituric acid-reactive substances (TG/TBARS) index), was not statistically significant.

Diabetes is one chronic condition where the evidence is changing at a pace. The collection of studies presented in this Research Topic of Frontiers in Endocrinology has further advanced the evidence for DM management in primary care.

AUTHOR CONTRIBUTIONS

IW prepared the original draft. KK, RV, and B-HC critically review and edit the manuscript. All authors have reviewed and approved of the final manuscript.

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SYSTEMATIC REVIEW
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Effects of Sodium-Glucose Cotransporter Inhibitor/Glucagon-Like Peptide-1 Receptor Agonist Add-On to Insulin Therapy on Glucose Homeostasis and Body Weight in Patients With Type 1 Diabetes: A Network Meta-Analysis

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Many patients with type 1 diabetes (T1D) do not achieve the glycemic target goal with insulin treatment. In this study, we aimed to evaluate the efficacy and safety of add-on to insulin therapy in patients with T1D. We conducted direct and indirect network meta-analyses using Bayesian models and ranked hypoglycemic agents via mixed treatment comparison, using data from the CENTRAL, MEDLINE, EMBASE, and Science Citation Index Expanded databases. Randomized controlled trials (RCTs) involving patients with T1D treated with insulin and add-on metformin or sodium-glucose cotransporter inhibitors or glucagon-like peptide-1 receptor agonists from January 1970 to September 2019 were included in this study. Twenty-three RCTs with 5,151 subjects were divided into the following groups: insulin alone, insulin+metformin, insulin+canagliflozin, insulin+dapagliflozin, insulin+empagliflozin, insulin+sotagliflozin, insulin+liraglutide, and insulin+exenatide. HbA1c level in the insulin+sotagliflozin group was significantly lower than that in the insulin alone group (mean difference: −0.43, 95% credible interval: −0.62 to −0.23). Total daily insulin dose in the insulin+sotagliflozin group was significantly lower than that in the insulin alone group. Compared with that in the insulin alone group, body weight in the groups treated with insulin+add-on canagliflozin, sotagliflozin, and exenatide was significantly decreased by 4.5, 2.8, and 5.1 kg, respectively. Hypoglycemic episodes did not differ among the groups. In patients with T1D, insulin+sotagliflozin decreased the HbA1c level, daily insulin dose, and body weight without hypoglycemia compared with insulin monotherapy. Insulin+canagliflozin or insulin+exenatide was effective in reducing body weight compared with insulin alone. In conclusion, sotagliflozin treatment decreased not only the HbA1c levels and insulin

dose but also the body weight without causing hypoglycemia in patients with T1D. Treatment with canagliflozin and exenatide effectively reduced body weight in patients with T1D. However, ketoacidosis associated with the use of SGLT inhibitors should be considered in these patients. Thus, our results suggest that sotagliflozin has a high probability of being ranked first as an adjunctive therapy to insulin in patients with T1D.

Keywords: SGLT inhibitor, GLP-1 receptor agonist, type 1 diabetes, add on to insulin therapy, body weight, glycemic level

INTRODUCTION

The incidence of type 1 diabetes (T1D) is continuously increasing. According to a report from the International Diabetes Federation (IDF), T1D currently affects 29 million adults worldwide (1). The IDF reported that the number of children and adolescents with T1D in 2017 was 1,106,500. Moreover, 132,600 patients are newly diagnosed with T1D every year. According to the T1D Exchange Registry data, in more than 70% of patients with T1D, glycated hemoglobin (HbA1c) levels lower than 7% was not achieved (2).

Compared with the treatment of type 2 diabetes (T2D) using various novel medications, that of T1D mostly depends on insulin. Several drugs have been investigated as an adjunct therapy for T1D, but the US FDA approved only pramlintide, which mimics a β-cell hormone that is co-secreted with insulin in the postprandial period, in 2005 (3). However, the effects of pramlintide on HbA1c level and weight changes are mild and unsatisfactory (4).

Metformin is the most studied oral antidiabetic drug used as an adjunct for T1D treatment. It suppresses hepatic gluconeogenesis and increases glucose uptake by muscles via the amplification of glucose transporter 4 (5). Treatment of T1D with metformin reportedly reduces insulin requirement and decreases body mass index (BMI), although the HbA1c level was similar to that of the placebo treatment (6, 7). Dipeptidyl peptidase-4 (DPP-4) inhibitors prolong the half-life of endogenous glucagon-like peptide-1 (GLP-1), which stimulates glucose-dependent insulin secretion and inhibits glucagon release. Although the effect of DPP-4 inhibitors in chronic T1D has not been elucidated, a study reported more than 20 IU reduction in daily insulin dose in newly diagnosed patients with T1D (4). GLP-1 receptor agonists (GLP-1RA), such as liraglutide and exenatide, are also reported to reduce insulin dose and decrease body weight in patients with T1D. However, their effect on HbA1c was not consistent among studies (8–15). Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which reduce glucose reabsorption in the proximal tubules of the kidney, are one of the most attractive drugs for T2D owing to their beneficial effects on cardiovascular and renal functions (16, 17). Compared with that of insulin administration alone, administration of SGLT-2 inhibitors, such as dapagliflozin, empagliflozin, and canagliflozin, decreased HbA1c level, body weight, and insulin requirement in patients with T1D (18–23). Recently, researchers have focused on SGLT-1/2 co-inhibitors because they can simultaneously inhibit the absorption of sugars in the kidneys and intestine (24). Garg et al. showed that sotagliflozin, an SGLT-1/2 co-inhibitor, decreased HbA1c level in patients with T1D (1).

Several trials with GLP-1 RA, SGLT-2 inhibitors, or SGLT-1/2 co-inhibitors as adjuncts to insulin therapy for T1D have been conducted. However, no conclusive suggestion has been made because of the following reasons: the glucose-lowering efficacy of these agents was not satisfactory; the trials had a small sample size; and most importantly, these agents were only compared with insulin and not with other agents. Therefore, the aim of our study was to identify the most efficient drug as an add-on to insulin therapy in patients with T1D through a network meta-analysis.

MATERIALS AND METHODS

Ethics Statement

The results are presented in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses statement (NMA Checklist) (25). All analyses were conducted using previously published studies; therefore, ethical approval and patient consent were not required.

Data Sources, Searches, and Inclusion and Exclusion Criteria

We performed a comprehensive search of the following databases, from the time of the inception of each database until September 2019: MEDLINE (via PubMed), EMBASE, CINAHL, Web of Science, and the Cochrane Central Register of Controlled Trials in the Cochrane Library. The following terms were used to identify RCTs: Metformin or Sodium-Glucose Transport Proteins or Sodium-Glucose Transporter 2 or Sodium-Glucose Transporter 2 Inhibitors or SGLT1/2 inhibitor or Exenatide or Liraglutide and Diabetes Mellitus, Type 1. Detailed search terms are provided in **Supplementary Information 1**.

The following studies were included in the review: RCTs, reviews, observational studies, and clinical trials. The search was limited to human studies but was not restricted to any particular language or publication date. Reference lists from all available review articles and RCTs were searched manually (**Figure 1**).

Study Selection

The abstracts and full texts obtained were independently checked by two researchers (YJK and SDH). Any disagreements were resolved through discussions and consultations with another researcher. The inclusion criteria for studies used in the analysis were as follows: (1) randomized controlled studies; (2) studies

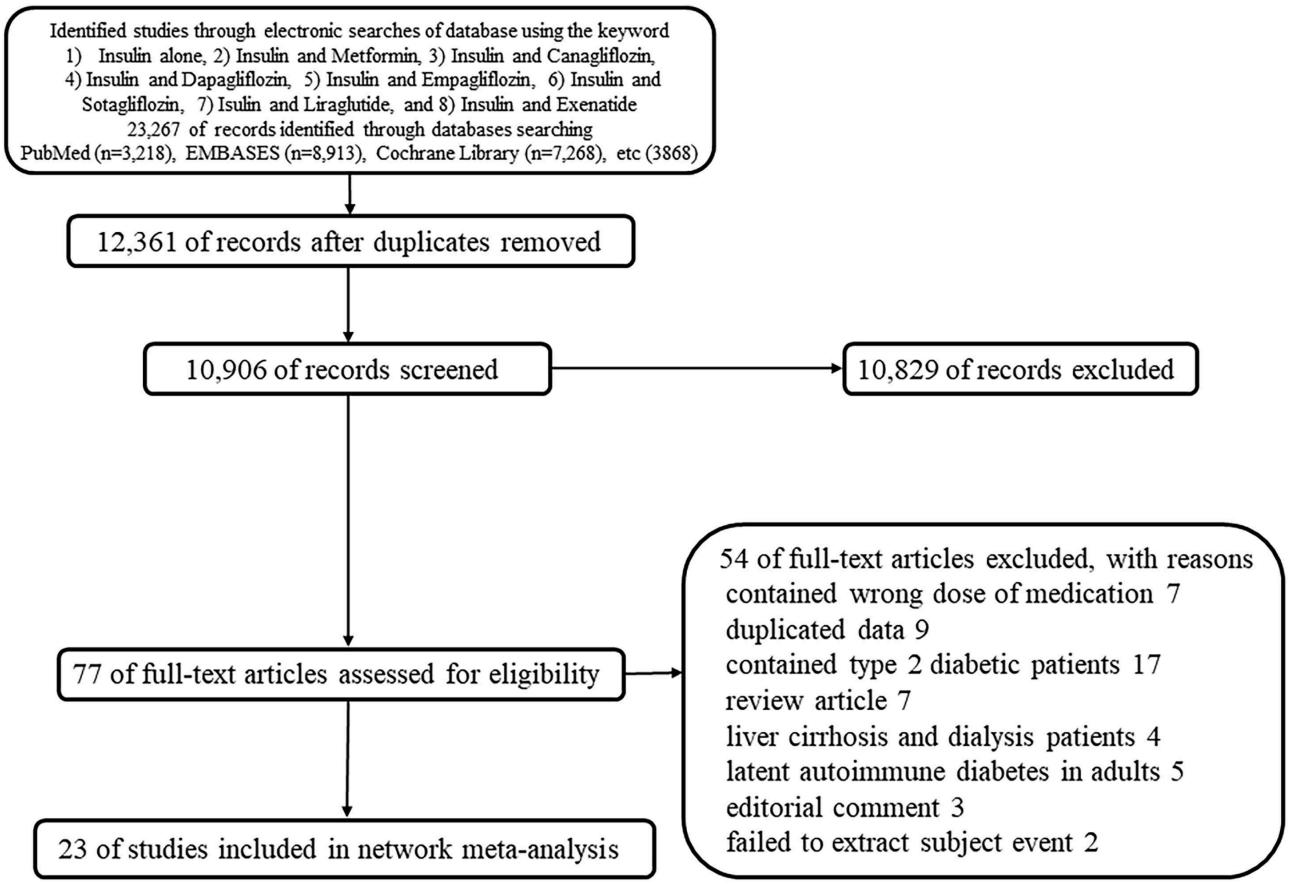

FIGURE 1 | Flow diagram of the current systematic review (PRISMA Flow Diagram).

referring to at least two of the following eligible antidiabetic medications: placebo, metformin, canagliflozin, dapagliflozin, empagliflozin, sotagliflozin, liraglutide, and exenatide; and (3) studies that reported one or more of the primary or secondary outcomes (**Figure 2**). Treatments with direct comparisons are linked with a line, whose thickness corresponds to the number of trials evaluating that comparison. For example, when insulin is used as a reference, the line comparing insulin and metformin is the boldest indicating that these two interventions are most evaluated, while being solid line (rather than dotted) indicates a direct evaluation. Conversely, dotted lines indicate indirect connections expressed using direct comparison and indirect comparison due to lack of head-to-head study. For example, line comparing insulin sotagliflozin and insulin dapagliflozin indicates no direct study; the indirect connection in the network was, therefore, was calculated. Trials that recruited patients with T2D or latent autoimmune diabetes were excluded.

Risk of Bias Assessment

Two researchers (YJK and SDH) independently assessed the risk of bias of each trial using the Cochrane Collaboration's Risk of Bias tool (26). The risk of bias was assessed during the generation of random sequence, concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, analysis of incomplete outcome data, selective reporting, and in other areas. All these judgments were categorized as "yes" (low risk of bias) or "unclear" or "no" (high risk of bias) (**Supplementary Figures 1, 2**) (26, 27).

Quality of Evidence Assessment

We assessed the overall evidence quality for the primary outcomes using an adapted Grading of Recommendations Assessment, Development, and Evaluation approach (28). The evidence quality for a specific outcome was based on performance vs. limitations of the study design, inconsistency of results, indirectness of evidence, imprecision of results, and publication bias of all studies measuring a particular outcome. The overall evidence quality for the outcome was determined by combining assessments from all domains (**Supplementary Figure 3**) (29).

Outcome Measures

We aimed to determine the efficacy of eligible medications on changes in HbA1c level (mean ± standard deviation [from the baseline to endpoint]) as the primary outcome. The occurrence of hypoglycemia, reduction in insulin daily dose, and change in body weight were determined as secondary outcomes.

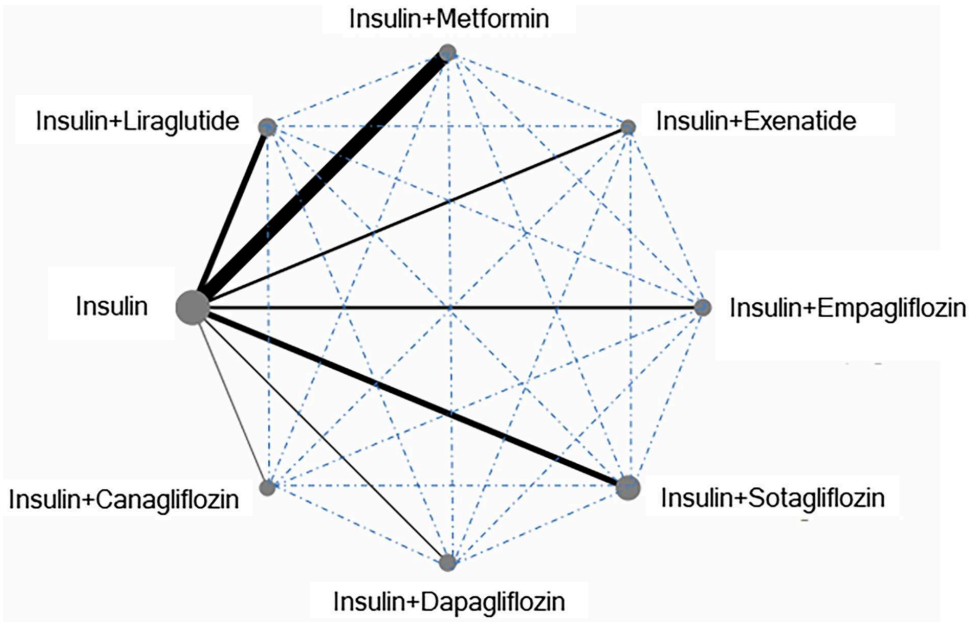

FIGURE 2 | Network flow among each intervention based on HbA1c data.

Moreover, the potential for adverse outcomes associated with these medications, including diabetic ketoacidosis, heart failure, stroke, diarrhea, pancreatitis, renal event, urinary tract infection, and genital infection, were investigated.

Statistical Analysis

Bayesian network meta-analysis was performed to compare the efficacy of eight types of diabetes treatments in terms of HbA1c and weight reduction outcomes and adverse outcomes in patients with type 1 diabetes. Direct and indirect network meta-analyses were performed using Bayesian models, and the different agents were ranked by mixed treatment comparison (GeMTC) and using Stata version 13 (StataCorp) (30–32). The relative ranking probability of each treatment was estimated, and the treatment hierarchy of competing interventions was obtained using rankograms, surface under the cumulative ranking curves, and mean ranks. The network meta-analysis was performed on studies evaluating multiple treatments, which allows the estimation of pooled effects within each treatment (33). For multi-arm trials, correlations among the treatment effects among arms were included in the investigations. Studies with j+1 treatment arms were based on comparison of the treatment effects with the reference treatment effects through multivariate normal distribution, whereas treatment-as-usual studies were based on the homogeneity among study variances across treatments (34, 35). Inconsistency tests, homogeneity analysis, and sensitivity analysis were performed using the node analysis method in R software (The R Foundation for Statistical Computing c/o Institute for Statistics and Mathematics, Vienna, Austria). The results of inconsistency tests were assessed according to the Bayesian p-value, where the results with $p < 0.5$ were considered an evidence for the existence of significant inconsistency (36, 37). An I^2 test was performed ($I^2 >$ 50% indicated significant heterogeneity) to assess homogeneity. Furthermore, a sensitivity analysis was conducted by comparing the differences between fixed-effect and random-effect models. The clinical outcome indicators were evaluated using the mean difference or odds ratio (OR) with a 95% credible interval (CrI) (mean difference for continuous outcomes and OR for binary outcomes) (34, 38). When a loop connected three treatments, it was possible to evaluate the inconsistency between direct and indirect evidence (39). We also used the node-splitting method to calculate the inconsistency of the model, which separated evidence for a particular comparison into direct and indirect evidence (37). Subsequently, the agreement between direct and indirect evidence was evaluated, and its Bayesian p-value was obtained. Sensitivity analyses were carried out using the same methods, after the omission of data obtained from specific studies (studies with a small number of patients and events in a specific treatment arm and studies with a large population that may dominate the data of specific treatment arms) (40).

RESULTS

In total, 23,267 records were initially retrieved from the electronic database search; of these, 12,361 duplicate records were removed. Among the remaining records, 10,829 were excluded based on a review of either the title or abstract and 77 records were retrieved for full-text review. Among these studies, 54 were excluded based on the following criteria: contained wrong dose of medication (n = 7), duplicated data (n = 9), contained patients with T2D (n = 17), review articles (n = 7), contained patients with liver cirrhosis and on dialysis (n = 4), contained adults with latent autoimmune

diabetes ($n = 5$), editorial comment ($n = 3$), and failed to extract subject event ($n = 2$) (**Figure 1**).

Finally, 23 trials reporting outcomes for 5,151 patients (2,610 women and 2,541 men) were included in the analysis (**Table 1**). The average study duration was 30.8 ± 14.5 weeks. The trials were conducted in the following countries: the United States (1, 9, 11, 18, 23, 48, 51, 52) Denmark (12, 13, 42, 44), Canada (21, 41), Italy (46, 49), Austria (20), Belgium (14), Chile (47), France (45), Germany (50), India (10), and United Kingdom (1 each) (43). The number of patients per study ranged from 12 to 1,402, and the mean follow-up period was 17.01 (range, 11.5–38.0) years (**Table 1**).

Risk of Bias in the Included Studies

Although all included studies were described as randomized, a few studies provided specific details of either the method of randomization or concealment of allocation. For all the included studies, blinding had been done adequately.

Effect of Interventions

Data obtained from all the 23 studies ($n = 5,151$) were subjected to the network analysis. The primary endpoint was a change in HbA1c level. Compared with the insulin alone treatment as the reference, sotagliflozin treatment significantly reduced the HbA1c level (MD: −0.43, 95% CrI: −0.62 to −0.23) (**Figure 3A**). However, canagliflozin (−0.28, 95% CrI:−0.65 to 0.11), dapagliflozin (−0.37, 95% CrI: −0.75 to 0.01), empagliflozin (−0.15, 95% CrI: −0.43 to 0.13), metformin (−0.12, 95% CrI: −0.28 to 0.03), liraglutide (−0.20, 95% CrI: −0.41 to 0.03), and exenatide (−0.42, 95% CrI: −0.88 to 0.06) showed no significant changes in HbA1c compared with insulin alone. Among the studies with sotagliflozin, a study by Sands et al. had a noticeably short study treatment duration (29 days) (52). The sensitivity analysis was performed after excluding this study and showed that sotagliflozin therapy reduced HbA1c level significantly (**Supplementary Figure 4** and **Supplementary Tables 2, 3**).

We further analyzed the total insulin daily dose (TIDD), weight change, and adverse effects as the secondary endpoints. Among the eight studied agents, sotagliflozin decreased the TIDD compared with insulin alone, whereas the other drugs showed no change in the TIDD (MD: −6.3 IU, 95% CrI: −12 to −1.20) (**Figure 3B**). A decrease in body weight from the baseline was observed after treatment with canagliflozin (−4.5 kg, 95% CrI: −8.90 to −0.27), sotagliflozin (−2.8, 95% CrI: −5.0 to −0.65), and exenatide (−5.1, 95% CrI: −8.4 to −2.0) (**Figure 3C**). However, the frequency of hypoglycemia was not significantly different among the intervention groups (**Figure 3D**).

Diabetic ketoacidosis (DKA) is one of the most serious adverse effects observed in patients with type 1 diabetes. In the present study, DKA was more frequently observed with canagliflozin (OR = 18.0, 95% CrI: 1.5 to 6.7e+0.2) and sotagliflozin (OR = 6.9, 95% CrI: 2.0 to 29.0) treatments.

Other adverse events, such as myocardial infarction, heart failure, stroke, hospitalization, peripheral artery disease, diarrhea, pancreatitis, renal event, and urinary tract infection or genital infection, did not differ among the medication groups. These side effects were similar to those of only sotagliflozin subgroup, which showed the best effect. Compared to placebo, the event of acidosis, defined as lactic acidosis, metabolic acidosis, renal tubular acidosis, and uremic acidosis, in the sotagliflozin group was approximately 2.82 times higher (Odds ratio: 2.82, 95% CI: 1.87 to 4.26). Using meta-analysis, diabetic ketoacidosis (DKA) was also observed in patients, more frequently with sotagliflozin (OR = 5.91, 95% CI: 2.45 to 14.2) treatment group (**Supplementary Figure 5**).

Rank Probabilities

In terms of changes in the HbA1c level as the primary outcome, network meta-analysis can statistically rank the outcomes by measuring their probability. **Figure 4A** shows several probabilities in Rank 1, indicating that the interventions will be ranked first in the network flow. The highest probability of insulin exenatide was 0.369 but was not statistically significant. However, the next probability, insulin sotagliflozin, was statistically significant in the network meta-analysis, and the probability of being first in the rankogram was 0.277, which was the highest reduction in the HbA1c level among the treatments (**Figure 4A**). Model fit was assessed by comparing deviance information criterion and residual deviance. Deviance information criterion (DIC) measures the deviance, estimated by the posterior mean of minus twice the log-likelihood plus the effective number of parameters in the model. The DIC measures the model fit that penalizes model complexity—lower DIC values suggest a more parsimonious model. The DIC and residual deviance for HbA1c were 90.0 and 46.6, respectively (**Figure 4B**). The model that analyzed HbA1c showed a small DIC number of <150, therefore, the change was minimized, and the model could be selected as an appropriate model.

The rank probabilities of mean change in body weight from the baseline for add-on drugs were in the following order: exenatide (0.482), canagliflozin (0.290), and sotagliflozin (0.169) (**Supplementary Figure 6A**). Model fit statistic of DIC of any weight reduction was 63.2 and the residual deviance was 33.8 (**Supplementary Figure 7A**).

DISCUSSION

In the present study, we evaluated the effect and safety of adding oral hypoglycemic agents (metformin, SGLT2 inhibitor, or SGLT1/2 co-inhibitor) or injectable GLP-1 RAs to insulin therapy in patients with T1D. Among these agents, sotagliflozin add-on therapy was found to be the most effective in reducing HbA1c levels. Treatment with canagliflozin, sotagliflozin, and exenatide decreased the body weight (a secondary outcome) by 4.5, 2.8, and 5.1 kg, respectively. The TIDD was significantly decreased in the sotagliflozin treatment group (6.3 IU/day) compared with that in the insulin monotherapy group. Hypoglycemic episodes and other adverse events did not differ between the groups. These data suggest that sotagliflozin and short-acting GLP-1RA and SGLT inhibitor add-on therapies could have beneficial effects in lowering the HbA1c level, insulin dose, and body weight in patients with T1D undergoing insulin treatment.

TABLE 1 | Important characteristics of the included studies and proportions of patients with using type 1 treatment.

References	Country/year	Added Treatment/Dose	Number of patients (n I/C)	Age Mean ± SD ()median range, years	Male *n* (%)	Mean baseline BMI, kg/m^2 mean (SD)	Mean baseline HbA1c, % mean (SD)	Mean baseline weight (kg)	Mean baseline Insulin dose, unit/kg/d	Mean duration of diabetes (year)
(10)	India/2013	Exenatide/ 10 μg	6/6	28.8 ± 7.6		21.5± 1.5	9.7 ± 0.8	56.2 ± 3.4	55.7± 2.9	29.6± 8.8
(12)	Denmark/2015	Liraglutide/ 1.2 mg	18/18	39.5 ± 2.7	21/(58)	24.2 ± 0.6	8.8 ± 0.2	75.8 ± 2.9	62 ±3.1	18.3 ± 2.0
(11)	USA/2016	Liraglutide/ 1.2 mg	16/17	42± 3	17/(52)	33 ±2	7.8 ± 0.2	96.0 ± 4.0	71.2 ±5.5	21 ± 3.0
(41)	Canada/2003	Metformin/ 500–2,000 mg	14/13	15.7 ± 1.9	12/(44.4)	29.5 ±2.7	9.4 ± 1.0	62.9 ± 13.7		9.7 ± 4.4
(42)	Denmark/2008	Metformin/ 500–2,000 mg	12/12	43.5± 13.1	14/(58)	24.2 ± 0.6	8.9 ± 0.1	87.6 ± 2.7	62.7 ±3.1	17.8 ± 10.3
(43)	UK/2006	Metformin/ 500–2,000 mg	15/15	48± 12	16/(53.3)	31.3 ± 2.6	8.6 ±1.4	92 ± 12	60 ± 14	19 ± 10
(44)	Denmark/2008	Metformin/ 500–2,000 mg	47/45	46.1± 11.6	64/(69.5)	26.2 ±3.4	9.5 ± 0.9	80.5 ± 12.5	59.8 ±0.74	5 ± 0.51
(45)	France/2002	Metformin/ 850–1,500 mg	31/31	39.9± 12.9	37/(59.6)	26.4 ± 4.6	7.58 ± 0.84	78.4 ± 18.1	0.7 ±0.2*	16.9 ± 8.9
(46)	Italy/2013	Metformin/ 850–1,500 mg	21/21	46± 8	18/(42.8)	28.7 ±2.1	7.2 ± 0.9	83 ± 12	0.61 ±0.22*	9.2 ± 0.7
(47)	Chile/2013	Metformin/ 850–1,500 mg	13/11	17.7± 1.6		23.7 ± 3.0	10.3 ±2.3		1.2 ± 0.4	9.3 ± 5.1
(48)	USA/2015	Metformin/ 500–2,000 mg	71/69	15.4 ± 1.7	42/(34.2)	24.2 ± 0.6	8.8 ± 0.4	77 ± 6	1.1 ±0.1*	7.0 ± 3.3
(49)	Italy/2015	Metformin/ 1,000 mg	15/13	15.0± 2.5	13/(46.4)	28.2 ± 6.6	9.3 ± 1.5	75.5 ± 25	84.0 ± 42.9	5.7 ± 4.4
(9)	USA/2014	Exenatide/ 10 μg	6/6	37.3± 10.7	11/(61)	26.1 ±3.5	7.0 ± 0.8	77.7 ± 11.0	0.6 ±0.1*	20.5 ± 11.8
(20)	Austria/2015	Empagliflozin/ 10 mg	19/19	39.6± 11.6	28/(73.6)	27.4 ±3.5	8.3 ± 0.8	87.1 ± 13.3	0.7 ±0.2	16.2 ± 8.4
(1)	USA/2017	Sotagliflozin/ 400 mg	699/703	43.3± 14.2	697/(49.7)	28.3 ± 5.1	8.3 ±0.9	82.4 ± 17.1	56.9 ±27.6	20.5 ± 12.4
(50)	Germany/2018	Sotagliflozin/ 400 mg	263/258	41.7± 13.23	250/(49.4)	29.6 ±5.3	7.6 ± 0.7	86.5 ±18.0	64.1 ±37.6	24.4 ±12.8
(51)	USA/2018	Sotagliflozin/ 400 mg	262/268	46.4± 13.1	257/(48.4)	24.2 ± 0.6	8.8 ± 0.2	75.8 ± 2.9	62 ±3.1	18.3 ± 2.0
(52)	USA/2014	Sotagliflozin/ 400 mg	16/17	42.5 (21,55)	16/(48.4)	26.2 ±3.0	7.9 ± 0.6	74.2(55.6, 107.9)	0.6*	16.8(3.4, 42.9)
(18)	USA/2018	Dapagliflozin/ 10 mg	296/260	42.7± 14.1	262/(50.5)	28.2 ±5.2	8.5 ± 0.6	82.1 ± 17.4	59.4 ±28.2	19.9 ± 11.1
(23)	USA/2014	canagliflozin/ 300 mg	117/117	42.8± 11.0	128/(54.4)	28.1 ±3.9	8.0 ± 0.5	82.9 ± 15.0		21.9 ± 10.6
(14)	Belgium/2016	Liraglutide/ 1.2 mg	346/347	43.9± 13.1	346/(50.6)	29.3 ±5.1	8.2 ± 0.8	85.4 ± 17.2	59.6 ± 49.8	21.6 ± 12.2
(21)	Canada/2018	Empagliflozin/ 10 mg	243/239	45.7± 12.5	227/(47.0)	29.5 ± 5.5	8.1 ±0.6	86.2 ± 18.2	0.7 ±0.2*	22.8 ± 12.6
(13)	Denmark/2016	Liraglutide/ 1.8 mg	50/50	47 ± 13	65/(65)	30.3 ± 3.5	8.7 ± 0.7	93.4 ± 14.2	32 ±16	20 ± 12

*I, intervention group; C, Control group; * = (units _kg_1 _day_1); UK, United Kingdom; USA, United States of America.*

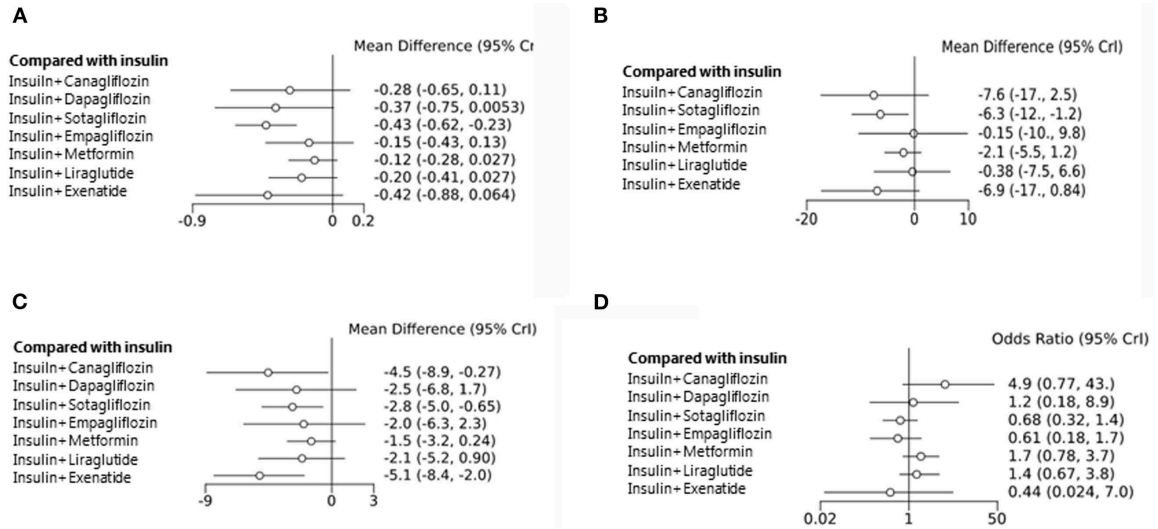

FIGURE 3 | Mean change in HbA1c level from the baseline **(A)**. Mean change in daily insulin dose from the baseline **(B)**. Mean change in body weight from the baseline **(C)**. Hypoglycemic events **(D)** associated with different types of treatment compared with the placebos used as the reference.

In previous clinical trials, early intensive glucose control in patients with T1D was reported to reduce all-cause mortality and prevent or delay late microvascular and macrovascular complications of diabetes (53). Therefore, insulin therapy is essential for T1D, but weight gain is a major concern. According to an analysis of physician electronic health records in the United States, 47.8% of people with T1D were found to be obese (54). Obesity is associated with insulin resistance and increased cardiovascular complications. Patients with T1D with more than two complications have significantly higher BMI than those with less than one complication (55).

Another important issue in the management of T1D is glycemic variability. A recent study demonstrated that variability in the HbA1c level was significantly and additively associated with mortality in participants (>13 years old) with T1D (56). Potential underlying mechanisms are unclear, but the variability in HbA1c could result in a poor response to insulin therapy or hypoglycemia. In a study on 1,706 adolescents with T1D, HbA1c variability significantly increased the risk of retinopathy, albuminuria, and cardiac autonomic neuropathy (57). Oxidative stress and systemic inflammation induced by inflammatory cytokines have been hypothesized as a potential mechanism underlying the association between glycemic variability and increased risk of diabetic complications (58, 59).

Taken together, intensive insulin treatment is essential for preventing diabetic complications caused by hyperglycemia, but it is associated with adverse effects, such as weight gain, hypoglycemia, and hyperglycemia, which cause low compliance leading to glycemic variability. In addition, the risk of hyperglycemia or hypoglycemia decreases the quality of life of patients with T1D (60).

Therefore, considerable effort has been made for better glycemic control without hypoglycemia using new antidiabetic medications. SGLT2 inhibitors target the proximal tubular SGLT2 transport protein, which is responsible for ∼90% of renal glucose reabsorption (16). Glucosuria caused by SGLT2 inhibition can result in a caloric loss of 250–300 kcal/day and, consequently, a weight loss of 2–3 kg. Given their insulin-independent mechanism, SGLT2 inhibitors have been used in several studies on T1D. In the Empagliflozin as Adjunctive to Insulin Therapy-2 and−3 studies, empagliflozin add-on to insulin improved glycemic control and weight change without increasing hypoglycemia in patients with T1D (21). However, adjudicated DKA occurred more frequently with 10 mg (4.3%) and 25 mg empagliflozin (3.3%). In the DEPICT-1 study, dapagliflozin treatment significantly reduced HbA1c by 0.42–0.45%, body weight by 2.96–3.72%, and TIDD by 8.8–13.2% after 24 weeks (19). DKA rates were higher after dapagliflozin treatment than after placebo treatment. Canagliflozin treatment also showed a similar efficacy in HbA1c reduction and body weight control, but the incidence of DKA requiring hospitalization was significantly increased with canagliflozin treatment compared with placebo treatment (22).

Sotagliflozin is a novel dual inhibitor of SGLT1 and SGLT2 that can reduce glucose absorption in the proximal intestine. SGLT1 inhibition was shown to increase the delivery of glucose to the distal small intestine and augment GLP-1 release (16, 61). In a phase III RCT of sotagliflozin administered in combination with insulin to 1,402 adults with T1D, 24 weeks of treatment with sotagliflozin decreased the HbA1c level by 0.46%, body weight by 2.98 kg, and insulin dose by 2.8 U/day (1). However, sotagliflozin treatment was associated with a higher rate of ketoacidosis (3.0%) than placebo (0.6%).

The present study data revealed that sotagliflozin add-on to insulin improved glycemic control and decreased weight. These positive effects may be related to an improvement in glucose variability. Although the clinical role of SGLT1 inhibition at

A

	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8
Insulin	0.000	0.000	0.000	0.000	0.005	0.040	0.242	0.714
Insulin+Canagliflozin	0.113	0.145	0.188	0.185	0.137	0.096	0.079	0.058
Insulin+Dapagliflozin	0.222	0.215	0.206	0.152	0.086	0.058	0.037	0.024
Insulin+Sotagliflozin	0.277	0.386	0.228	0.082	0.020	0.005	0.001	0.000
Insulin+Empagliflozin	0.011	0.033	0.079	0.140	0.193	0.214	0.212	0.119
Insulin+Liraglutide	0.008	0.042	0.114	0.222	0.257	0.200	0.130	0.029
Insulin+Metformin	0.000	0.006	0.031	0.114	0.235	0.334	0.260	0.019
Insulin+Exenatide	0.369	0.175	0.154	0.105	0.069	0.053	0.039	0.038

B

Residual deviance	46.6
Leverage	43.4
DIC	90.0
Number of data points	48.0

FIGURE 4 | Comparison of the included diabetes treatments for HbA1c, odds ratio (95% CI). Each cell indicates the effect of the column-defining intervention relative to the row-defining intervention **(A)**, model fit statistics **(B)**.

therapeutic doses is unlikely, the beneficial effects of sotagliflozin on glycemic improvement and weight loss in the present study suggest that a more marked inhibition of SGLT1 should be explored.

Canagliflozin, which also inhibits SGLT1, was also effective in body weight reduction in patients with T1D. A study showed that canagliflozin inhibited intestinal glucose absorption at a concentration 10-times the IC50 of SGLT1 in the intestinal lumen (62). A recent randomized trial in patients with type 2 diabetes showed that pre-meal administration of canagliflozin increased the plasma GLP-1 levels (63). These findings suggest that canagliflozin has a positive role in weight reduction in patients with T1D.

A brief report on cardiovascular effects of exenatide add-on therapy in 69 metformin-treated patients with T2D showed a significant reduction in total body fat mass, trunk fat mass, and waist circumference compared with the insulin glargine therapy. According this study, treatment with exenatide for 1 year reduced body weight (6%), waist circumference (5%), and total body (11%) and truncal fat mass (13%) (64).

A recent prospective, randomized study investigated exenatide or glargine add-on therapy in 37 overweight or obese patients with T2D, who were inadequately treated with metformin. After 16 weeks, the exenatide treatment group had lower body weight (−4.5 kg), BMI (−1.6 kg/m^2), body fat mass, and percent fat mass (except for gynoid fat) than the insulin glargine group. Weight loss by exenatide was mainly owing to reduced body fat content rather than lean tissue (65).

A study on metformin-treated patients with T2D showed that 1 year treatment with exenatide reduced the total body fat mass by 6% and the waist circumference by 5% compared with the insulin glargine-treated patients (37). In another recent prospective, randomized study in overweight or obese patients with T1D, 16 weeks of treatment with exenatide significantly decreased the body weight by 4.5 kg and BMI by 1.6 kg/m^2 compared with insulin glargine treatment (38). Moreover, exenatide resulted in weight loss mainly by reducing body fat but not lean tissue mass. The findings of our study suggest that sotagliflozin has potential benefits of HbA1c reduction and weight loss, whereas canagliflozin and exenatide have a potential benefit of weight loss in patients with T1D.

Our study had several strengths. A traditional meta-analysis can compare only two groups based on one intervention, which is a limitation. However, our network meta-analysis is a complement method to the groups, interventions, or conflict interests that are difficult to be directly compared with each other. In this study, we performed an indirect analysis that can explain the accuracy of model by 20,000 repetitive learning in

computer and rank among interventions by comparing several groups at the same time. This is pivotal to guideline development for T1D since, in the absence of head-to-head evidence, guideline development groups will rely more strongly on expert opinion. Hence, they may make comparisons that do not adequately account for potential biases in study designs, intervention characteristics, and study populations. Indirect comparisons connect treatments via a common control or comparator (e.g., a placebo like insulin or a standard of care) thus having a comparative effect between treatments that have not been compared head-to-head in randomized controlled trials. Another benefit of this analysis is that it comprises a simultaneous analysis of all potential treatment options and makes full use of the available evidence within a single analysis. Doing so, provides a more concise assessment of the clinical landscape and enables better decision-making. This analysis can be helpful in selecting add-on drugs for a specific condition. Secondly, this is the first network meta-analysis involving the SGLT1/2 inhibitor, sotagliflozin. Finally, we exclusively included well-designed RCTs. Therefore, less accurate studies were excluded, and the results were less biased to increase reliability.

Our study also had some limitations. Some of the trials included had a relatively small number of participants, and they were conducted for a short duration. Thus, the assessment of long-term outcomes such as cardiovascular events and renal complications was not performed. Another limitation is that the sotagliflozin study included HbA1c reduction results with an insufficient drug duration, which may weaken the findings. However, the sensitivity analysis proved that sotagliflozin therapy reduced HbA1c level significantly in patients with T1D.

In conclusion, sotagliflozin treatment decreased not only the HbA1c levels and insulin dose but also the body weight without causing hypoglycemia in patients with T1D. Treatment with canagliflozin and exenatide was effective in body weight reduction in patients with T1D. However, when we performed a meta-analysis using only four studies, including sotagliflozin, the sotagliflozin group had an increased risk of acidosis and diabetic ketoacidosis compared to the placebo. Therefore, adverse effects associated with SGLT inhibitors should be considered in these patients.

In March 2019, the US FDA rejected the use of sotagliflozin as an adjunct to insulin for the treatment of T1D. The decision followed a split vote in January 2019 by the FDA's Endocrinologic and Metabolic Drugs Advisory Committee, during which panel members expressed concerns over an increased risk of ketoacidosis with the drugs used for T1D. However, after 1 month, the European Commission approved sotagliflozin for prescription in the European Union for certain overweight patients with T1D. According to the results of our network meta-analysis, we suggest that sotagliflozin has a high probability of being ranked first as an adjunctive therapy to insulin in patients with T1D. However, to avoid ketoacidosis and other adverse events, risk mitigation strategies, such as continuation of insulin and discontinuation of SGLT inhibitors on sick days, should be strictly implemented when these drugs are introduced for patients with T1D (66).

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

YK, SH, and SL: conceptualization, methodology and data acquisition, data analysis and interpretation, statistical analysis, writing—original draft preparation, writing—review and editing, and funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2020.00553/full#supplementary-material

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Shared Medical Appointments and Mindfulness for Type 2 Diabetes—A Mixed-Methods Feasibility Study

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Introduction: Type 2 diabetes (T2DM) is a major health concern with significant personal and healthcare system costs. There is growing interest in using shared medical appointments (SMAs) for management of T2DM. We hypothesize that adding mindfulness to SMAs may be beneficial. This study aimed to assess the feasibility and acceptability of SMAs with mindfulness for T2DM within primary care in Australia.

Materials and Methods: We conducted a single-blind randomized controlled feasibility study of SMAs within primary care for people with T2DM living in Western Sydney, Australia. People with T2DM, age 21 years and over, with HbA1c > 6.5% or fasting glucose >7.00 mmol/L within the past 3 months were eligible to enroll. The intervention group attended six 2-h programmed SMAs (pSMAs) which were held fortnightly. pSMAs included a structured education program and mindfulness component. The control group received usual care from their healthcare providers. We collected quantitative and qualitative data on acceptability as well as glycemic control (glycated hemoglobin and continuous glucose monitoring), lipids, anthropometric measures, blood pressure, self-reported psychological outcomes, quality of life, diet, and physical activity using an ActiGraph accelerometer.

Results: Over a 2-month period, we enrolled 18 participants (10 females, 8 males) with a mean age of 58 years (standard deviation 9.8). We had 94.4% retention. All participants in the intervention group completed at least four pSMAs. Participants reported that attending pSMAs had been a positive experience that allowed them to accept their diagnosis and empowered them to make changes, which led to beneficial effects including weight loss and better glycemic control. Four pSMA participants found the mindfulness component helpful while two did not. All of the seven participants who contributed to qualitative evaluation reported improved psychosocial wellbeing and found the group setting beneficial. There was a significant difference in total cholesterol levels at

12 weeks between groups (3.86 mmol/L in intervention group vs. 4.15 mmol/L in the control group; $p = 0.025$) as well as pain intensity levels as measured by the PROMIS-29 (2.11 vs. 2.38; $p = 0.034$).

Conclusion: pSMAs are feasible and acceptable to people with T2DM and may result in clinical improvement. A follow-up fully-powered randomized controlled trial is warranted.

Clinical Trial Registration: Australia and New Zealand Clinical Trial Registry, identifier ACTRN12619000892112.

Keywords: type 2 diabetes, primary care, shared medical appointments, mindfulness, glycemic control, feasibility study, pSMAs for type 2 diabetes

INTRODUCTION

Diabetes is a major cause of morbidity and mortality globally. An estimated 8.5% of the world's population lives with diabetes, and diabetes was the direct cause of 1.6 million deaths, or 11% of all deaths, in 2014 worldwide (1). In 2019, global health expenditure on diabetes was estimated at USD$760 billion (2). In Australia, type 2 diabetes (T2DM) is diagnosed once every 5 min (3) and the number of diagnoses is expected to double by 2033 to 3.5 million (4). T2DM is a National Health Priority Area (5) with an annual financial cost of AUD $14.6 billion (3). Health consequences of T2DM are devastating and include stroke and coronary heart disease, blindness, renal failure, neuropathy, and peripheral vascular disease (4). Moreover, T2DM is one of the leading causes of morbidity and mortality in Australia and commonly causes psychological distress (4). It is estimated that every 1% reduction in HbA1c significantly reduces risk of T2DM related deaths (−21%) and microvascular complications (−37%) (6).

There is growing interest in the possible role of shared medical appointments (SMAs) in managing chronic disease (7). SMAs are defined as "*consecutive individual medical visits carried out in a supportive group setting of similar patients where all can listen, interact, and learn*" and may have the advantages of being cost-effective, encouraging peer support, improving clinician satisfaction, and reducing repetition of health information (8). SMAs involve a medical practitioner [e.g. general practitioner (GP) or specialist] consulting with patients sequentially among a group of patients who can interact throughout the consultation under the guidance and direction of a trained facilitator (usually a practice nurse or other allied health professional). A variant of SMAs is the programmed SMA or pSMA, which incorporates a structured educational component. SMAs are also a time-efficient way of providing chronic disease management, and are becoming increasingly popular within primary care (9).

The evidence on SMAs for T2DM is inconsistent, mostly due to heterogeneity of the interventions and sample characteristics; however, there is some evidence for reduction of HbA1c, weight, blood pressure, lipids, and improved quality of life and patient satisfaction (10). SMAs are also cost-effective compared to one-on-one care (8). There is a compelling need to further explore the role of SMAs in the management of diabetes and its complications as well as resulting psychological distress within primary care. Of note, there are no published randomized controlled trials evaluating the effectiveness of SMAs for T2DM in Australia.

Mindfulness-based interventions may be beneficial for quality of life, anxiety, and depression in people with T2DM but the evidence for physiological outcome changes is inconsistent (11). However, mindfulness meditation may play an important adjunctive role in managing other metabolic conditions. For example, there is evidence from systematic reviews that mindfulness meditation in the general population can improve eating behaviors and increase physical activity (11–16) by teaching participants to become more accepting of the physical discomfort of portion control and physical exercise and is effective for weight loss.

SMAs may therefore represent an innovative model of care that could improve glycemic control in people with T2DM and enhance T2DM management within primary care; however, more robust evidence is required. Prior to undertaking expensive randomized controlled trials, feasibility studies are recommended in order to assess the likelihood of successful recruitment of a fully-powered trial as well as the acceptability of trial procedures to participants. To this end, we conducted a mixed-methods study evaluating the feasibility and acceptability of pSMAs for people with T2DM. We hypothesized that including a mindfulness component to pSMAs would improve adherence to lifestyle recommendations and facilitate healthier behaviors.

MATERIALS AND METHODS

The primary objective for the study was to assess recruitment, retention, and adherence rates as well as acceptability of trial procedures. Secondary objectives were to determine an effect size for pSMAs vs. usual care and examine for a trend between groups for change in glycemic control, blood pressure, lipids, anthropometric measures, quality of life, psychological outcomes, and lifestyle habits.

Study Design

This was a mixed-methods study that included a prospective parallel pragmatic single-blind randomized controlled feasibility

trial. Feasibility was also assessed using qualitative methods (a focus group and semi-structured interviews).

Ethics approval was granted by the Western Sydney University Human Research Ethics Committee (H12925 16/11/2018). The trial was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12619000892112).

Randomization and Blinding

Participants were randomized in a 1:1 ratio to receive either the intervention (pSMA) or usual care. The randomization sequence was created using a computer program (www.sealedenvelope.com) by a researcher external to the research team. Permuted blocks of six were used. Allocation was concealed using consecutively number sealed opaque envelope. Before opening each envelope, the research assistant wrote the participant's name on the envelope, the date, and signed the envelope as a record of randomization. Investigators (apart from the research assistant who implemented the randomization process) were blinded to treatment allocation but participants were not. The research assistant who collected anthropometric measurement collection (JH) was also blinded to allocation.

Sample Size

As this was a feasibility study, a sample size calculation was not required. SMAs typically involve 10–12 participants per group. We aimed to randomize 24 participants altogether (12 to a pSMA group, 12 to usual care).

Participants

The study took place in an academic primary care clinic setting (Western Sydney Integrative Health—an academic clinic within Western Sydney University) in Sydney.

Recruitment began on 12th March 2019 and ended on 15th May 2019. The study was advertised on Diabetes NSW & ACT social media pages on 15th March and in the Diabetes NSW & ACT newsletter in 4 April. The study was advertised on Facebook from 19th March for six days and on Google from 23rd March for 7 days. Other promotion channels were the Western Sydney University online staff newsletter on 12th March and 16th April 2019, and the India Club newsletter 4th April 2019 (a voluntary organization established to promote the interests of the Indian Australian community).

Participants were eligible if they were aged over 21 years, lived in the Greater Western Sydney region in Australia, had a diagnosis of T2DM, and had evidence of HbA1c > 6.5% or fasting blood glucose > 7.00 mmol/L within the preceding 3 months. Exclusion criteria were:

- Unable to attend for pSMAs;
- Pregnant or planning pregnancy in the next 3 months;
- Serious medical or psychological conditions (e.g., metastatic cancer and poorly controlled schizophrenia);
- Not fluent in English (unable to follow conversations and instructions in English and unable to read English); and
- Known allergy to medical adhesives (because of the risk of allergy to adhesive from the continuous glucose monitoring system)

Outcomes

Primary outcome measures were recruitment rate, retention rate, and adherence rate. Acceptability was also assessed by an exit questionnaire and qualitative methods.

We used the following to define our feasibility measures:

- Recruitment rates: number of enquiries and number of enrolments per month of active recruitment; percentage conversion to enrolment measured as *n* enrolled/*n* of enquiries, and *n* enrolled/*n* potentially eligible.
- Retention rate: *n* completing 12-week intervention and outcome measures/*n* enrolled.
- Adherence rate: *n* completing at least 4 of 6 PSMAs/total *n* allocated to the intervention group.

Secondary outcome measures were:

- Glycemic management (from HbA1c, and also time in range/mean glucose measured by a 14-day FreeStyle Libre Continuous Glucose Monitor);
- Fasting lipids;
- Anthropometric measures (weight, body mass index/BMI, waist and hip circumference, and waist/hip circumference ratio);
- Blood pressure;
- Anxiety and depression using the Beck Depression Inventory (BDI) (17) and State Anxiety Index (SAI) (18);
- Diabetes-related distress using the Problem Areas in Diabetes (PAID) scale (19);
- Generic quality of life and wellbeing using the EuroQol-5D (EQ5D) (20) and Patient-Reported Outcomes Information System questionnaire (PROMIS-29) (21);
- Self-reported diet quality using three questions about fruit, vegetable and takeaway intake taken from the NSW Population Health Survey Questionnaire 2017, which is an annual telephone-based survey of 15,000 adults in the state of New South Wales, Australia (22);
- Physical activity levels as measured by an ActiGraph accelerometer (minutes per week of light, moderate and vigorous activity; number of steps per day; number of sedentary hours per day); and
- Number of minutes of mindfulness practice per week (measured using a home meditation log)

Pre-Intervention and Baseline Visit Data Collection

At a pre-intervention visit, a research assistant obtained written informed consent and details on concomitant medications and past medical history. Weight was measured to the nearest 0.1 kg using a calibrated medical-grade digital scale (Seca 803) and waist and hip circumference to the nearest 0.1cm using a medical-grade steel tape measure (Seca 201). Height was measured using a wall-mounted stadiometer. Anthropometric measures and blood pressure were measured according to standard procedures (23). Participants completed a demographic and medical questionnaire that collected information about age, ethnicity, education, cigarette use, year of diagnosis of T2DM, and presence of complications of

diabetes. Study data were collected and managed using REDCap electronic data capture tools hosted at Western Sydney University (24, 25). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

A 14-day FreeStyle Libre Continuous Glucose Monitor sensor was inserted into the posterior upper arm. We asked participants to wear an ActiGraph accelerometer (GT3X, LLC, Fort Walton Beach, FL) on their right hip for 5–7 days to measure light, moderate, and vigorous physical activity, as well as their number of steps per day and time spent in sedentary behavior. A sufficient number of days are needed for the resulting average MVPA per day to reflect the participants usual PA level. However, it is equally important to not overburden participants. Evidence across multiple accelerometer studies shows that at least 3 days of PA data are needed to reliably estimate usual or habitual PA levels (26). As accelerometer compliance is sometimes low, asking participants to wear the device for 5–7 consecutive days is likely to ensure at least three valid days of PA data, without overburdening participants more than necessary. We removed non-wear-time from the participants' data files by identifying strings of consecutive zero count-values lasting ≥60 min, while allowing for a 1- to 2-min spike tolerance of counts between 0 and 100. After removing wear-time, a calendar day was considered valid if the accelerometer was worn for ≥10 h, and participants with at least 3 valid days were included in the analysis. Using established cut-points we calculated participants' sedentary, light, moderate, and vigorous physical activity (27).

Participants attended for blood collection at private pathology centres (Laverty Pathology) after an overnight fast, a few days prior to the baseline visit. Whole blood was analyzed for glycated haemoglobin using ion-exchange high-performance liquid chromatography/HPLC (D-100™ HbA_{1c} test; Bio-Rad Laboratories). Serum was analyzed for total cholesterol using the enzymatic method (ADVIA® Chemistry Concentrated Cholesterol Reagent/CHOL_c; ADVIA® Chemistry Systems) and for triglycerides using the Fossati three-step enzymatic reaction with a Trinder endpoint (ADVIA® Chemistry Triglycerides_2 Concentrated/TIRG_c assay; ADVIA® Chemistry Systems).

At the baseline visit, the Freestyle Libre sensor was removed and disposed of, and data was downloaded from the sensor. The accelerometer was collected from the participant, and any adverse events that had been experienced were recorded.

End of Treatment Data Collection

Participants attended a Week 12 clinic visit during which adverse events that were reported were recorded and concomitant medications and medical history were updated. Anthropometric measures, blood pressure, and PROMs were collected as per the pre-intervention visit. Participants also completed an exit survey about acceptability of trial procedures; however, due to an administrative error only the first question was completed at Week 12, with the remainder of the questions completed in December 2019 when the research team discovered the missing data. Participants were fitted with another 14-day FreeStyle Libre Continuous Glucose Monitor sensor and wore that for 14 days, then returned for removal of the sensor. Participants were provided with an accelerometer to wear for 5–7 days and had further testing for HbA1c and fasting lipids.246.

Intervention: Programmed Shared Medical Appointments With Mindfulness

The intervention was a series of face-to-face pSMAs with an adjunctive mindfulness meditation component. The frequency, length and duration of pSMAs is based on a study by Egger et al. on weight loss for people with obesity (9) as well as from reviewing the literature. The frequency of SMAs for people with T2DM in other studies has varied from every 3 weeks to every 3 months, with more frequent SMAs being generally associated with improved outcomes for weight loss. The feedback from study by Egger et al. was that monthly SMAs were too infrequent for weight loss, and fortnightly SMAs were feasible. Most SMAs are between 6-12 people of an optimum of six sessions based on the earlier GutBuster's Program by Egger (28).

The 12-week program included six fortnightly 2-h pSMAs delivered by a GP, facilitator (accredited diabetes educator), documenter, and a meditation teacher. The pSMA ran as follows:

- A confidentiality agreement was signed by all participants at the beginning of the first SMA;
- Each participant was asked for their questions for the GP, and these were written down on a whiteboard;
- 60 min of SMAs where the GP consulted with each participant consecutively for approximately 5–7 min at a time per individual consultation;
- 30 min of structured education delivered by the facilitator/diabetes educator. These were made interactive through the use of props and handouts, for example, food models, nail files, and fact sheets from the National Diabetes Services Scheme, an initiative of Diabetes Australia (Australia's national body for people affected by diabetes); and
- 20 min of guided mindfulness meditation delivered by a meditation teacher (see **Appendix 2** for more information).

For quality assurance, and to ensure fidelity of the intervention, a researcher (CE) observed one of the pSMAs and provided corrective feedback as appropriate.

Eight topics on diabetes education were offered to the participants who were then able to choose the six topics that they wished to have delivered (see **Appendix 1** for details on the education program). Participants were encouraged to set their own lifestyle goals based on the RACGP handbook on general practice management of T2DM (29). Key goals included weight loss of 5%.

The mindfulness component was delivered by an experienced meditation teacher and consisted of 15–20 min of guided mindfulness meditation. Mindfulness was defined as "paying attention in a particular way; on purpose, in the present moment, and nonjudgementally" (30). Each guided mindfulness session

was recorded and made available for home practice. Participants were encouraged to practice mindfulness meditation at home and to record it in meditation logs. More details are available in **Appendix 1**.

Control

Participants allocated to the control group received usual care only, defined as care as provided by their usual GP. They were encouraged to register for the GetHealthy NSW program (31), which is a free telephone-based lifestyle coaching service, and to use the free Smiling Mind (32) mindfulness meditation app regularly.

Prior and Concomitant Medications

There were no restrictions on concomitant medications in this trial. Concomitant medications were monitored using a Concomitant Medication Log.

Participant Reimbursement

All participants were reimbursed AUD$50 in total after attending the 12-week visit, for travel costs associated with the study.

Qualitative Interviews

We conducted a qualitative evaluation of the acceptability and feasibility of the pSMA program. Participants who received the pSMAs intervention were invited to provide feedback on the acceptability of the intervention in a 90 to 120-min focus group or a one-on-one, semi-structured interview.

The focus group and interviews were conducted by researchers external to the main study (SD and KM) so as to not influence participant responses in any way. Key questions in the interview schedule included feedback on the content, structure and frequency of the pSMAs, perceived value of the mindfulness component, and suggestions for improvement. Focus groups and interviews were audio-recorded and transcribed verbatim by a professional transcribing service.

Statistical Methods and Data Analysis

Recruitment, retention, and adherence rates are presented with descriptive statistics. We used ANOVA to identify between-group differences, adjusting for baseline score as a co-variate. Where data was not normally distributed, we used non-parametric measures (Mann-Whitney U tests). Intention-to-treat analysis was used. Analysis and interpretation of the findings was conducted by blinded investigators. Investigators agreed on the interpretation of the findings before revealing the allocation of either group. At the time of interpretation of findings, the two groups were only referred to as "Group 1" or "Group 2". Group numbers were also not revealed as this could have compromised blinding.

The de-identified transcripts were analyzed using thematic analysis. Thematic analysis encompasses identifying and analyzing reoccurring patterns of significance in regard to the research question being addressed (33). Themes and sub-themes meaningful to the research matter emerged as a result of these reoccurring patterns within the data. Transcripts were coded using Quirkos v.1.5.1 software (34). Participant excerpts are included in the results labelled by a participant identification number to highlight key themes and sub-themes.

RESULTS

Recruitment

Facebook advertisement received 11,576 total impressions with an engagement rate of 12% and CPR of $0.69c, at a total cost of AUD $100 over six days. The Google advertisements generated 144 clicks and 4,320 impressions at a cost of AUD$380 over 7 days.

Figure 1 describes participant flow through the trial.

Baseline Data

Tables 1, **2** describe demographic and medical characteristics, and between-group comparison of outcomes at baseline. There were no statistically significant between-group differences for demographic characteristics or outcomes measures at baseline.

Primary Outcomes

Recruitment, Retention, and Adherence

Our recruitment resulted in an average of 26 enquiries and nine enrolments per month of active recruitment. The conversion rate from enquiry to enrolment was 37.5% (18/48) and from eligible to enrolled was 85.7% (18/21). From those that were excluded, 40% (12/30) did not meet the study's inclusion criteria, 33.3% (10/30) were lost to follow up, 13.3% (4/30) declined to participate (no reason provided), 10% (3/30) were eligible for the study but were unable to attend the baseline visit and one participant declined to participate over safety concerns (see **Figure 1**). Of the 18 participants enrolled, 17 completed the 12-week intervention and outcome measures (94.4% retention). All of the participants in the intervention group completed at least 4 of 6 PSMAs.

Acceptability: Exit Questionnaire Data

Based on exit questionnaire data, most of the participants in the pSMA group found the education sessions helpful (8/9), enjoyed being able to talk to other people with diabetes (7/9), contributing to research (7/9), found the mindfulness sessions helpful (6/9), and enjoyed the extra attention toward their health and wellbeing (5/9) (**Table 1**). However, few participants reported finding the mindfulness home practice or workbooks helpful (2/9), or reported losing weight (2/9).

Some quotes around this question included: "*it was a great experience attending group sessions*" (ID3); "*being in the control group I did not get much out of the study, except the opportunity to wear a sensor*" (ID1); "*Nothing to me was detrimental. The experience helped me to better understand my diabetes through the course contents and interaction with the other participants*" (ID6). Participants reported for example "*It was great being able to share with others, and hearing others talk about their health and see the same things we go through*" (ID10), "*This is my first experience in SMA. I liked it and feel better than a one-on-one GP appointments*" (ID16).

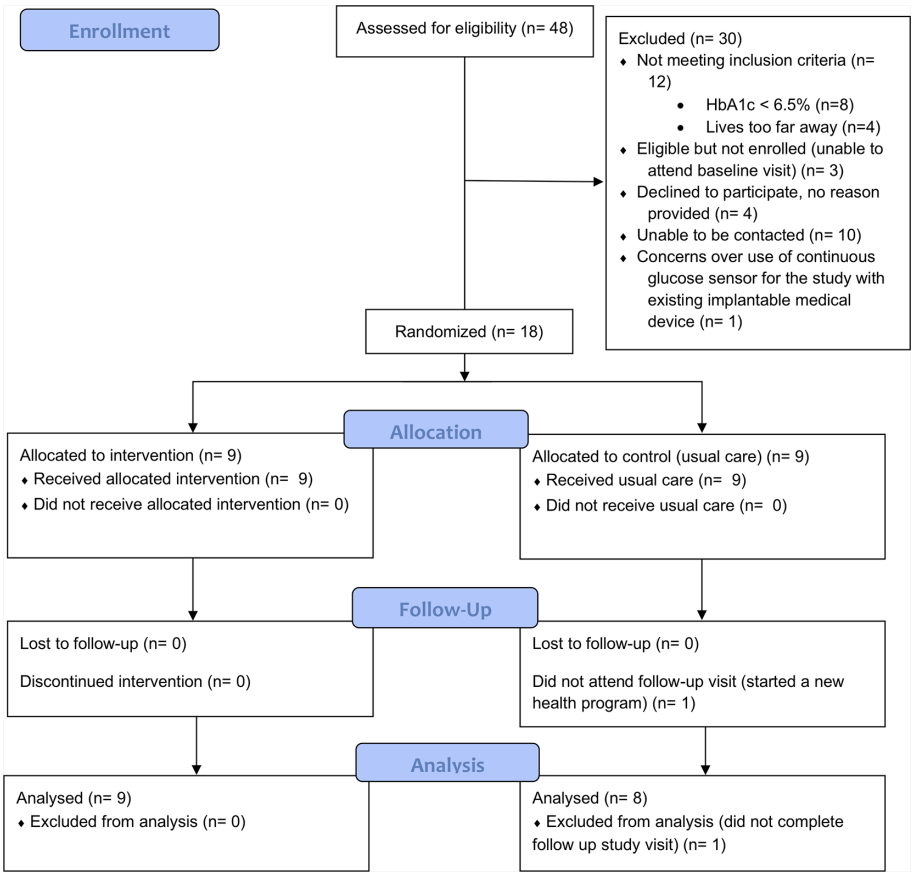

FIGURE 1 | CONSORT flowchart of participant flow.

When participants were asked what they did not enjoy about the trial, six from the pSMA group and four from the control group reported there was "*nothing*" that they did not enjoy. One participant said the SMAs were too far away from where he/she lived/worked, one did not enjoy the mindfulness practice, and one reported a technical error with a CGMS sensor. In the control group, one participant noted that the exit survey should have been tailored to the allocation groups (i.e., not asking control group participants the questions about PSMAs), and one noted that they could not access continuous glucose monitoring results in real time using a mobile application as advised, because the sensors that were used were not compatible with the Australian mobile application. Three participants from the control group reported that the "*did not learn anything new*".

Shared Medical Appointments

There were six responses from the question about feedback on the SMA's overall. All of the six responses were positive comments, e.g., "*very good*" (ID16), and "*excellent and should do more for these sessions*" (ID3).

The most important features of PSMAs according to participants were:

- The ability to share experiences and tips in a group discussion (6/9), including "*a better idea of the effect diabetes has on people [and] how they managed their diabetes and lived their lives*" (ID6);
- Expanded knowledge of diabetes from health professionals (5/9), which included education on results of tests, side effects of medications, a better understanding of diabetes overall, and increased confidence and awareness about diabetes;
- Sense of not being alone in experience of diabetes (5/9), including realizing that other people with diabetes were also struggling with their weight; and
- The style and approach of the facilitator and GP (friendly and non-judgmental, "*knowledgeable" (ID 18), "just made it easier to talk about things" (ID 10), "relaxed environment*" (ID 6) where participants felt free to ask questions) (5/9).

Table 3 describes the additional feedback on pSMAs.

Representative quotes include: "*Timing, duration and frequency was just right for me*" (ID16); "*was able to understanding how other where struggling/controlling their diabetes*" (ID3); "*being able to share and relate to others was very helpful*" (ID10); "*GP was knowledgeable and explained side effects of medications. In my experience doctors haven't done this*" (ID18).

TABLE 1 | Baseline data table.

	pSMA group	Usual care group	P value
Mean age in years (SD)	55.89 (11.60)	60.11 (7.67)	0.376†
Gender			0.637*
- ***Male***	6	2	
- ***Female***	3	7	
Ethnicity			0.842*
- ***European***	3	3	
- ***Oceanic***	3	2	
- ***Asian***	3	4	
Mean years diagnosed with T2DM (SD)	16.67 (5.97)	14.11 (10.54)	0.536†
Smoking status			1.000‡
- ***Ex-smoker***	2	2	
- ***Never smoked***	7	7	
Complications of T2DM			
- ***Ischemic heart disease***	1	2	
- ***Stroke***	0	0	
- ***Peripheral vascular disease***	0	0	
- ***Foot ulcers***	0	1	
- ***Retinopathy***	0	1	
- ***Chronic renal failure***	0	0	
- ***Neuropathy***	1		
Co-morbidities			
- ***Non-alcoholic steatotic hepatitis***	0	1	
- ***Hypercholesterolemia***	3	5	
- ***Hypertension***	5	4	
- ***Hypothyroidism***	2	2	
- ***Depression***	0	2	
On insulin therapy	4	2	0.620‡

†T^2 test; ‡Fisher's exact test; Mann-Whitney U test *Pearson Chi square; SD, standard deviation.

Facilitator and GP. We received eight responses for feedback on the facilitator and seven for the GP. All were positive with the facilitator rated from "*fantastic*" (ID16), to "*good*" (ID6). Participants described the facilitator as "*really good and knowledgeable*" (ID3), "*made us all feel relaxed*" (ID10), "*thoughtful*" (ID4). The characteristics of being friendly, approachable, and knowledgeable, were highly valued by the participants. Similarly, the GP was rated from "*good*" to "*the best person*" (ID3). ID4 noted "*Wow what a gentle caring GP*".

Mindfulness. Six participants provided feedback on the mindfulness sessions. Four of these participants had positive feedback including "*exceptionally good*" (ID16) and "*very helpful and relaxing*" (ID10). ID4 wrote "*In walked this quite softly spoken woman and I thought what is this. Within 15 mins I was hooked. Relaxing and insightful*". Two participants did not find the sessions useful.

Six participants from the pSMA group provided feedback on home mindfulness practice. Feedback was mixed. One participant noted that more assistance was needed (ID16). Another noted that, while mindfulness could be helpful, it was "*very difficult for busy people*" (ID10). Two participants found home practice helpful while another did not find it helpful.

Trial Procedures. **Table 4** describes the results on acceptability of trial procedures.

TABLE 2 | Between-group comparison of measures at baseline.

	pSMA group mean (SD)	Usual care group mean (SD)	P value
Glycemic control and lipids			
Hb1Ac-NGSP (%)	7.92 (1.09)	7.30 (0.44)	0.117‡
Hb1Ac-IFCC (mmol/mol)	62.89 (11.90)	56.25 (4.86)	0.117‡
Mean glucose (from CGMS) (mmol/L)	11.56 (4.06)	9.66 (2.01)	0.392‡
Time in range (from CGMS) (%)	40.89 (22.84)	60.71 (26.79)	0.132†
Triglycerides (mmol/L)	1.93 (0.63)	1.71 (1.15)	0.583‡
Total Cholesterol (mmol/L)	4.13 (0.61)	3.95 (0.63)	0.552†
Anthropometric measures and blood pressure			
Height (cm)	168.78 (5.17)	166.19 (12.32)	0.572†
Weight (kg)	96.67 (19.91)	81.67 (20.60)	0.136†
Waist circumference (cm)	112.39 (12.44)	102.50 (9.80)	0.091†
Hip circumference (cm)	114.67 (17.71)	108.63 (3.29)	0.945‡
BMI (kg/m^2)	34.08 (7.86)	27.61 (2.99)	0.167‡
Waist/hip circumference ratio	0.99 (0.08)	0.94 (0.74)	0.259†
Systolic BP (mm/Hg)	139.11 (16.83)	133.25 (11.00)	0.416†
Diastolic BP (mm/Hg)	84.99 (7.15)	81.25 (4.65)	0.239†
Beck Depression Inventory	6.11 (4.83)	9.63 (10.13)	0.725‡
State Anxiety Index	33.11 (8.34)	33.86 (10.67)	0.877†
EQ5D5L			
- anxiety	1.44 (0.53)	1.63 (0.92)	1.000‡
- mobility	1.33 (0.50)	1.38 (0.74)	1.000‡
- pain discomfort	2.11 (0.93)	1.88 (0.84)	0.591†
- self-care	1.00 (0.00)	1.00 (0.00)	NA
- usual activity	1.56 (0.53)	1.50 (0.76)	0.819‡
- VAS	74.00 (16.96)	80.75 (15.66)	0.409†
PAID	23.06 (17.07)	31.88 (30.66)	0.468†
PROMIS29			
- pain intensity	2.33 (2.55)	2.00 (2.77)	0.682‡
- anxiety	2.11 (1.69)	3.25 (4.06)	0.935‡
- depression	1.67 (2.24)	2.38 (3.11)	0.904‡
- fatigue	4.00 (4.03)	4.88 (4.49)	0.678†
- pain interference	2.89 (3.59)	2.00 (3.89)	0.499‡
- physical function	1.78 (1.92)	1.38 (1.77)	0.636‡
- sleep	7.00 (1.12)	7.00 (1.15)	1.000†
- social	11.67 (5.17)	11.88 (3.64)	0.867‡

†T^2 test; ‡Mann-Whitney U test.
HbA1c, glycated haemoglobin; NGSP, National Glycohemoglobin Standardization Program; IFCC, International Federation of Clinical Chemistry.
EQ5DL, EuroQol-5D; PROMIS-29, Patient-Reported Outcomes Information System questionnaire; PAID, Problem Areas in Diabetes scale; BMI, Body Mass Index; BP, blood pressure; VAS, Visual Analogue Scale.

Qualitative Evaluation of Trial Feasibility and Acceptability

Seven out of the nine participants from the pSMA group contributed to the qualitative assessment of trial feasibility and acceptability (five males and two females). One focus group was held on the 2nd of October 2019, attended by five participants, and two interviews were conducted over the telephone.

Four central themes meaningful to the study were identified from the data: (1) perceptions and attitudes toward pSMAs, (2) perceived effects of the pSMAs, (3) support and materials, and (4) future directions (see **Figure 2**).

TABLE 3 | Additional overall feedback about pSMAs from exit questionnaire.

Positive	N of responses	Other feedback/ suggestions	
Continuous glucose monitoring experience was beneficial	2	Sessions could have been a bit longer	1 (ID11)
Enjoyed mindfulness meditation	2	Information provided in the last session about decisions to eat healthy/ unhealthy food should have been presented in the first session as it was valuable information	1 (ID4)
Improved eating habits	1 (ID15)		
Learned that diabetes is not my fault	1 (ID4)		
Time and location was convenient	1 (ID8)		
"*they could be very effective with the right people*"	1 (ID10)		
Sessions could have been more frequent	1 (ID16)		

pSMAs, programmed Shared Medical Appointments.

TABLE 4 | Acceptability of trial procedures from the exit questionnaire.

Positive	N of responses	Other feedback/ suggestions	N of responses
Overall feedback on trial procedures			
No change required	6 (2xSMA, 4xcontrol)	Should be expanded to a larger group	2 (1xSMA, 1x control)
		More advertisement is required to raise awareness about the trial	1 (ID 16)
No response			8
Surveys			
No problems noted	5	Too long	2
		Questions were too private and personal	1
No response			9
Location of clinic visits			
No problems noted	8		
On-site parking was helpful	1		
No response			8
Glucose sensor			
No problems noted	5	Better to have used Australian sensors which synchronized to an app for real-time monitoring	4
		Difficulty with sensor remaining in place	1
No response			7
Pathology			
No problems noted	7	Test results were wrongly recorded by pathology company	1
		"*a few things needed to be improved*" (no further information given)	1
No response			8
Accelerometers			
Positive or neutral (from "good" to "okay")	5	A little inconvenient to wear	1
		Took a while to get used to	1
		Not helpful as could not access results in real time	1
No response			9

SMA, Shared Medical Appointment.

Theme 1: Perceptions and Attitudes Toward PSMAs

Positive Experience. Participants generally spoke positively about the program with many mentioning that they felt that it was "a very good project" (ID 6) and that the pSMAs were enjoyable to attend (excerpt 1.1a, b). Participants were generally satisfied with the frequency and duration of the pSMAs (excerpts 1.1c), as well as the time and location of them (excerpt 1.1d). Further, the longer duration of the pSMAs was also seen to be beneficial when compared to the shorter timeframe of individual medical visits (excerpt 1.1e, f). Participants were also prompted to discuss any negative impacts they may have experienced during the program. None of the participants reported having any negative or adverse events occur during the pSMAs, besides an adverse reaction to the glucose sensor mentioned below under *data collection* (excerpt 1.1g).

Reasons for Participation. The most commonly mentioned reasons for attending the pSMAs were to receive more information about the disease and treatment (excerpt 1.2a, b), and participants' expectation to share experiences as well as learn from fellow patients with T2DM (excerpt 1.2c). Other reasons for attending the pSMAs included encouragement from family (excerpt 1.2d), and an interest in the mindfulness aspect of the program (excerpt 1.2e).

Barriers to Consistent Participation. Nearly all of the participants that were interviewed reported missing one out of the eight pSMAs in the study. Reasons listed for missing a pSMA included work commitments (excerpt 1.3a), a pre-booked holiday (excerpt 1.3b), and family reasons.

Theme 2: Perceived Effects of the pSMAs

Acceptance. Denial of the importance of diabetes, or even the diagnosis itself, was mentioned by participants with ID1 describing that they had "*tolerated being a diabetic and not accepted it*" (excerpt 2.1a). Some participants indicated that the stigma surrounding T2DM created feelings of "guilt" (ID 5) which inhibited their willingness to accept having the disease (excerpt 2.1b, c). However, these participants felt that attending the pSMAs helped to reduce the stigma and guilt associated with having T2DM, particularly due to the education they received surrounding its hereditary component. This, in turn, led to a sense of acceptance for those who had previously struggled to come to terms with having T2DM (excerpt 2.1c, d).

Empowerment. All of the participants reported an increase in diabetes knowledge and awareness since attending the pSMAs. Some participants felt that they were now better equipped to manage their diabetes and improve their health (excerpt 2.2a, b). Further, many participants noted feeling a sense of empowerment from the education they received during the pSMAs, with ID1 saying that the sessions were "*all about empowering you*" (excerpt 2.2c, d). Several participants utilized the education they received during the pSMAs, and applied it in their everyday lives as listed below under *lifestyle modifications*. Even those that had yet to make any lifestyle modifications felt that they were now more inclined to try and make changes to improve their health and diabetes (excerpt 2.2e)

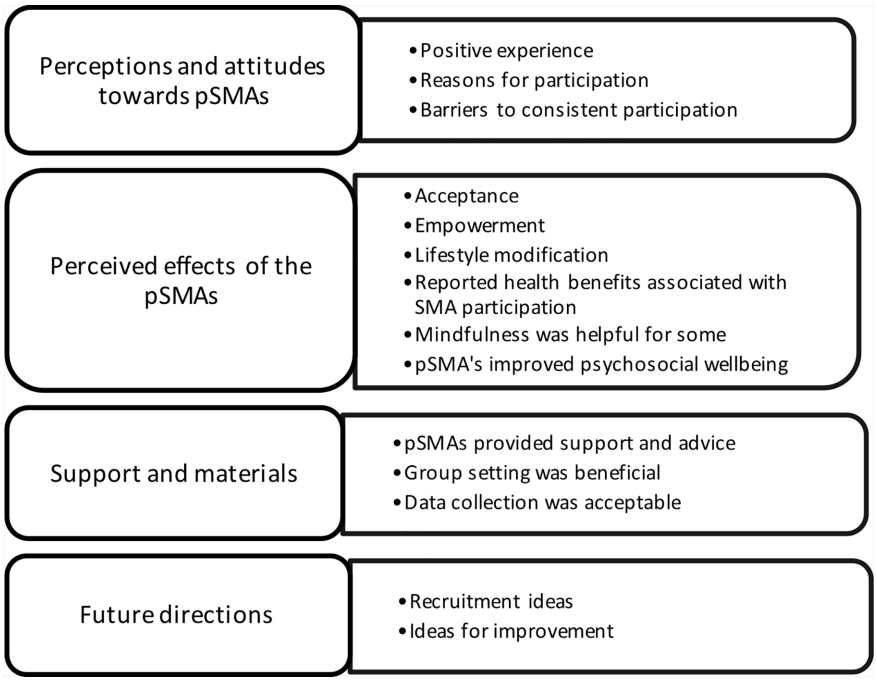

FIGURE 2 | Themes and subthemes from qualitative evaluation. pSMAs, programmed Shared Medical Appointments.

Lifestyle Modification. Participants reported applying the education they received on diabetes, diet, and health during the pSMAs to their lifestyles. Many of the participants reported an improved awareness of their diets and the food that they were consuming (2.3a). This was indicated *via* changes made to their diet including reducing consumption of refined carbohydrates such as rice, bread and pasta (excerpt 2.3b), eating smaller portion sizes (excerpt 2.3c), and making a conscious effort to swap junk food for healthier options (excerpt 2.3d). Other lifestyle modifications included making an increased commitment to looking after health *via* regular exercise and the practice of mindfulness made by one participant (excerpt 2.3e). Another participant mentioned focusing on reducing stress from their life after learning of the impact it can have on health in one of the pSMAs (excerpt 2.3f). Several of the participants had not yet made any lifestyle modifications associated with their participation in the pSMAs (excerpt 2.3g). Reasons for this included issues in their personal life (excerpt 2.3h)and difficulty in gaining motivation to make healthy lifestyle changes (excerpt 2.3i). One participant also noted that it was more difficult for them to reduce their carbohydrate intake due to rice being the staple food in their Asian culture (excerpt 2.3j).

Reported Health Benefits Associated With SMA Participation. Several participants reported noticing benefits to their health since participating in the pSMAs. Two of the participants reported experiencing weight loss (excerpt 2.4a), crediting the education they received surrounding diet and food choices and consequent lifestyle changes, as the reasons for this weight loss. One participant noted a decrease in their HbA1c levels at the end of the pSMAs (excerpt 2.4b), whilst another reported experiencing an increase in energy levels as a result of their participation in the pSMAs (excerpt 2.4c). An increase in joint and muscle flexibility was also mentioned as a health benefit experienced by one participant (excerpt 2.4d). A few of the participants stated that they were yet to experience any health benefits associated with their participation in the pSMAs (excerpt 2.4e). These participants were typically the ones that had not yet made any lifestyle modifications, as mentioned above.

Mindfulness was Helpful for Some. pSMA participants enjoyed practicing mindfulness and found it beneficial for various reasons. Several participants found that practicing mindfulness helped to improve the decision-making process behind one's dietary choices, which in turn, helped reduce mindless snacking and the consumption of "junk" food (excerpt 2.5a, b). Others found that practicing mindfulness improved sleep and enhanced relaxation and reduced stress (excerpt 2.5c–e). In regard to the practice of mindfulness at home, approximately half of the participants reported doing so whilst the other half stated that they had not yet done so (excerpt 2.5f, g). There were also a few participants that believed that mindfulness did not have any impact on their health or wellbeing, specifically stating that "mindfulness didn't work" (excerpt 2.5h).

pSMAs Improved Psychosocial Wellbeing. Participating in pSMAs appeared to positively impact on the mood of many of the participants (excerpt 2.6a). Many of the participant responses indicated

that they enjoyed attending the fortnightly pSMAs. Some of the participants also mentioned the mindfulness sessions included in the pSMAs as a contributing factor to their enhanced mood and decreased stress levels.

Theme 3: Support and Materials

pSMAs Provided Support and Advice. Content provided during the education sessions was found to be useful, beneficial, and easy to understand (excerpt 3.1a). Participants generally found that the information handouts they received throughout the pSMAs were useful and straightforward, and a few also mentioned using the notebook/diary provided to take notes during the session (excerpt 3.1b, c). Participant responses also indicated that they were pleased with the support and advice provided throughout the pSMAs, with many stating that they found the facilitators to be helpful and understanding (excerpt 3.1d). Further, importance was placed on the ability of the facilitators to create a comfortable environment and encourage the group to ask questions and share their experiences without feeling insignificant (excerpt 3.1e, f). One participant described being initially shy to talk in a group setting but once the pSMAs began they felt comfortable to engage and to ask questions (excerpt 3.1g). Overall, none of the participants reported any issues with the level of support and advice they were provided with throughout the pSMAs.

Group Setting Was Beneficial. The group setting was seen as beneficial by all participants, particularly because they reported finding it useful to hear about others experiences with diabetes as well as to share their own (excerpt 3.2a–c). Further, participants found it easy to learn from others in this group environment, mainly in regard to the management of diabetes (excerpt 3.2d, e). Participants also noted feeling that their different views were valued (excerpt 3.2f), and stated that they enjoyed bonding with other people in the "*same boat*" (ID 1) as them (excerpt 3.2g). Some participants mentioned an initial concern regarding how comfortable and willing everyone would be to share their experiences in front of strangers, but one participant found that it "*very quickly became comfortable*" (excerpt 3.2h, ID 5). It was also agreed by many of the participants that it was more favorable to attend the pSMAs with strangers as opposed to people you know, such as relatives and friends (excerpt 3.2i). One participant felt that being with strangers results in a "*lack of inhibition and embarrassment*" (ID 2), making it easier to share experiences and ask questions.

Data Collection Was Acceptable. The participants generally felt that the data collection process was easy and ran smoothly (excerpt 3.3a). Participants felt that it was useful to find out their measurements, including weight and blood sugar levels, and it was considered a good progress checkpoint by some participants (excerpt 3.3b, c). There were no major issues with the data collection process; however, one participant had an adverse reaction to the glucose sensor resulting in blisters and itchiness (excerpt 3.3d). Another participant mentioned receiving incorrect instructions in regard to the use of the accelerometer. One participant also felt that there were "too many questions" (ID 6) included in the data collection process (excerpt 3.3e).

Theme 4: Future Directions

Recruitment Ideas. Promotion of pSMAs *via* GPs, endocrinologists, and the National Diabetes Services Scheme (NDSS), as well as *via* word of mouth, were all considered to be important for future SMA recruitment (excerpt 4.1a, b). Further, many of the participants stated that they would recommend pSMAs to other T2DM patients (excerpt 4.1c). The challenges to recruiting others to attend SMAs discussed by participants included potential feelings of shyness inhibiting one's willingness to share their experiences in a group setting (excerpt 4.1d) as well as a lack of time and willingness to commit (excerpt 4.1e).

Ideas for Improvement. Participants were prompted to discuss aspects of the pSMAs that could be improved to enhance their effectiveness. Two participants mentioned that they would like the information delivered during the pSMAs to be provided digitally *via* a PDF rather than in hard copy, with one suggesting the creation of an app that contains this information (excerpt 4.2a, b). With regards to long-term use of pSMAs, participant responses indicated that they were satisfied with attending over the 8-week period but would not want to attend for longer periods of time. However, some of the participants mentioned continued contact and updates would be useful (excerpt 4.2c).

Secondary Outcomes

Anthropometric Measures

There were no statistically significant differences between groups at post intervention for weight, waist circumference, hip circumference, BMI, WHR, or blood pressure (see **Table 5**).

Glycemic Control and Lipids

There was a trend to improvement in glycemic control (glycated hemoglobin, continuous glucose levels, and time in range) in the pSMA group and a deterioration in the usual care group; however, these differences were not statistically significant. There was a statistically significant difference between groups for change in total cholesterol levels, which decreased by 6.5% in the pSMA group and increased by 5% in the usual care group (see **Table 6**).

Psychological Outcomes and Quality of Life

Table 7 presents the findings for psychological outcomes and quality of life. Psychological outcomes improved in the pSMA group compared to little change in the usual care group; however, these changes were not statistically significant. This included a 36.3% reduction in the Beck Depression Inventory and 41.5% improvement in the PAID score in the pSMA group.

Fatigue, pain, and physical function improved in the PROMIS 29 domains in the pSMA group but only the change in pain intensity was statistically significant; however, the mean score for this suggested low levels of pain intensity at baseline.

Diet and Physical Activity Changes

Table 8 describes the findings for diet and physical activity changes. There was a significant difference between groups at

TABLE 5 | Anthropometric measures and blood pressure at baseline and 12 weeks.

	pSMA group mean baseline (SD)	pSMA mean post intervention (SD)	Usual care group mean baseline (SD)	Usual care group mean post intervention (SD)	P value
Weight (kg)	96.67 (19.91)	95. 78 (19.84)	76.63 (14.96)	75.75 (14.98)	0.993†
Waist circumference (cm)	112.39 (12.44)	111.86 (15.41)	102.50 (9.80)	103.75 (8.24)	0.132‡
Hip circumference (cm)	114.67 (17.71)	114.20 (17.49)	108.63 (3.29)	107.38 (3.70)	0.510†
BMI (kg/m^2)	34.08 (7.86)	33.78 (8.02)	27.61 (2.99)	27.23 (2.83)	0.885†
Waist/hip circumference ratio	0.99 (0.08)	0.98 (0.66)	0.94 (0.74)	0.97 (0.06)	0.183†
Systolic blood pressure (mm/Hg)	139.11 (16.83)	137.67 (14.34)	133.25 (11.00)	131.50 (15.79)	0.962†
Diastolic blood pressure (mm/Hg)	84.99 (7.15)	83.00 (4.50)	81.25 (4.65)	79.88 (8.90)	0.880†

†T^2 test; ‡Mann-Whitney U test.
BMI, Body Mass Index.

TABLE 6 | Glycemic control and lipids at baseline and 12 weeks.

	pSMA group mean baseline (SD)	pSMA group mean post intervention (SD)	Usual care group mean baseline (SD)	Usual care group mean post intervention (SD)	P value
Hb1Ac-NGSP (%)	7.92 (1.09)	7.81 (0.80)	7.30 (0.44)	7.5 (1.03)	0.336†
Hb1Ac-IFCC (mmol/mol)	62.89 (11.90) (11.90) (11.90)	61.89 (8.67)	56.25 (4.86)	58.50 (11.41)	0.356†
Mean glucose (from CGMS) (mmol/L)	11.56 (4.06)	10.52 (1.95)	9.66 (2.01)	10.37 (2.49)	0.555‡
Time in range (from CGMS) (%)	40.89 (22.84)	49.60 (24.23)	60.71 (26.79)	55.14 (30.85)	0.296†
Triglycerides (mmol/L)	1.93 (0.63)	2.13 (1.06)	1.71 (1.15)	2.01 (1.03)	0.583‡
Total Cholesterol (mmol/L)	4.13 (0.61)	3.86 (0.66)	3.95 (0.63)	4.15 (0.73)	**0.025‡**

†T^2 test; ‡Mann-Whitney U test; NGSP, National Glycohemoglobin Standardization program; IFCC, International Federation of Clinical Chemistry; CGMS, Continuous Glucose Monitoring System. Bold figures represent statistically significant differences.

baseline for weekly takeaway intake (p = 0.0451) with the intervention group consuming a greater number of takeaway meals than the control group. There was no difference between groups at post intervention for physical activity levels and dietary habits.

We were only able to calculate mean minutes per day and days per week of meditation as many of the logs were incomplete or reported only according to a brief estimate of time spent meditating. Minutes per day, days per week of meditation, and minutes per week of meditation were not normally distributed in the usual care group due to an outlier who practiced meditation for an hour a day 7 days a week, and so a non-parametric test was used. There was no difference between groups for minutes per day (p = 0.360), days per week (p = 0.479), or minutes per week (p = 0.626) spent meditating over the intervention period. When we removed the outlier from the usual care group, there was still no difference between groups for minutes per day (p = 0.629), days per week (p = 0.289), or minutes per week (p = 1.00). **Table 9** provides details of mean time spent meditating in both groups, with one outlier removed from the usual care group.

Harms

Eighteen adverse events (AE) were reported. Of these, five were determined to be definitely caused by participation in the trial (but not due to the intervention itself), and 13 were deemed to not be related to the intervention. There were three reports of mild pain around the CGM sensor, which were short-lived and completed resolved within 10 min. There was one report of itch and redness around the sensor, which was mild and partially resolved at the time of follow-up. There was one report of a mild bruise around the phlebotomy site. The other AEs (which were deemed not related to the intervention) were back pain, blurred vision, cough, headache, high glucose level due to a urinary tract infection, elective surgery for an abdominal hernia, a toe injury (which did not occur while attending to trial activities), loose teeth, migraine, tightness of the chest, a tooth extraction, an upper respiratory tract infection, and visual disturbance. Ten AEs occurred in the pSMA group (including two definitely related AEs) and eight in the usual care group (including three definitely related AEs). One serious AE was reported (elective surgery as described above), which was not related to the intervention.

TABLE 7 | Psychological outcomes and quality of life at baseline and 12 weeks.

	pSMA group mean baseline (SD)	pSMA group mean post intervention (SD)	Usual care group mean baseline (SD)	Usual care group mean post intervention (SD)	P value
BDI	6.11 (4.83)	3. 89 (3.30)	9.63 (10.13)	9.88 (11.45)	0.832‡
SAI	33.11 (8.34)	30.11 (8.09)	33.86 (10.67)	36.29 (15.27)	0.281‡
EQ5D5L					
- anxiety	1.44 (0.53)	1.44 (0.53)	1.63 (0.92)	1.75 (1.67)	0.817‡
- mobility	1.33 (0.50)	1.22 (0.44)	1.38 (0.74)	1.38 (0.74)	0.939‡
- pain discomfort	2.11 (0.93)	1.67 (0.50)	1.88 (0.84)	2.00 (0.93)	0.187‡
- self-care	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	NA
- usual activity	1.56 (0.53)	1.22 (0.44)	1.50 (0.76)	1.13 (0.35)	1.000‡
- VAS	74.00 (16.96)	75.44 (14.14)	80.75 (15.66)	75.88 (23.66)	0.646‡
PAID	23.06 (17.07)	13.47 (7.75)	31.88 (30.66)	30.16 (34.03)	0.129†
PROMIS29					
- pain intensity	2.33 (2.55)	2.11 (2.37)	2.00 (2.77)	2.38 (2.93)	**0.034‡**
- anxiety	2.11 (1.69)	1.67 (1.58)	3.25 (4.06)	3.13 (4.39)	0.601‡
- depression	1.67 (2.24)	1.00 (1.58)	2.38 (3.11)	3.75 (4.23)	0.054‡
- fatigue	4.00 (4.03)	3.56 (2.92)	4.88 (4.49)	5.63 (4.81)	0.252†
- pain interference	2.89 (3.59)	2.67 (3.57)	2.00 (3.89)	2.63 (5.68)	0.388‡
- physical function	1.78 (1.92)	1.00 (1.12)	1.38 (1.77)	1.88 (2.90)	0.129‡
- sleep	7.00 (1.12)	6.89 (0.78)	7.00 (1.15)	7.75 (0.71)	0.217†
- social	11.67 (5.17)	11.67 (4.72)	11.88 (3.64)	11.75 (4.56)	0.938†

†T^2 test; ‡Mann-Whitney U test; BDI, Beck Depression Inventory; SAI, State Anxiety Index; EQ5D5L, EuroQol 5 D; PROMIS-29, Patient-Reported outcomes Information System questionnaire; PAID, Problem Areas in Diabetes Scale. Bold figures indicate statistically significant differences.

TABLE 8 | Diet and physical activity habits at baseline and 12 weeks.

	pSMA group mean baseline (SD)	pSMA group mean post intervention (SD)	Usual care group mean baseline (SD)	Usual care group mean post intervention (SD)	P value
Sedentary behavior per day (min/h per day of wear time)	859.57/14.3 (134.26/8.59)	868.60/14.47 (131.21/2.19)	778.48/12.97 (234.25/3.90)	739.13/12.32 (208.08/3.47)	0.203†
Light PA (min/h per day of wear time)	168.36/2.806 (51.74)	153.79/2.56 (44.48)	193.37/3.22 (71.85)	197.95/3.30 (63.04)	0.521†
Moderate PA (min per day of wear time)	34.26 (19.11)	37.37 (26.69)	39.13 (16.54)	39.01 (21.87)	0.308†
Vigorous PA (min per day of wear time)	0.48 (0.71)	0.40 (0.76)	0.77 (0.86)	0.79 (1.31)	0.876‡
Average MVPA Per Day (min)	34.74 (19.50)	37.77 (27.10)	39.89 (16.65)	39.81 (21.65)	0.365†
Calendar days with wear time	6.71 (0.76)	6.86 (1.07)	6.40 (0.55)	6.00 (0.71)	0.235‡
Total wear Time	7,205.60 (1,457.93)	7363.44 (1785.76)	6,608.25 (1,716.10)	6,411.43 (1,720.19)	0.180†
Daily step count	6,165.66 (2,579.86)	6,476.41 (3,419.28)	8,498.48 (2,329.73)	7,201.38 (1,862.91)	0.699†
% sedentary*	80.60 (5.39)	81.23 (4.02)	74.55 (12.31)	74.07 (10.42)	0.670†
% light PA	16.42 (4.45)	15.30 (3.21)	20.81 (11.20)	21.68 (10.05)	0.419†
% moderate PA	2.97 (1.54)	3.42 (2.41)	4.54 (1.25)	4.13 (1.23)	0.457†
% vigorous PA	0.02 (0.02)	0.41 (0.07)	0.09 (0.10)	0.11 (0.18)	0.935‡
% MVPA	2.99 (1.55)	3.46 (2.44)	4.64 (1.26)	4.24 (1.17)	0.463†
Daily serves of vegetables	2.06 (1.57)	1.75 (1.14)	1.52 (1.04)	1.48 (0.51)	0.799‡
Daily serves of fruit	1.06 (0.39)	1.13 (0.47)	1.37 (0.85)	1.52 (0.62)	0.974†
Weekly serves of takeaways	5.78 (4.74)	4.78 (3.03)	1.89 (2.52)	1.625 (1.30)	1.00‡

*T^2 test; ‡Wilcoxon rank-sum (Mann-Whitney); *percentages are reported as percentage of wear time.*
Calendar days with wear time at Baseline: 0.222‡.
Calendar days with wear time at Post-intervention: 0.151†.

TABLE 9 | Time spent meditating throughout intervention period.

	pSMA group (n = 9)	Usual care group (n = 7)
Mean minutes per day (SD)	2.14 (2.50)	10.24 (20.33)
Mean days per week (SD)	3.67 (3.54)	1.07 (1.43)
Mean minutes per week (SD)	14.11 (17.12)	13.10 (20.77)

DISCUSSION

In our mixed-methods study of pSMAs with mindfulness for people with T2DM within primary care, we demonstrated high levels of acceptability and feasibility of implementation of both the intervention and follow-up trial. Notably, the majority of participants from the pSMA group and half of the participants in

the control group reported that there was nothing that they did not enjoy about taking part in the study. Qualitative evaluation demonstrated that pSMA participants found the program to be positive overall, with multiple benefits such as increased acceptance of their diagnosis, feeling empowered, making changes with their lifestyle, and enjoying the opportunity to meet people who were in the "same boat" as them. Our findings are consistent with previous studies on SMAs for people with T2DM with patient satisfaction generally being high, diet and physical activity habits improving, and patients being able to achieve or almost achieve their self-prescribed goals (10).

SMAs have been promoted as an effective way for clinicians to deliver care to multiple patients with the same clinical problem, therefore, increasing provider satisfaction (35–38). The impact on people with T2DM is multifactorial. The most important features of the SMAs, according to our participants, were the ability to share experiences in a group setting, an expanded knowledge of diabetes, a sense of not being alone, and the style and approach of the facilitator and GP.

The provision of additional support and advice was an important component of our pSMAs, according to participants. The design of SMAs allows for each participant to listen and gain from questions and answers during others' medical consultations. This may have led to the positive changes in lifestyle habits that were described by some participants. This is supported by the objective increase in minutes and percentage of wear time spent in moderate to vigorous physical activity (MVPA) noted in the pSMA group, whereas there was no change in the control group. This difference equates to an additional 3 min of MVPA per day or 21 additional min per week (an increase of 8.6%). Similarly, other studies have reported improvements in patient engagement after attending SMAs, such as being able to set and achieve measurable goals and improvement in knowledge, self-efficacy and self-management (39). However, no difference between groups was observed for diet changes in our study, although we did find a statistically significant difference between groups for total cholesterol.

The group setting was seen as beneficial for several reasons. Participants described the benefits of being able to learn from each others' experiences. The process of sharing one's experiences and tips on management of a chronic disease may increase self-efficacy. It has been described that peer support for people with T2DM improves clinical and psychological outcomes particularly in minority populations, and may be associated with improvements in lifestyle habits, self-care, and self-efficacy (40–42).

Participants in the pSMA group described the positive impact of the program on their mental health. This included the ability to finally accept their diagnosis, the feeling of not being alone in their experience of T2DM, and being able to finally overcome guilt and stigma. This was reflected in the improvement in depressive symptoms and diabetes-related distress in the pSMA group, although the average score for depression was in the normal range and it is not clear if these differences are clinically relevant.

The process of overcoming guilt and stigma not only benefited mental health in our study; it was described by participants as empowering. Patient empowerment is defined as "*a process through which people gain control over decisions and actions affecting health*" and has been shown to improve self-management skills in people with T2DM, and have positive impacts on clinical, lifestyle and psychosocial outcomes, including diabetes complications (43). Empowerment requires not only the acquisition of skills and knowledge, but also a psychologically safe environment that facilitates self-reflection and self-awareness. People with T2DM commonly experience feelings of guilt and shame and experience stigma, which may become barriers toward the management of T2DM such as with initiating insulin or making lifestyle changes (44–46). These feelings, as well as fear of being judged by medical doctors, may act as a barrier to effective communication within a consultation (47). It was clear that participants felt a strong rapport with, and benefited from, the therapeutic relationship with the chosen facilitator and GP. The qualities of being knowledgeable, friendly and supportive were perceived highly, and led to participants feeling confident in asking questions and feeling cared for. Likewise, other studies have highlighted the importance of establishing trusting and nonjudgmental relationships within the patient-clinician dyad for people with T2DM in order to facilitate self-efficacy and improved clinical outcomes (48).

The combination of provision of knowledge in the educational component of the pSMAs, the ability to share knowledge with peers, and the therapeutic alliance with health providers in a safe environment may have facilitated the trends toward improvement in some clinical outcomes in the pSMA group. Although the differences in glycemic control were not statistically significant between groups, we report HbA1c improvement of 0.11% in the pSMA group and worsening by 0.2% in the control group. Similarly, mean glucose from CGMS decreased and time in range increased in the SMA group whereas the opposite was observed in the control group. This is consistent with findings from other studies reporting lower HbA1c (10), however, remains to be confirmed in a fully-powered RCT. However, there was little change in anthropometric measurements or blood pressure.

There was a mixed response to the mindfulness component with some participants providing positive feedback on the guided mindfulness sessions while others reporting they did not find the sessions useful. Although systematic reviews on mindfulness meditation in the general population report improvements in eating behaviors and physical activity (11–16), the evidence in T2DM is mixed. Trials that used Mindfulness-Based Stress Reduction, an intensive 8-week program pioneered by Jon Kabat-Zinn, have reported improvements in glycemic control (49) and psychological outcomes (49, 50) with an improvement in microalbuminuria at one year which was not sustained at two and three year follow-up (51). Other mindfulness-based interventions, such as mindful self-compassion, mindfulness-based cognitive therapy, and Acceptance and Commitment Therapy, described reductions in depression (52, 53) diabetes-related distress (52), glycemic control (52, 54), and better diabetes self-care (54). However, a program of mindful eating

was similar to diabetes self-management education for improvements in depression, nutrition and eating-related self-efficacy, and cognitive control (55). It is not clear if mindfulness contributed to improvements in psychological outcomes, lifestyle habits and glycemic control in our study, although some participants did describe mindfulness helping them with making healthier food choices (for example, reducing mindless snacking) and reducing stress. Reductions in catecholamines have been described after the practice of mindfulness (51). A clinical trial comparing SMAs with mindfulness to SMAs alone is required to evaluate the impact of mindfulness on T2DM outcomes. Additionally, participants reported needing some assistance or guidance with home practice, and a more structured approach to home mindfulness practice may be required. Last, a limitation of this study design is the lack of an active control comparator. In order for a follow-up trial to be methodologically rigorous and add to the body of evidence on mindfulness, an active control should be utilized (56–58).

Recruitment in this study was highly feasible with 18 participants enrolled within two months. Unfortunately, we did not collect information on how participants found out about our study; however, we note that the majority of enquiries were made after a Diabetes NSW newsletter was emailed to members. The conversion rate from enquiry to enrolment was relatively high at 34.6%. This reflects our broad inclusion criteria. Our retention rate was excellent with only one participant withdrawing (from the control group). These findings demonstrate the feasibility of a follow-up fully-powered RCT within primary care. Additionally, our mixed methods evaluation of the acceptability of trial procedures demonstrates that participants were mostly satisfied with trial procedures. The only issues raised were relatively minor such as technical problems with the accelerometer or CGMS monitor.

Modifications for a follow-up trial, based on the feedback from our participants, should include support materials being delivered electronically, more support and guidance with home mindfulness practice (for example, direction and reminders to practice at a particular time of day such as before bed), and use of Australian CGMS sensors which would allow for real-time monitoring using a mobile app, reduction in the number of PROMs to be collected, and presenting information about diet early on in the program. Additionally, a waitlist control design would be ideal to maintain engagement within the control group. To evaluate the effect of SMAs + mindfulness vs. SMAs alone or waitlist control, a three-armed trial is warranted. Further, the personal qualities of the GP and facilitator are of great importance; these health professionals should be non-judgmental, approachable, supportive, and create trust within the therapeutic relationship.

Strengths of this study include its mixed-method design which allowed us to explore, in a profound way, the experiences of the participants in the pSMA group and how the pSMAs impacted on their health and wellbeing as well as their views on the reasons why pSMAs were helpful. We added a novel component, mindfulness, in order to explore the relationship between this technique and the ability to make decisions about healthy lifestyle habits and the impact on psychological health. We utilized objective and reliable measures of physical activity, collected outcomes on mental health and diabetes-related distress, and used continuous glucose monitoring as an additional measure of glycemic control. Limitations are the small sample size, including the sample size for the qualitative evaluation, and the relatively short duration of treatment of 12 weeks. Due to the pSMAs being conducted in English, we could not enrol people who could not understand or converse in English, therefore our findings are unable to be generalized to non-English speaking populations. Despite this, there was evidence of cultural diversity within our sample, with about a third of participants in both groups being of Asian origin, and a quarter to a third being of Oceanic peoples' origin. Moreover, scaling up this intervention means that the same GP and facilitator may not be able to provide the intervention to all participants, and it is unknown what the impact of different personalities would be on the overall experience of pSMAs. This has implications on training and monitoring of the fidelity of the intervention in a future trial. Additionally, we did not collect data on provider satisfaction, nor on whether control group participants used any additional services such as the GetHealthy NSW coaching service that was suggested to them, or the meditation app. Future modifications may also include anthropometric measurements using bioimpedance to evaluate changes in fat free mass as well as total body weight, which has a greater impact on clinical outcomes, and incorporating health economic evaluation.

CONCLUSION

Our program of pSMAs with mindfulness within primary care was acceptable and generally enjoyable for participants and led to improvements in diabetes knowledge, lipids, and psychological health. It is likely that these benefits were mediated by multiple factors such as the group setting (with peer support and realization that one is not alone in their experience of T2DM), improved knowledge and support facilitating improved lifestyle behaviors, and a strong therapeutic relationship with the facilitator and GP resulting in improved engagement and self-efficacy. Therefore, pSMAs may represent a cost-effective and time-efficient enhancement to T2DM management within primary care. Mindfulness may also have played a role in helping improve dietary choices and reducing stress for some participants. Our mixed methods study demonstrates feasibility of both the intervention and a follow-up fully-powered RCT to confirm or refute these benefits.

DATA AVAILABILITY STATEMENT

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

full protocol is available from corresponding authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Western Sydney University Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CE conceived of the study and obtained funding. CE, DC, BC, GE, JS, SG, MM, CF, RW, FM, KM and GD contributed to the design of the study. NA, AB, MA-D, JH, KM, and SB contributed to data collection. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2020.570777/full#supplementary-material

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Improved Nocturnal Glycaemia and Reduced Insulin Use Following Clinical Exercise Trial Participation in Individuals With Type 1 Diabetes

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Aim: To explore the influence of clinical exercise trial participation on glycaemia and insulin therapy use in adults with type 1 diabetes (T1D).

Research Design and Methods: This study involved a secondary analysis of data collected from 16 individuals with T1D who completed a randomized clinical trial consisting of 23-h in-patient phases with a 45-min evening bout of moderate intensity continuous exercise. Participants were switched from their usual basal-bolus therapy to ultra-long acting insulin degludec and rapid-acting insulin aspart as well as provided with unblinded interstitial flash-glucose monitoring systems. To assess the impact of clinical trial participation, weekly data obtained at the screening visit (pre-study involvement) were compared against those collated on the last experimental visit (post-study involvement). Interstitial glucose [iG] data were split into distinct glycaemic ranges and stratified into day (06:00–23:59) and night (00:00–05:59) time periods. A p-value of ≤ 0.05 was accepted for significance.

Results: Following study completion, there were significant decreases in both the mean nocturnal iG concentration (Δ-0.9 $\pm$ 4.5 mmol.L^{-1}, $p < 0.001$) and the time spent in severe hyperglycaemia (Δ-7.2 $\pm$ 9.8%, $p = 0.028$) during the night-time period. The total daily (Δ-7.3 $\pm$ 8.4 IU, $p = 0.003$) and basal only (Δ-2.3 $\pm$ 3.8 IU, $p = 0.033$) insulin dose requirements were reduced over the course of study involvement.

Conclusions: Participation in clinical research may foster improved nocturnal glycaemia and reduced insulin therapy use in people with T1D. Recognition of these outcomes may help encourage volunteers to partake in clinical research opportunities for improved diabetes-related health outcomes.

Clinical Trial Registration: DRKS.de; DRKS00013509.

Keywords: type 1 diabetes (T1D), exercise, insulin, glycaemia, research participant experience

INTRODUCTION

Volunteering as a research participant displays altruism and a willingness to help advance medical science. However, research trial participation often requires unaccustomed adjustments to routine care, as well as considerable time commitments for those involved. As such, patient enrollment, and indeed retention, represent long-standing obstacles in the conduction of clinical research (1–3). Nevertheless, research participation can provide patients access opportunities to novel pharmacological therapies and/or technological devices, as well as intense and frequent interactions with clinical research teams who provide educational support. For individuals with type 1 diabetes (T1D), pharmaceutical developments in modern ultra-long acting basal insulins with refined pharmacokinetic and pharmacodynamic profiles have led to improved glycaemic outcomes (4–10). Furthermore, recent advances in interstitial glucose (iG) monitoring systems have challenged the sole dependency on self-monitoring of blood glucose, and proven useful in aiding patient adherence to frequent glycaemic assessment (11–14). In addition, interactive opportunities with health care professionals who offer medical information and support can foster positive psychosocial and glycaemic outcomes (15–17). These pharmaceutical, technological, and physiological aids are complemented by lifestyle factors, including both diet and physical activity. Though exercise is endorsed by several international consensus panels as an integral component of the treatment plan of those with T1D (18–21), participation rates remain low, with fears around loss of glycaemic control and uncertainty in how to appropriately adjust exogenous insulin therapy cited as leading factors dissuading regular engagement (22). The heightened bioenergetic demands of exercising muscle can induce increases in intramuscular glucose uptake by up to 50-fold that of basal rates (23, 24). When combined with an inability to lower exogenous insulin concentrations as well as an often blunted glucoregulatory rescue system (25), the maintenance of normoglycaemia during exercise is challenging for those with T1D. Though acutely apparent, the metabolic challenges evoked by physical exercise may persist for several hours subsequent to its cessation (26–29). This often extends the risk of dysglycaemia leading into and throughout the nocturnal period, at a time when self-monitoring of blood glucose is inherently difficult. As such, glycaemic management strategies that seek to address these concerns are integral in encouraging safe exercise performance whilst minimizing the extent of glycaemic fluctuations. The ideal therapeutic care of those with T1D involves a multimodal approach including access to current pharmacological, technological, and support opportunities that collectively help to cultivate optimal self-management. Thus, research trials that include any of these elements may have clinically relevant outcomes beyond the those solely pertinent to answering the primary outcome.

Aim

To explore the influence of clinical exercise trial participation on glycaemic and insulin therapy outcomes in adults with type 1 diabetes (T1D).

METHODOLOGY

Study Design

This study was a secondary analysis of data collected from a single-centered, randomized, open-label, four-period, cross-over clinical trial (DRKS.de; DRKS00013509) consisting of four 23-h in-patient phases with a 45-min evening bout of semi-recumbent cycling at 60 ± 6% VO_{2max}. The study was performed in accordance with good clinical practice and the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Approval was granted by both the national research ethics committee (16/WA/0394) and the local health authority (EudraCT number: 2017-004774-34; UTN: U1111-1174-6676). The primary outcome was to detail the extent and prevalence of post-exercise and nocturnal hypoglycaemia following peri-exercise bolus insulin dose adjustments in individuals with T1D using multiple daily injections of insulins aspart (IAsp) and degludec (IDeg). As part of a secondary, retrospective analysis, the present study sought to explore the influence of clinical exercise trial participation on glycaemia and insulin therapy use in adults with T1D.

Screening Visit

Ahead of trial inclusion, participants were screened for anthropometric, cardiovascular, and T1D specific markers prior to the performance of a cardio-pulmonary exercise test on a semi-recumbent cycle ergometer (Corival Recumbent, Lode, NL) (30). Main inclusion criteria were: diagnosis of T1D for ≥12 months; age 18–65 years (both inclusive); body mass index of 18.0–29.4 $kg.m^2$; use of multiple daily injections of insulin for ≥12 months; body mass-specific peak oxygen uptake of ≥20 $mL.kg^{-1}.min^{-1}$, and a status of being physically active as assessed by the International Physical Activity Questionnaire Short Form. All participants were considered hypoglycaemic aware, having avoided recurrent severe hypoglycaemia (defined as >1 severe hypoglycaemia event during the previous 12 months) and demonstrated a sound understanding of the symptomatic traits of hypoglycaemia to the investigator. After successful completion against the reference inclusion criteria, participants were switched from their usual basal/bolus insulin therapies ($n = 8$; glargineU100/IAsp, $n = 1$; glargineU300/IAsp, $n = 1$; IDeg/IAsp, $n = 6$; detemir/IAsp) to ultra-long-acting IDeg (Tresiba®, NovoNordisk, Denmark) in 3 mL pre-filled investigational pens (PDS290) and rapid-acting IAsp (NovoRapid® NovoNordisk, Denmark) in 3 mL pre-filled investigational pens (FlexPen®). Therapy with IDeg began on the morning following trial inclusion with a starting dosage of 70–80% of total daily basal insulin dose (TDBD) calculated by means of a titration algorithm. Participants were required to achieve a mean overnight-fasted morning blood glucose (BG) value of 4.4–7.2 $mmol.L^{-1}$ over 3 consecutive days within 4 weeks of the first basal insulin dose. If glycaemic instability persisted for ≥3 days following titration, a dose adjustment alteration was made until criteria was met. A run-in period of >7 days was required to assure optimal adaptation to IDeg prior to the experimental period.

Unblinded flash glucose monitoring readers and sensors (Freestyle® Libre, Abbott, Lake Bluff, Illinois, USA) were provided by the study site for the duration of the trial. The sensor was inserted into the posterior aspect of the upper arm and measured interstitial glucose (iG) in 15-minute intervals. Participants were trained in use of the system and asked to change the sensor at least 48 h before each trial visit to avoid sensor expiration during the research period. With the exception of one individual, all participants were new to use of interstitial glucose monitoring, having previously used a range of point of care self-blood glucose monitoring systems. Though familiar with carbohydrate counting and insulin: carbohydrate dosing ratios, participants were guided through how to accurately record dietary information and shown insulin dose adjustment algorithms by the research team. This included the calculation of their individualized carbohydrate ([CarbF] = 5.7*kg/total daily dose of insulin [TDD]) and correction ([CorrF] = 109 mmol/l/TDD) factors as previously described (31). For the remainder of their involvement, participants were monitored by the study personnel to ensure glycaemic stability prior to each experimental visit. Stability was assessed via inspection of their iG patterns with particular scrutiny in the avoidance of hypoglycaemia ($\leq$3.9 mmol.L^{-1}) prior to laboratory attendance. As to control for any potential influence of extraneous variables on experimental trial day activities, participants were asked to replicate their habitual diet, physical activity, and insulin dosing strategies in the 24 h prior to each laboratory visit. Participants were contacted frequently by the research team to provide details of any adjustments.

Experimental Visits

Following preliminary testing (visit 1) and a run-in period for adjustment to IDeg, visits 2, 3, 4, and 5 were experimental visits that involved 23-h of in-patient monitoring with an overnight stay in a clinical research facility. After a standardized day-time period (08:00–15:59), participants undertook a bout of evening (17:00) cycling exercise at 60 $\pm$ 6 % $\dot{V}O_{2max}$ One hour prior to, and following exercise, participants administered either a full (100%) or reduced (50%) dose (100%; 5.1 $\pm$ 2.4 vs. 50%; 2.6 $\pm$ 1.2 IU, $p < 0.001$) of individualized IAsp alongside the consumption identical low-glycaemic index carbohydrate (CHO) rich meals (1.0 g.CHO.kg^{-1}). An unaltered and regular dose of IDeg was kept consisted across each experimental visit. Trial day glycaemia was determined via capillary (08:00–15:59), venous (16:00–07:00), and interstitial (08:00–07:00) glucose monitoring over the 23-h in-patient stays.

Pre vs. Post Study Data Analysis Methodology and Statistical Analysis

Over the course of the study it became apparent that many individuals were perceiving their participation experience as beneficial to aspects of their diabetes related care outside of the experimental periods. Thus, as part of a retrospective, observational, secondary analysis we investigated weekly data taken from a "pre-study" period and compared them against data taken in the final week of their enrolment i.e., "post-study." The pre-study period was classified as the 6-days after the screening visit but before any experimental trial visits (between visits 1 and 2), whilst the post-study period was classified as the 6-days prior to the final experimental trial visit immediately ahead of study completion (between visits 4 and 5). A 6-, rather than 7-day average was taken to avoid any potential interference of trial-related activities on habitual behaviors. **Figure 1** provides a schematic overview of the study design with reference to the primary interventional manipulations and experimental visit schedule.

On trial days, participants intake weighed whilst fasted and asked to report their previous 6-day average basal and bolus insulin doses, CHO intake and physical activity patterns (International Physical Activity Questionnaire). iG data were stratified into time spent within glycaemic thresholds i.e., time in range (TIR), time below range (TBR) and time above range (TAR). The targets are further bracketed into levels 1 and 2 to detail the severity of both hypo-and hyper-glycaemia; TBR 2 ($<$3.0 mmol.L^{-1}), TBR 1 ($\geq$3.0–$<$3.9 mmol.L^{-1}), TIR ($\geq$3.9–$\leq$10.0 mmol.L^{-1}), TAR 1 ($\geq$10.1–$\leq$13.9 mmol.L^{-1}), TAR 2 ($>$13.9 mmol.L^{-1}) (32). iG data were also split into day (06:00–23:59) and night (00:00–05:59) time periods. Due to a significant loss of data points, four participants were excluded from iG analysis. The significance of change in measurements from pre- to post-study was assessed via paired student's *t*-test or non-parametric equivalents used when necessary. SPSS (version 26.0) was used for all data analyses and reporting. *P* values of a $p \leq 0.05$ (two-sided) accepted as statistically significant.

RESULTS

Participant Characteristics

Baseline characteristics of study participants are included in **Table 1**. The average length of time for trial participation was 55 $\pm$ 29 days.

Interstitial Glucose Outcomes

Device coverage was $\geq$89% over the 6-day data capture in both the pre- and post-study phases (pre; 91 $\pm$ 19 vs. post; 89 $\pm$ 14%, $p = 0.716$). Overall and stratified iG are presented in **Table 2**. Analysis revealed significant decreases in both the mean nocturnal iG concentration (Δ-0.9 $\pm$ 4.5 mmol.L^{-1}, $p < 0.001$) and the TAR2 (Δ-7.2 $\pm$ 9.8%, $p = 0.028$) during the night-time hours.

Anthropometry and Insulin Therapy Outcomes

There were significant reductions in both the total daily (Δ-7.3 $\pm$ 8.4 IU, $p = 0.003$) and basal only (Δ-2.3 $\pm$ 3.8 IU, $p = 0.033$) insulin dose requirements from pre-to-post-study involvement (**Table 3**). There were no changes in any of the anthropometric, dietary CHO or physical activity metrics.

DISCUSSION

This exploratory study investigated the wider glycaemic impact of participation in a clinical exercise trial involving a therapeutic switch to ultra-long acting insulin degludec as

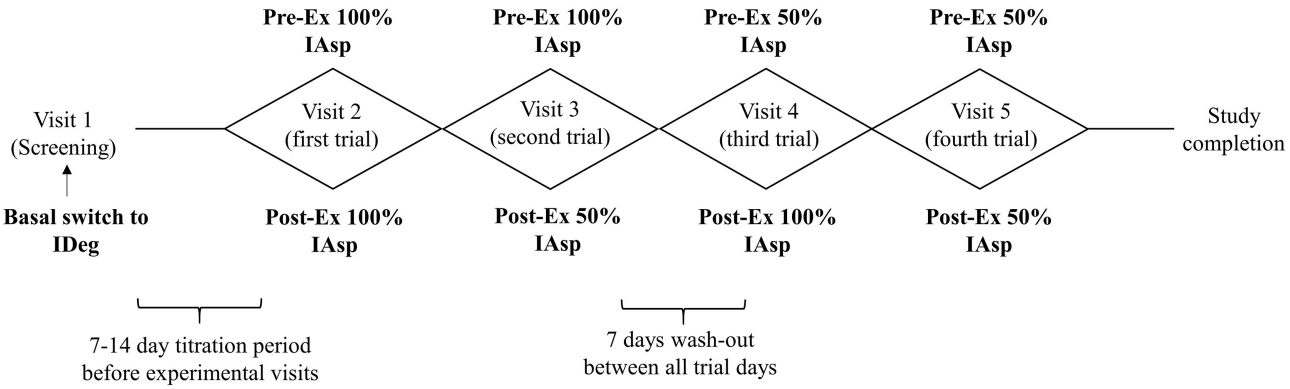

FIGURE 1 | Schematic overview of the trial design with reference to the four interventional cross over arms involving peri-exercise adjustments to bolus insulin aspart on a stable background of insulin degludec. IAsp, insulin aspart; IDeg, insulin degludec.

TABLE 1 | Baseline characteristics of study participants.

Baseline characteristics of study participants	
Characteristic	***n* = 16**
Gender M vs. F (*n*)	13 vs. 3
Age (years)	34.5 ± 13.9
BMI (kg/m^2)	26.0 ± 3.4
Lean mass (%)	23.4 ± 3.3
HbA_{1c} (%)	7.2 ± 1.3
HbA_{1c} (mmol/mol)	56 ± 15
Diabetes duration (years)	14.4 ± 11.1
Pre study TDD (IU)	51.7 ± 26.6
Pre study TDBD (IU)	31.3 ± 21.3
$\dot{V}O_{2\,max}$ (ml.kg^{-1}.min.$^{-1}$)	40.3 ± 10.3

Data are presented as mean ± SD. n, number of participants.
M, Male; F, Female; BMI, body mass index; Kg, kilograms; M, meters; TDD, Total daily insulin dose (inclusive of basal and bolus amounts); TDBD, total daily basal insulin dose; Bm, body mass; ml, millimeters; Min, minutes.

TABLE 2 | Time spent in each glycaemic range as part of a 6-day analysis from the first to last experimental trial visits.

Parameter	**Pre-study**	**Post-study**	***P*-value**
Overall glucose (mmol.L^{-1})	9.23 ± 4.38	9.07 ± 4.30	0.355
Standard deviation (mmol.L^{-1})	3.83 ± 0.91	3.84 ± 1.02	0.965
CoV (%)	40.99 ± 4.42	42.21 ± 7.37	0.598
Stratified (24 h)			
Overall TBR2 (%)	2.83 ± 3.91	3.84 ± 2.29	0.246
Overall TBR1 (%)	3.97 ± 1.90	4.00 ± 3.08	0.971
Overall TIR (%)	55.28 ± 18.80	55.26 ± 13.99	0.995
Overall TAR1 (%)	22.15 ± 8.33	23.87 ± 9.82	0.571
Overall TAR2 (%)	15.77 ± 14.74	13.02 ± 10.55	0.391
Stratified Day; 06:00–23:59 vs. Night; 00:00–05:59			
Day glucose (mmol.L^{-1})	9.03 ± 4.38	9.15 ± 4.18	0.270
Day TBR2 (%)	2.55 ± 4.35	3.25 ± 3.08	0.495
Day TBR1 (%)	4.58 ± 2.02	4.20 ± 3.64	0.701
Day TIR (%)	57.06 ± 19.59	56.79 ± 14.62	0.954
Day TAR1 (%)	21.60 ± 8.16	23.19 ± 9.31	0.589
Day TAR2 (%)	14.22 ± 14.18	12.57 ± 10.26	0.662
Night glucose (mmol.L^{-1})	9.84 ± 4.52	8.98 ± 4.48	<0.001*
Night TBR2 (%)	3.23 ± 5.64	5.13 ± 5.31	0.138
Night TBR1 (%)	2.00 ± 3.10	3.43 ± 3.62	0.367
Night TIR (%)	50.06 ± 21.18	52.06 ± 16.56	0.673
Night TAR1 (%)	24.22 ± 14.30	26.02 ± 11.57	0.748
Night TAR2 (%)	20.54 ± 18.65	13.35 ± 16.63	0.028*

*CoV, coefficient of variation; TBR 2, time below range level 2 (<3.0 mmol.L^{-1}); TBR 1, time below range level 1 (≥3.0–<3.9 mmol.L^{-1}); TIR, time in range (≥3.9–≤10.0 mmol.L^{-1}); TAR 1, time above range level 1 (≥10.1–≤13.9 mmol.L^{-1}); TAR 2, time above range level 2 (>13.9 mmol.L^{-1}). *p ≤ 0.05 between first pre- and post-study values. Data are reported as mean ± SD. n =12.*

well as the introduction to, and *ad-hoc* education support with, an interstitial glucose monitoring system in individuals with T1D.

Comparative analysis of interstitial glucose (iG) data obtained over a 6-day period taken before vs. after clinical trial participation revealed significant reductions in both the mean nocturnal glucose concentration and the amount of time spent in severe hyperglycaemia during the night-time hours. Additionally, upon trial completion, substantial reductions in both total daily, and basal only, insulin dose requirements were noted in the absence of changes in any anthropometric, dietary, and physical activity factors.

The reduction in insulin dosing requirements in the present study aligns with previous investigations that have demonstrated the efficacy of IDeg therapy in maintaining glycaemic outcomes at significantly lower dosing amounts (33, 34). The end of study IDeg dosing quantities used in this study are similar to those reported in recent work by Heise et al. (9) (Heise; 0.38 ± 0.23 IU.kg^{-1} vs. Our data; 0.34 ± 0.20 IU.kg^{-1}), which reaffirms the safe integration of IDeg as a stable basal therapy at clinically relevant dosing levels. These dose reductions occurred in the absence of any changes in body mass, carbohydrate intake and physical activity patterns. Though we cannot out rule the possibility that great diligence to dietary tracking may have triggered individuals to select healthier

TABLE 3 | Participant insulin regime, anthropometric data, and physical activity patterns on the first vs. last trial visits.

Weekly data from pre-to post-study involvement			
Parameter	**Pre-study**	**Post-study**	***P*-value**
TDD (IU)	51.7 ± 26.6	44.4 ± 20.7	0.003*
TDBD (IU)	31.3 ± 21.3	29.0 ± 18.4	0.033*
Body mass (kg)	80.0 ± 9.9	80.1 ± 9.6	0.785
CHO intake (g)	194.2 ± 58.0	190.8 ± 64.5	0.666
Physical activity (METs)	3600.3 ± 2943.7	3359.7 ± 2491.9	0.678

*TDD, Total daily insulin dose (inclusive of basal and bolus); TDBD, Total daily basal insulin dose; IU, International units; CHO, carbohydrates; METs, metabolic equivalents. *$p \leq 0.05$ between pre- and post-study values. Data are presented as mean ± SD.*

food options, including lower glycaemic index carbohydrates, which may have contributed to drop in insulin dose, in light of the potential obesogenic implications associated with an over reliance on exogenous insulin administration (35), the dose reductions observed in this study carry important clinical undertones that stretch beyond those relating to dysglycaemia. Furthermore, 14/15 (93%) participants opted for continued use of IDeg as their basal analog and applied locally for continued Freestyle Libre provision upon study completion, perhaps emphasizing the value of these therapeutics in terms of patient satisfaction.

The significant decreases in both mean iG concentrations and the amount of TAR2 during nocturnal hours are meaningful from both a practitioner and patient point of view. Given the lack of endogenous autoregulation in the synthesis and secretion of insulin, the prevalence of the dawn phenomenon is a common feature of T1D which continues to represent a serious clinical concern (36). Combined with the inherent difficulties of performing regular self-monitoring of blood glucose during sleep, dysglycaemia during the night-time constitutes a major worry not only for those with T1D, but also for those who take an active role in their care (37–39). These fears are perhaps magnified following evening exercise, which, due to its long-lasting insulin-sensitizing effects, can disrupt glycaemia for the many hours subsequent to its performance (29, 40–42). Several international panels of diabetes specialists have convened to outline the merits of utilizing iG metrics to support decision making in clinical care (32, 43). The improvements in nocturnal glycaemia observed in this study may be the result of the introductory provision of an iG monitoring device, which allowed for the assessment of glycaemic patterns throughout the night-time period and hence, the ability to act accordingly to prevent glycaemic excursions. These results offer encouragement for the integration of modern ultra-long acting insulin analogs alongside iG monitoring systems in aiding glucose management around physical exercise in those with T1D. An important caveat is that our study cohort had a relatively long diabetes duration (∼14 years), thus may have had greater experience in glycaemic management around physical exercise than those with a newer diagnosis.

For those with T1D, the fear of hypoglycaemia around exercise prevails as the main barrier to regular engagement, whilst a greater knowledge of insulin pharmacokinetics and/or using appropriate approaches to minimize exercise-related hypoglycaemia are associated with fewer perceived hurdles (22). The volatility in blood glucose levels around exercise may be one of the reasons that >60% of individuals with T1D currently fail to meet physical activity guidelines (44). To that end it is encouraging to learn of the potential value interactions with health care professionals and exercise physiologists throughout trial participation may have on the individuals involved, who's willingness to participate in clinical trials help advance our research efforts.

Due to the provision of two therapeutic aids alongside access to clinical diabetes care and support, it is difficult to discern the exact source of the observed improvements. Rather, we put forth these findings as part of a multi-faceted analysis, that, irrespective of being able to irrefutably demonstrate a clear cause and effect relationship, highlights the beneficial effects of research participation in a mutually reciprocal manner. Recognition of these outcomes may help incite volunteers to partake in clinical trials as well as encourage scientists to explore hypotheses outside of the primary objective.

CONCLUSION

Participation in clinical research may foster improved nocturnal glycaemia and reduced insulin therapy use in people with T1D. Beyond pursuing the primary outcomes of a research hypothesis, these data provide a basis for exploring the wider, clinically relevant health outcomes that may be associated with research trial participation.

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 national research ethics committee (16/WA/0394) and the local health authority (EudraCT number: 2017-004774-34, UTN: U1111-1174-6676). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

OMc, OMo, RD, ME, JP, and RB were responsible for data collection. OMc, JP, BW, and RB were responsible for data interpretation and statistical analyses. OMc, JP, and RB wrote the manuscript. SB and RB were the chief and principle investigators of the study. SB provided medical oversight for the study. RB

wrote and secured funding for the study. All authors contributed to feedback and revisions for the final manuscript.

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Effect of Tai Chi on Quality of Life, Body Mass Index, and Waist-Hip Ratio in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Background: Type 2 diabetes mellitus (T2DM) is a worldwide public health concern with high morbidity and various progressive diabetes complications that result in serious economic expenditure and social burden. This systematic review aims to evaluate the effect of Tai Chi on improving quality of life (QoL), body mass index (BMI) and waist-hip ratio (WHR) in patients with T2DM.

Method: A systematic review and meta-analysis was performed following PRISMA recommendation. Four English databases and three Chinese databases were searched. The PEDro scale was used to assess the methodological quality of including studies. Study inclusion criteria: randomized controlled trials (RCTs) and quasi-experimental studies were included, patients with T2DM that adopted Tai Chi as intervention and QoL, BMI and/or WHR as outcome measurements.

Results: Eighteen trials were included. The aggregated results of seven trials showed that Tai Chi statistically significantly improved QoL measured by the SF-36 on every domains (physical function: MD = 7.73, 95% confidence interval (CI) = 1.76 to 13.71, p = 0.01; role-physical function: MD = 9.76, 95% CI = 6.05 to 13.47, p < 0.001; body pain: MD = 8.49, 95% CI = 1.18 to 15.8, p = 0.02; general health: MD = 9.80, 95% CI = 5.77 to 13.82, p < 0.001; vitality: MD = 6.70, 95% CI = 0.45 to 12.94, p = 0.04; social function: MD = 9.1, 95% CI = 4.75 to 13.45, p < 0.001; role-emotional function: MD = 7.88, 95% CI = 4.03 to 11.72, p < 0.001; mental health: MD = 5.62, 95% CI = 1.57 to 9.67, p = 0.006) and BMI (MD = –1.53, 95% CI = –2.71 to –0.36, p < 0.001) compared with control group (wait list; no intervention; usual care; sham exercise).

Conclusion: Tai Chi could improve QoL and decrease BMI for patients with T2DM, more studies are needed to be conducted in accordance with suggestions mentioned in this review.

Keywords: Tai Chi, quality of life, body mass index, meta-analysis, type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a chronic endocrine metabolic disorder characterized by hyperglycemia resulting from insulin secretion dysfunction (1). Type 2 DM (T2DM) is the most common form of DM, with over 90% of adults with DM presenting T2DM (2). It is a worldwide public health concern because of its high morbidity and various progressive complications. It was reported that there were approximately 415 million adults with DM, leading to 5.0 million deaths. Moreover, the total global health-related economic expenditure due to DM was about 673 billion US dollars in 2015 (3). The number of adults with DM was predicted to increase to 642 billion by 2040 (3). As a country with the largest population and the largest number of DM patients, the estimated DM prevalence in China was 10.9% (4). The total medical costs due to DM and its complications accounted for over 4% of the total national medical expenses in China (5). T2DM patients are at high risk of experiencing associated cardiovascular diseases, diabetic neuropathy, and kidney diseases (1). Previous studies have emphasized that the quality of life (QoL) in these adults is usually poorer than that of normal controls without DM (6, 7). Both diabetic complications and comorbid conditions could determine the QoL of T2DM patients. Hence, the treatment of DM aims to prevent complications and improve the QoL in these patients.

In the current guidelines, the main strategy to manage T2DM has been intensive glycemic control (8–10). However, a body of evidence has demonstrated that intensive glycemic control increases the risk of severe hypoglycemia, polypharmacy, and side effects (11). Glycemic control should be aligned to each patient's situations and goals in order to minimize diabetic complications, reduce the economic burden, and improve the QoL. Physical exercise also plays an important protective role in altering the body composition, blood pressure, and glycemic control as a non-pharmaceutical and cost-effective treatment in T2DM patients (12, 13). Observation studies have shown that higher levels of physical exercise could improve the QoL in T2DM patients (14, 15). Furthermore, it has been confirmed that physical exercise reduces morbidity and mortality and increases insulin sensitivity in these patients (12, 13). Tai Chi is a low to moderate intensity, mind-body exercise that originated in China and gained popularity worldwide (16). A national health survey in America reported that Tai Chi was one of the top three most frequently adopted complementary therapies with general effectiveness and no serious adverse events (17). Tai Chi had similar health benefits as that of general exercise in terms of resting energy expenditure, body composition, aerobic fitness, and self-perceived health, but lower energy metabolism levels (18).

QoL reflects an individual's perception of their physical, psychological, and social status. T2DM has negative effects on both physical and mental states (19). Diabetic peripheral neuropathy can lead to body pain and foot ulcers, even resulting in amputation, which could have a serious negative impact on the QoL (20). A previous systematic review showed that aerobic exercise, resistance exercise, or a combination of both could improve the QoL of patients with T2DM (21). Individuals with T2DM had higher medical expenditures and raising more with increment of body mass index (BMI) than those without T2DM (22). Management of weight-related indicators has been demonstrated to reduce the incidence of T2DM and its complications dramatically (23). Weight management is an important therapeutic strategy in T2DM, and the reduction in BMI has been associated with good metabolic control with appreciable economic benefits (24, 25).

The evidence regarding the effect of exercise on the QoL and weight management in T2DM patients from recent systematic reviews is insufficient (26, 27). Moreover, there were limited studies on the treatment of T2DM with Tai Chi. Only certain reviews and/or meta-analyses have explored the benefits of Tai Chi in T2DM patients (28–31). Although three reviews (28, 29, 31) investigated the outcome of Tai Chi using biomarkers, none of them investigated the outcomes with respect to QoL, BMI, and waist-hip ratio (WHR) together. Zhou et al. (28). investigated its impact on QoL and BMI, while Lee's review (30) only assessed the impact on QoL. Lee's review (30) included only three trials of pooled analysis reporting the superior effect of Tai Chi, whereas Zhou's review (28) reported only three sub-items (physical function, bodily pain, and social function) of the SF-36. Lee's review was conducted for a relatively long time and did not retrieve Chinese studies due to language or search source limitations (30). Zhou's review (28) included relatively incomprehensible eligible original studies with several missing studies (32–35). Ongoing research has continuously generated new evidence. This systematic review critically evaluated and synthesized published studies on the effectiveness of Tai Chi in treating T2DM patients by evaluating its impact on QoL, BMI, and WHR when compared with different control groups (e.g., waitlist, no intervention, usual care, and other exercises).

MATERIALS

Search Strategy

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis. We did not publish a protocol before conducting the systematic review. Ethical approval and patient informed consent were not applicable since all data collection and analysis were based on previously published articles.

Literature searches were performed in seven electronic databases, including PubMed, Web of Science, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang, and Chinese Science and Technique Journals Database (VIP), from their inception time to February 2020. The language of the searched literature was limited to English and Chinese. The search terms focused on two key terms: "Tai Chi" and "Diabetes Mellitus." Combinations of Medical Subject Headings and text words using Boolean operators were adopted for search strategy. The reference lists of all relevant studies and reviews were manually searched to identify potentially eligible literature. Gray literatures with full text (e.g., thesis, dissertations) were also included while conference proceedings abstracts were excluded. **Table 1** shows an example of the search strategy used for PubMed.

Inclusion and Exclusion Criteria

Both randomized controlled trials (RCTs) and quasi-experimental studies were included to evaluate the effect of Tai Chi in patients with T2DM, regardless of the intervention length. Tai Chi should be performed as a major intervention method. The following experimental comparisons were eligible in our systematic review: Tai Chi vs. control (wait-list, no intervention, usual care, and sham exercise); Tai Chi vs. other exercises (walking, aerobic dancing, aerobic exercise, etc.); and Tai Chi + standard diabetic care vs. standard diabetic care alone. Outcome measurements of the included studies should have covered at least one of the essential assessments of QoL, BMI, or WHR. All instruments measuring QoL were included, such as SF-36 and diabetes-specific quality of life (DSQoL). As important indicators for T2DM patients, BMI and WHR were the most commonly used outcomes to measure body composition (36).

Data Extraction and Quality Assessment

Two reviewers (SG, YY) independently scanned the titles and abstracts of each identified study in order to exclude irrelevant literature. The full texts were then independently read by the two reviewers to decide whether these studies were consistent with the selection criteria, and detailed data were independently extracted from the selected studies. Standard data-extraction forms adapted from the Cochrane Collaboration model were used to extract information regarding authors, year and language of the studies published, experiment locations, sample size, age, disease duration, characteristics of the intervention group and control group, outcome measures, drop outs, adverse events and main findings. Missing data were requested directly from the original author *via* e-mail if necessary. Discrepancies were discussed to reach a consensus.

Two reviewers (JQ, YC) assessed the selected studies' methodological quality according to the Physiotherapy Evidence Database (PEDro) scale. The PEDro scale contained the following 11 items: random allocation, concealed allocation, baseline comparability, blinding participants, blinding therapists, blinding assessors, adequate follow-up, intention-to-treat analysis, between-group comparisons, point estimates, and variability. The maximum score on the PEDro scale was 10 points (item 1 was not counted in the total score), wherein a score of 9 to 10 was categorized as excellent quality, 6 to 8 as good quality, 4 to 5 as fair quality, and < 4 as poor quality. Points were only awarded when a criterion was clearly fulfilled according to its instruction (37). The reliability of PEDro scale for assessing the quality of RCTs was "fair" to "good" (37), and it was deemed appropriate for this systematic review. Disagreements were discussed and resolved by a third reviewer (JQ).

Statistical Analysis

Review Manager 5.3 (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for the pooled analysis. The statistical heterogeneity among the selected studies was examined using a chi-square test and I^2 value. The heterogeneity was considered low if I^2 was <50% and high if I^2 was >50% (38). We conducted data synthesis by using a random effects model, regardless of the level of heterogeneity. The endpoint value was employed for outcome data and expressed as mean difference (MD) or the standard mean difference and the 95% confidence interval (CI) for further data synthesis. For the multiple group studies, the "shared" group was evenly divided into more groups with relatively small sample sizes, and further comparisons were conducted. A p-value <0.05 was considered statistically significant. Subgroup analysis for different intervention comparisons was performed to explore the heterogeneity source. Sensitivity analysis was also conducted to explore the heterogeneity source and check the pooled results' stability by excluding the selected studies one by one. A funnel plot was used to assess possible publication bias if more than 10 trials were pooled for meta-analysis (39).

RESULTS

Literature Search

In total, 718 studies were identified after searching the electronic databases, and 480 studies remained after excluding duplicates.

TABLE 1 | Searching strategy in PubMed.

Search	Query
#1	Tai Ji [MeSH Terms] OR Tai-ji [All Fields] OR Tai Chi [All Fields] OR Chi, Tai [All Fields] OR Tai Ji Quan [All Fields] OR Ji Quan, Tai [All Fields] OR Quan, Tai Ji [All Fields] OR Taiji [All Fields] OR Taijiquan [All Fields] OR T'ai Chi [All Fields] OR Tai Chi Chuan [All Fields]
#2	Diabetes Mellitus, Type 2 [MeSH Terms] OR Diabetes Mellitus, Noninsulin-Dependent [All Fields] OR Diabetes Mellitus, Noninsulin Dependent [All Fields] OR Diabetes Mellitus, Ketosis-Resistance [All Fields] OR Diabetes Mellitus, Ketosis Resistance [All Fields] OR Diabetes Mellitus, Non Insulin Dependent [All Fields] OR Diabetes Mellitus, Non-Insulin-Dependent [All Fields] OR Diabetes Mellitus, Slow Onset [All Fields] OR Diabetes Mellitus, Slow-Onset [All Fields] OR Diabetes Mellitus, Maturity-Onset [All Fields] OR Diabetes Mellitus, Maturity Onset [All Fields] OR Diabetes Mellitus, Type II [All Fields] OR Type 2 Diabetes Mellitus [All Fields] OR Type 2 Diabetes [All Fields] OR Diabetes, Type 2 [All Fields] OR NIDDM [All Fields] OR MODY [All Fields]
#3	#1 and #2

Among these studies, 418 records were removed due to the bias of titles and abstracts, and 44 records were excluded after screening the full texts.

Finally, 18 clinical trials, including three quasi-experimental studies (40–42) and 15 RCTs, were retrieved for systematic review and meta-analysis (**Figure 1**). Of the 18 articles, five (32, 35, 40, 43, 44) were published in English, and 13 (33, 34, 41, 42, 45–53) were in Chinese.

Characteristic of the Included Studies

In this review, 18 studies involving 1418 participants (94 attritions) were included, of which two trials (35, 44) were conducted in Australia, and one trial each in South Korea (40) and Thailand (43), and the remaining 14 were in China. The sample size of these studies ranged from 16 to 216, and the mean age ranged from 47 to 70 years. The average disease duration ranged from 0.5 to 18 years. Among the included trials, 11 studies (33–35, 40, 42, 44–47, 49, 52) compared the experimental intervention between Tai Chi and control (waitlist, no intervention, usual care, and sham exercise), six (32, 34, 41, 48, 50, 51) compared Tai Chi with other exercises (walking, dancing, aerobic exercise, etc.), and two (43, 53) compared Tai Chi + standard diabetic care with standard diabetic care alone. Fifteen articles (32–35, 41, 43–48, 50–53) adopted Tai Chi Quan with various styles, including 24 forms, Chen style, Yang and Sun style, and Lin style, whereas one article adopted Tai Chi sticks (52) and one adopted Tai Chi balls (33). For Tai Chi intervention, the training time ranged from 30-120 min per day, frequencies ranged from one to seven times per week, and treatment duration ranged from 12 to 24 weeks. For outcome measurements, eight studies reported outcomes with respect to QoL, 11 studies reported for BMI, and four studies reported for WHR. The main characteristics of all included trials are shown in **Table 2**.

Methodological Quality

The methodological quality of the included trials ranged from 3 to 7 points, and the mean PEDro scale score was 5.3. Eight studies (33, 35, 43, 45–47, 49, 53) were of "good" quality, nine studies (32, 34, 41, 42, 44, 48, 50–52) were of "fair" quality, and one study (40) was of "poor" quality (**Table 3**). Blinding of participants, therapists, and evaluators was not conducted in most trials. Three trials (41, 50, 51) did not report whether the baseline information was comparable. Only one trial (43) reported concealed allocation, and one trial (40) showed >15% attrition. Eight trials (32, 34, 40, 42–44, 48, 52) did not use intention-to-treat analysis. The remaining items were positive in all trials.

Effect of Tai Chi on Body Mass Index

Eleven trials (32–34, 41–43, 45, 50–53) including 13 comparisons explored the effect of Tai Chi on BMI. When compared to the

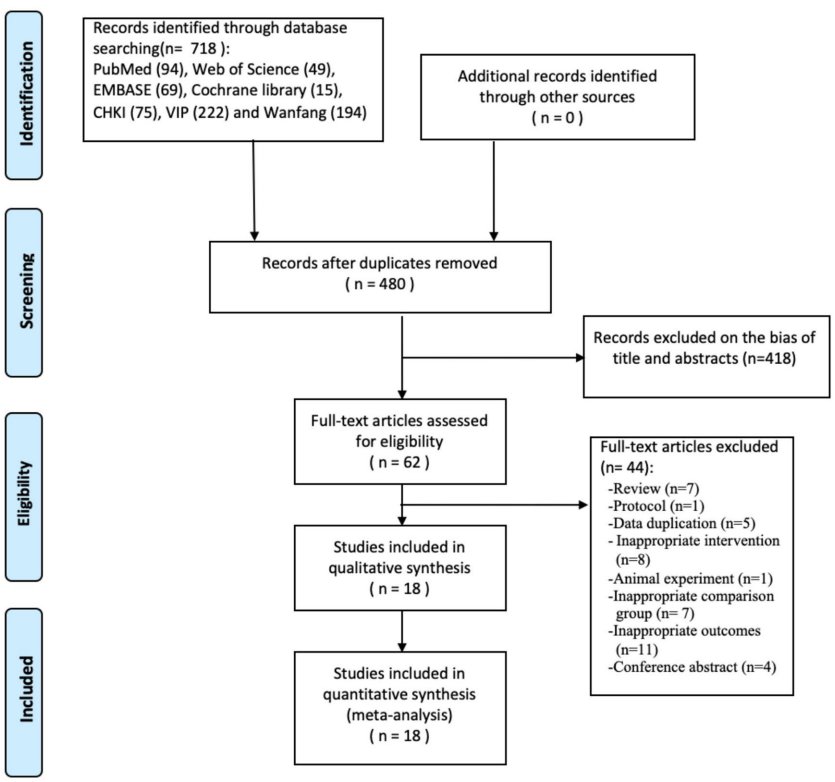

FIGURE 1 | Flowchart of the study selection.

TABLE 2 | The characteristics of all including trials.

Reference	Location (Language)	Sample size	Mean age or age range	Disease duration	Intervention Group time/per week/duration	Control group	Outcome measure	Attrition	AE	Main findings (p value of intergroup/intragroup difference)
Shen XY et al. (48)	China (Chinese)	TG: 54 CG: 54	TG: 67.8 ± 5.1 CG: 66.2 ± 4.6	TG: 9.6 ± 6.8 y CG: 7.6 ± 5.9 y	24 form Tai Chi 60 min/3/12 weeks	Walking 60 min/3/ 12 weeks	DSQOL	TG: 2 CG: 5	NR	DAQOL: TG showed significant improvement in DAQOL compared to CG($p<0.05$).
Wu F et al. (46)	China (Chinese)	TG: 20 CG: 20	TG: 51.3 ± 7.9 CG: 52.4 ± 5.5	TG: 1.35 ± 0.62 y CG: 1.36 ± 0.71 y	24 form Tai Chi 60 min/3/24 weeks	No intervention	SF-36	NR	NR	SF-36: TG showed significant improvements in PF/RP/GH/ RE/SF/MH compared to CG ($p<0.05$).
Lam P et al. (44)	Australia (English)	TG: 28 CG: 25	TG: 63.2 ± 8.6 CG: 60.7 ± 12.2	> 6 m	Yang and Sun style 20 form Tai Chi 60 min/3/ 12 weeks; 60 min/1/further 12 weeks	Wait list	SF-36	TG: 7 CG: 3	NR	SF-36: TG showed significant improvements in PF/SF/GH from baseline to post-treatment (all $p<0.05$). No significant difference in all SF-36 domains between two groups ($p>0.05$).
Li ZB et al. (34)	China (Chinese)	TG: 54 CG(a): 54 CG(b): 54 CG (c): 54	TG: 54.21 ± 9.47 CG(a): 50.42 ± 9.68 CG(b): 51.62 ± 7.83 CG(c): 52.69 ± 8.37	TG: 83.42 ± 43.52 m CG(a): 72.18 ± 39.57 m CG(b): 75.74 ± 42.39 m CG(c): 86.65 ± 49.72 m	24 form Tai Chi 30 min/7/12 weeks	CG(a): Baduanjin CG(b): Aerobic Exercise (brisk walking. etc) CG(c): No intervention	BMI	TG: 11 CG(a): 4 CG(b): 6 CG(c): 10	NR	BMI: TG showed significant improvement in BMI from baseline to post-treatment ($p<0.05$). Intergroup comparison was NR.
Meng E (49)	China (Chinese)	TG: 100 CG: 100	68. ± 3.2	2-23 y	Tai Chi 3 months	Wait list	SF-36	NR	NR	SF-36: TG showed significant improvement in GH and SF-36 total score compared to CG ($p<0.05$).
Wang P et al. (47)	China (Chinese)	TG: 34 CG: 30	TG: 48.24 ± 10.06 CG: 47.86 ± 11.12	TG: 1-18 y CG: 1-17 y	24 form Tai Chi 45–60 min/5-7/24 weeks	No intervention	SF-36	NR	NR	SF-36: TG showed significant improvement in RE ($P<0.01$), PF/RP/BP/GH/VT/SF ($p<0.05$), and SF-36 total score/ PCS/MCS ($p<0.01$) compared to CG.
Wei DL et al. (33)	China (Chinese)	TG: 26 CG: 26	56.0 ± 7.2	0.5-3 y	Tai Chi ball 36 form 60 min/6/12 weeks	Usual care	BMI; WHR	NR	NR	BMI/WHR: TG showed significant improvement in BMI/ WHR from baseline to post-treatment($p<0.05$). Intergroup comparison was NR.
Ahn S (40)	South Korea (English)	TG: 30 CG: 29	TG: 66.05 ± 6.42 CG: 62.73 ± 7.53	TG: 12.30 ± 8.81 y CG: 13.00 ± 10.03 y	Tai Chi 60 min/2/12 weeks	Usual care	SF-36	TG: 10 CG: 10	NR	SF-36: TG showed significant improvement in PF/BP/RP/ RE/SF compared to CG ($p<0.05$). No significant difference in SF-36 subcomponents (PCS/ MCS) between two groups ($p>0.05$).
Chen SC et al. (32)	China (English)	TG: 62 CG: 55	TG: 59.1 ± 6.2 CG: 57.4 ± 5.8	TG: 8.5 ± 3.5 y CG: 7.8 ± 3.1 y	Chen style 99 form Tai Chi 60 min/3/12 weeks	Aerobic dancing 60 min/3/ 12 weeks	BMI	TG: 6 CG: 7	NR	BMI: TG showed significant improvement in BMI compared to CG ($p=0.017$).
Trang T et al. (35)	Australia (English)	TG: 18 CG: 20	TG: 60 ± 8 CG: 65 ± 8	TG: 8.5 y CG: 9.0 y	Yang and Sun style Tai Chi, 60 min/2/12 weeks	Sham exercise	SF-36	TG: 1	Y	SF-36: TG showed significant improvement in SF compared to CG ($p=0.04$).
Cai H (42)	China (Chinese)	TG: 27 CG: 28	TG: 65.54 CG: 64.51	TG: 4.93 y CG: 5.44 y	Tai Chi 30 min/3/12 weeks	Wait list	BMI	CG:5	NR	BMI: TG showed significant improvement in BMI compared to CG ($p=0.004$).
Chen ZC (52)	China (Chinese)	TG: 30 CG: 30	TG: 60.71 ± 7.06 CG: 61.14 ± 5.27	TG: 5.58 ± 2.77 y CG: 6.00 ± 2.58 y	Tai Chi stick 60 min/4/12 weeks	No intervention	BMI; WHR; SF-36	TG: 2	NR	BMI/WHR: TG showed significant improvement in BMI/ WHR from baseline to post-treatment($p<0.05$). SF-36: TG showed significant improvement in all SF-36 domains compared to CG (all $p<0.05$).

(Continued)

TABLE 2 | Continued

Reference	Location (Language)	Sample size	Mean age or age range	Disease duration	Intervention Group time/per week/duration	Control group	Outcome measure	Attrition	AE	Main findings (p value of intergroup/intragroup difference)
Li HC et al. (50)	China (Chinese)	TG: 50 CG: 50	TG: 62.91 ± 2.48 CG: 63.27 ± 2.86	TG: 7.83 ± 2.16 y CG: 8.14 ± 3.19 y	Chen style Tai Chi 40–50 min/7/24 weeks	Aerobic Exercise	BMI; WHR	NR	NR	BMI/WHR: No significant difference in BMI and WHR between two groups (p>0.05).
Bao QW et al. (53)	China (Chinese)	TG: 58 CG: 49	TG: 60.4 ± 6.9 CG: 68.4 ± 7.1	NR	Tai Chi + standard diabetic care 120 min/14/24 weeks	Standard diabetic care	BMI; WHR	NR	NR	BMI/WHR: TG showed significant improvement in BMI and WHR compared to CG (p<0.05).
Zhao G et al. (45)	China (Chinese)	TG: 8 CG: 8	TG: 54.75 ± 6.09 CG: 52.38 ± 7.65	NR	Chen style 60 min/7/16 weeks	No intervention	BMI	NR	NR	BMI: No significant difference in BMI between two groups (p>0.05).
Youngwanchsetha S et al. (43)	Thailand (English)	TG: 34 CG: 35	TG: 60.71 ± 7.06 CG: 61.14 ± 5.27	TG: 2.47 ± 1.24 y CG: 2.78 ± 1.18 y	Lin Housheng style Tai Chi + standard diabetic care 50 min/5/12 weeks	Standard diabetic care	BMI	TG: 2 CG: 3	NR	BMI: No significant difference in BMI between two groups (p=0.10).
Kan Y et al. (51)	China (Chinese)	TG: 26 CG: 22	52 ± 6.7	>3 y	24 form Tai Chi 60 min/7/12 weeks	Aerobic Exercise	BMI	NR	NR	BMI: TG showed significant improvement in BMI compared to CG (p<0.05).
Wang JH et al. (41)	China (Chinese)	TG: 10 CG: 6	60–70	>2 y	24 form Tai Chi 60 min/7/12 weeks	Aerobic Exercise	BMI	NR	NR	BMI: TG showed significant improvement in BMI compared to CG (p<0.05).

TG, Tai Chi Group; CG, control group; AE, adverse events; y, year; m, month; DSQOL, diabetes-specific quality of life; SF-36, Medical Outcomes Study Short Form-36; BMI, body mass index; WHR, waist-hip ratio; NR, not reported; SF-36 domains (PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; PCS, physical component summary, MCS=mental component summary).

controls (wait list, no intervention, usual care, and sham exercise), the Tai Chi group showed significant improvements in BMI (n = 234; MD = −1.53; 95% CI, −2.71 to −0.36; p = 0.01; heterogeneity, I^2 = 64%, p = 0.03; **Figure 2**). However, when compared to the other exercises (walking, dancing, and aerobic exercise), the Tai Chi group did not show significant improvements in BMI (n = 385; MD = −0.69; 95% CI, −1.40 to 0.01; p = 0.05; heterogeneity, I^2 = 16%, p = 0.31; **Figure 2**). Similarly, in the analysis of Tai Chi + standard diabetic care vs. standard diabetic care alone, the former showed no significant improvements in BMI (n = 171; MD = −1.92; 95% CI, −4.05 to 0.21; p = 0.08; heterogeneity, I^2 = 76%, p = 0.04; **Figure 2**).

Effect of Tai Chi on Waist-Hip Ratio

Four trials (33, 50, 52, 53) explored the effect of Tai Chi on WHR. In the analysis of Tai Chi vs. control (wait list, no intervention, usual care, and sham exercise), the former did not show significant improvements in WHR (n = 110; MD = −0.09; 95% CI, −0.17 to 0.00; p = 0.05; heterogeneity, I^2 = 95%, p < 0.001; **Figure 3**). In the analysis of Tai Chi vs. other exercises and Tai Chi + standard diabetic care vs. standard diabetic care alone, one trial showed that Tai Chi significantly improved WHR in both comparisons (n = 100; MD = −0.07; 95% CI, −0.09 to −0.05; p < 0.001; **Figure 3**; and n = 107; MD = −0.12; 95% CI, −0.16 to −0.08; p < 0.001; **Figure 3**, respectively).

Effect of Tai Chi on the Quality of Life

Eight trials (35, 40, 44, 46–49, 52) assessed the effect of Tai Chi on QoL. One trial (48) that compared Tai Chi with walking used DSQoL as an assessment tool, whereas the others used SF-36 to compare the effect of Tai Chi with that of the control group (wait list, no intervention, usual care, and sham exercise). For the DSQoL, the trial demonstrated favorable effects of Tai Chi when compared with walking. The SF-36 contains eight domains: physical functioning (PF); role-physical function (RP); body pain (BP); general health (GH); vitality (VT); social functioning (SF); role-emotional function (RE); and mental health (MH). The meta-analysis of seven trials (35, 40, 44, 46, 47, 49, 52) showed that Tai Chi significantly improved the scores of all SF-36 sub-items: PF (n = 447; MD = 7.73; 95% CI, 1.76 to 13.71; p = 0.01; heterogeneity, I^2 = 78%, p < 0.001; **Figure 4**); RP (n = 447; MD = 9.76; 95% CI, 6.05 to 13.47; p < 0.001; heterogeneity, I^2 = 0%, p = 0.74; **Figure 5**); BP (n = 447; MD = 8.49; 95% CI, 1.18 to 15.8; p = 0.02; heterogeneity, I^2 = 80%, p < 0.001; **Figure 6**); GH (n = 447; MD = 9.80; 95% CI, 5.77 to 13.82; p < 0.001; heterogeneity, I^2 = 42%, p = 0.13; **Figure 7**); VT (n = 447; MD = 6.70; 95% CI, 0.45 to 12.94; p = 0.04; heterogeneity, I^2 = 82%, p < 0.001; **Figure 8**); SF (n = 484; MD = 9.1; 95% CI, 4.75 to 13.45; p < 0.001; heterogeneity, I^2 = 48%, p = 0.07; **Figure 9**); RE (n = 447; MD = 7.88; 95% CI, 4.03 to 11.72; p < 0.001; heterogeneity, I^2 = 0%, p = 0.67; **Figure 10**); and MH (n = 447; MD = 5.62; 95% CI, 1.57 to 9.67; p = 0.006; heterogeneity, I^2 = 61%, p = 0.03; **Figure 11**).

Sensitivity analysis was conducted to explore the possible sources of heterogeneity and evaluate the stability of the pooled results by removing these studies one by one. Heterogeneity was reduced to 0% by removing Meng's trial (49), Chen's trial (52),

TABLE 3 | PEDro score for methodological quality assessment of including studies.

Reference	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	score
Shen XY et al. (48)	1	1	0	1	0	0	0	1	0	1	1	5/10
Wu F et al. (46)	1	1	0	1	0	0	0	1	1	1	1	6/10
Lam P et al. (44)	1	1	0	1	0	0	0	1	0	1	1	5/10
Li ZB et al. (34)	1	1	0	1	0	0	0	1	0	1	1	5/10
Meng E (49)	1	1	0	1	0	0	0	1	1	1	1	6/10
Wang P et al. (47)	1	1	0	1	0	0	0	1	1	1	1	6/10
Wei DL (33)	1	1	0	1	0	0	0	1	1	1	1	6/10
Ahn S (40)	1	0	0	1	0	0	0	0	0	1	1	3/10
Chen SC et al. (32)	1	1	0	1	0	0	0	1	0	1	1	5/10
Trang T et al. (35)	1	1	0	1	0	0	0	1	1	1	1	6/10
Cai H (42)	1	0	0	1	0	0	0	1	0	1	1	4/10
Chen ZC (52)	1	1	0	1	0	0	0	1	0	1	1	5/10
Li HC et al. (50)	1	1	0	0	0	0	0	1	1	1	1	5/10
Bao QW et al. (53)	1	1	0	1	0	0	0	1	1	1	1	6/10
Zhao G et al. (45)	1	1	0	1	0	0	0	1	1	1	1	6/10
Youngwanichsetha S et al. (43)	1	1	1	1	0	0	1	1	0	1	1	7/10
Kan Y et al. (51)	1	1	0	0	0	0	0	1	1	1	1	5/10
Wang JH et al. (41)	1	0	0	0	0	0	0	1	1	1	1	4/10

Item 1, eligibility criteria; item 2, random allocation; item 3, concealed allocation; item 4, similar baseline; item 5, subjected blinded; item 6, therapists blinded; item 7, assessors blinded; item 8, < 15% dropouts; item 9, intention-to-treat analysis; item 10, between-group comparison; item 11, point measures and variability data; 1, described explicitly and in details; 0, unclear, inadequately described.

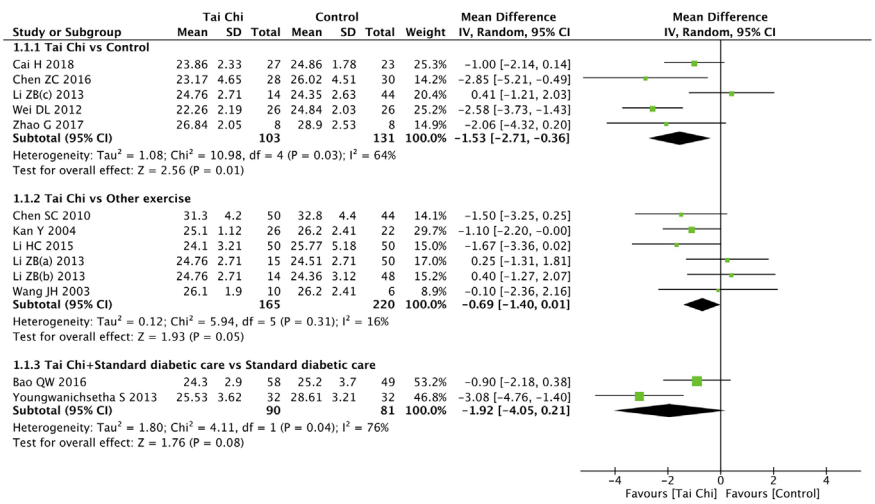

FIGURE 2 | Forest plot of effect for Tai Chi in BMI.

and Wu's trial (46) with respect to PF, VT, and SF, respectively. Nonetheless, the pooled results of all SF-36 sub-items appeared relatively consistent.

Adverse Events

Only Tsang's trial (35) reported adverse events in which one participant in the Tai Chi group presented exercise intolerance due to pain and fatigue. This participant had pre-existing spinal stenosis but was not symptomatic during the process of screening and baseline assessment, and quit the project after attending one Tai Chi exercise session in Tsang's trial (35).

DISCUSSION

The objective of this systematic review and meta-analysis was to evaluate the effect of Tai Chi in T2DM patients on their QoL, BMI, and WHR. The pooled results showed that Tai Chi could significantly improve the QoL of T2DM patients with respect to all SF-36 sub-items (PF, RP, BP, GH, VT, SF, RE, and MH) when compared to the control group (waitlist, no intervention, usual care, and sham exercise). The Tai Chi group showed a significant decrease in the T2DM severity of patients in terms of BMI when compared to the control group. Limited studies have shown that

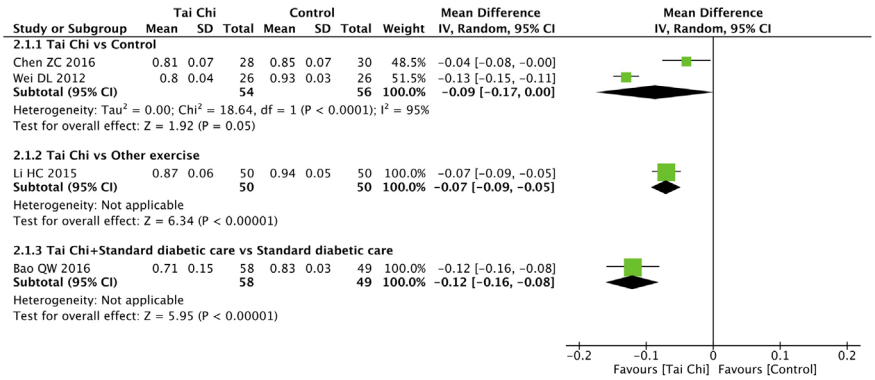

FIGURE 3 | Forest plot of effect for Tai Chi in WHR.

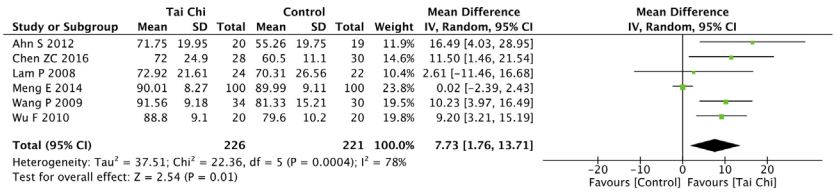

FIGURE 4 | Forest plot of effect for Tai Chi in SF-36 (PF).

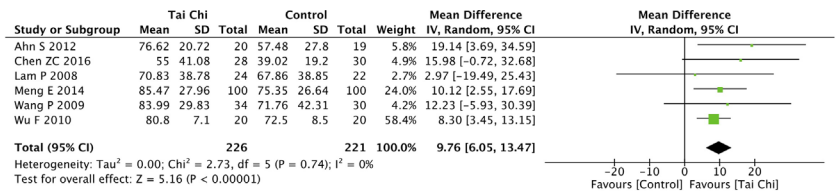

FIGURE 5 | Forest plot of effect for Tai Chi in SF-36 (RP).

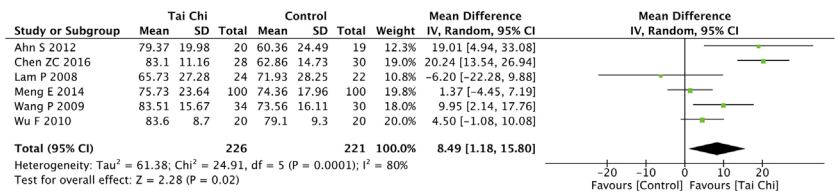

FIGURE 6 | Forest plot of effect for Tai Chi in SF-36 (BP).

Tai Chi could reduce the WHR in T2DM patients when compared with other exercises or as an adjunctive treatment.

This systematic review and meta-analysis aimed to update the evidence by including recent clinical trials of Tai Chi in patients with T2DM. Compared to two previous related reviews (28, 30), we identified three and five new trials that examined the effect of Tai Chi on the QoL and BMI of T2DM patients, respectively. The results of our review were consistent with those of previous reviews

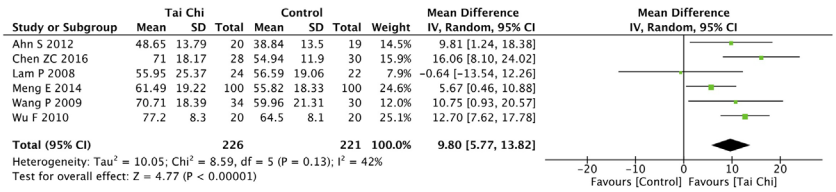

FIGURE 7 | Forest plot of effect for Tai Chi in SF-36 (GH).

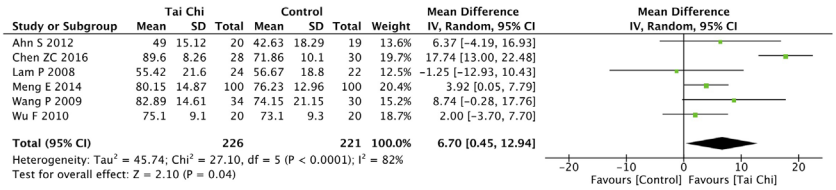

FIGURE 8 | Forest plot of effect for Tai Chi in SF-36 (VT).

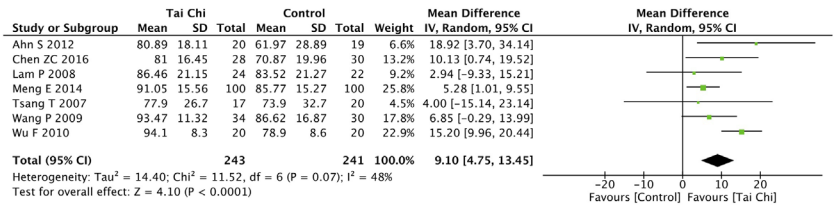

FIGURE 9 | Forest plot of effect for Tai Chi in SF-36 (SF).

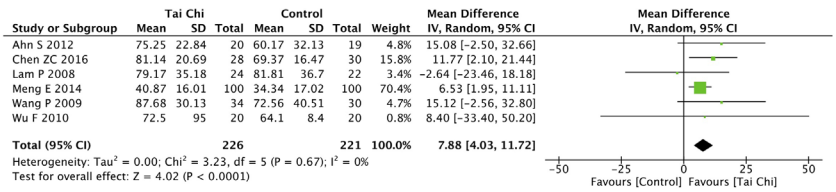

FIGURE 10 | Forest plot of effect for Tai Chi in SF-36 (RE).

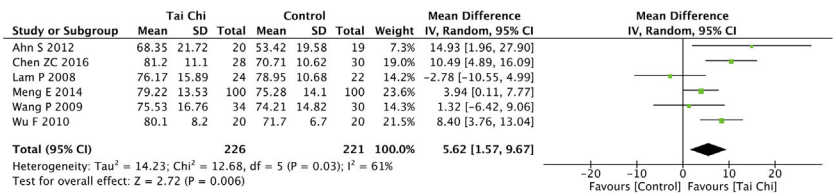

FIGURE 11 | Forest plot of effect for Tai Chi in SF-36 (MH).

(28, 30). Lee's review narratively reported the superior effects of Tai Chi on QoL when compared with the control group (no treatment or waitlist) (30). Zhou's review suggested that Tai Chi could improve QoL in the domains of PF, BP, and SF by synthesizing the results of five trials (28). Our review showed that Tai Chi significantly improved the scores of all SF-36 sub-items in T2DM patients when compared with the control group (wait list, no intervention, usual care, and sham exercise) by synthesizing the results of seven trials.

Tai Chi has become popular worldwide as an important branch of traditional Chinese mind-body exercise. The major characteristics of Tai Chi include mind concentration with breath control, full-body exercise in a semi-squat position, and continuous spiral body movements (16). During the process of Tai Chi training, body movements and deep diaphragmatic breathing are integrated to achieve a harmonious balance between the mind and body to facilitate internal energy flow (16). Previous research has confirmed the significant benefits of various Tai Chi styles in health promotion. Moreover, Tai Chi practice could improve the muscular strength, aerobic capacity, balance, QoL, and psychological well-being (16, 54–57). It has significant benefits on physical, psychological, and social functions.

Previous studies have concluded that exercise is beneficial for DM patients (58–60). Furthermore, related reviews (30, 31) have shown that Tai Chi training modulates the blood pressure, triglyceride, high-density lipoprotein cholesterol, serum malondialdehyde, and C-reactive protein in DM patients. Several studies (32, 40, 44) reported that Tai Chi training improved balance, neuropathic symptoms, and some dimensions of QoL. In total, eight trials were selected to assess the effect of Tai Chi on the QoL of T2DM patients in this review. Seven of them used SF-36 as the assessment tool, and the comparisons were made with the control group (waitlist, no intervention, usual care, and sham exercise). The pooled results revealed that T2DM patients presented statistically significant differences in all dimensions of SF-36 in the Tai Chi as compared to the control group. Minimal clinically important difference was considered as the smallest improvement of symptoms in a score of assessment tools that patients perceived as beneficial.

In a previous study (61, 62), the minimal clinically important differences for eight SF-36 domains were defined as ≥5 points. The pooled results of our review demonstrated that the two SF-36 domains of GH and RP were both statistically and clinically significant. The other six SF-36 domains (PF, BP, VT, SF, RE, and MH) were statistically significant and possibly clinically significant. The lower limits of 95% CI in the two SF-36 domains of GH and RP were greater than the minimal clinically important difference, but not in the other six SF-36 domains of PF, BP, VT, SF, RE, and MH. Heterogeneity was reduced to 0% by removing Meng's trial (49), Chen's trial (52), Wu's trial (46) for PF, VT, and SF, respectively. The sources of heterogeneity in the aspects of PF, VT, and SF could be the larger sample size (n = 200) in Meng's trial (49), different Tai Chi style training (Tai Chi stick) in Chen's trial (52) and longer treatment duration (24 weeks) in Wu's trial (46) when compared with the other trials. Nonetheless, the pooled results of all SF-36 sub-items appeared relatively consistent.

Tai Chi also showed significant benefits in BMI when compared to the control group, which was consistent with previous literature (28). In addition, the pooled result of this review showed that the Tai Chi group had a BMI reduction of 1.53 points as compared to the control group. The result of BMI reduction in this review could achieve clinical significance, indicating the beneficial effect of Tai Chi in patients with T2DM (63). On the other hand, no significant improvements were noted in the Tai Chi group when compared with other exercises and in the Tai Chi + standard diabetic care group when compared with standard diabetic care alone. Tai Chi and exercise may have similar mechanisms for managing weight in T2DM patients. It is widely accepted that exercise could modulate insulin-dependent and insulin-independent mechanisms, and regular long-term exercises would involve "over crosstalk" that could mediate the related systemic effects on glycated hemoglobin, blood glucose levels, blood pressure, and serum lipid profiles (64). Only one trial showed that the WHR improved significantly with Tai Chi when compared with other exercises and with Tai Chi + standard diabetic care when compared with standard diabetic care alone. Interestingly, the pooled results of two trials showed no significant improvements in WHR in the comparison between the Tai Chi and control groups. The aggravated results had low reliability, possibly due to limited studies and a small sample size. Larger samples and high-quality studies are needed to identify the effect of Tai Chi on weight management in T2DM patients. Most trials did not systematically assess intervention safety. Furthermore, they were poorly described, and only one study reported adverse events. Tai Chi seems to be a safe alternative therapy for T2DM patients.

This systematic review and meta-analysis had some limitations. First, 14 of 18 included studies were conducted in China, and the other four trials were conducted in Australia, Korea, and Thailand. Thirteen studies were published in Chinese and five in English. Second, only one trial (43) reported conceal allocation and assessor blinding. It was impractical to blind the participants and Tai Chi supervisors in all trials. Third, the methodological quality was rated as low (3/10) in one trial (40). There were three quasi-experimental trials and 15 RCTs in our review. The quasi-experimental trials may have had confounding biases due to poor methodological quality. Fourth, many studies had a small sample size. Half of the included studies reported dropout conditions, and one trial (40) showed a high dropout rate of 33.9%. It seems suspicious that nine trials conducted in China and published in Chinese had zero dropouts. Fifth, the style, time, frequency, and duration of treatment of Tai Chi were variable.

For future research, a larger sample size and good methodological quality studies are needed to explore the effect of Tai Chi in T2DM patients. The intervention intensity should be quantitatively measured. The exercise protocols of both the experimental group and control group should be described in detail so that other researchers can reproduce the intervention

protocols. Tai Chi participants should be taught to familiarize themselves with Tai Chi movements in several training sessions.

The findings of this systematic review and meta-analysis revealed positive evidence regarding the effectiveness of Tai Chi in improving the QoL, BMI, and WHR of T2DM patients. Various types of Tai Chi can be applied to T2DM patients aged between 50 and 70 years. The minimum valid training duration of Tai Chi for T2DM patients is about 12 weeks. The recommended Tai Chi training frequency is at least thrice a week and 30 to 60 min per training session. Tai Chi could be an alternative for physical activity in T2DM patients to improve the QoL and for weight management.

CONCLUSION

Tai Chi showed benefits in T2DM patients by improving the QoL and BMI when compared with controls. As a safe, cost-effective, and convenient mind-body exercise, Tai Chi might be recommended for T2DM patients as an alternative for physical activity. Future research should be conducted with reference to the aforementioned suggestions.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

Conceptualization: JQ, LC, and JT. Methodology: JQ, ZL. Formal analysis: JQ and YC. Data curation: SG and YY. Writing—original draft preparation: JQ. Writing—review and editing: YX, JW, JH. Supervision: LC and JT. All authors contributed to the article and approved the submitted version.

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Effectiveness of the Beyond Good Intentions Program on Improving Dietary Quality Among People With Type 2 Diabetes Mellitus: A Randomized Controlled Trial

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Background and Aims: An appropriate diet is an essential component of the management of Type 2 Diabetes Mellitus (T2DM). However, for many people with T2DM, self-management is difficult. Therefore, the Beyond Good Intentions (BGI) education program was developed based on self-regulation and proactive coping theories to enhance people's capabilities for self-management. The aim of this study was to determine the effectiveness of the BGI program on improving dietary quality among a preselected group of people with T2DM after two-and-a-half years follow-up.

Methods: In this randomized controlled trial, 108 people with T2DM were randomized (1:1) to the intervention ($n = 56$) (BGI-program) or control group ($n = 52$) (care as usual). Linear regression analyses were used to determine the effect of the BGI program on change in dietary quality between baseline and two-and-a-half years follow-up. In addition, potential effect modification by having a nutritional goal at baseline was evaluated. Multiple imputation ($n = 15$ imputations) was performed to account for potential bias due to missing data.

Results: According to intention-to-treat analysis, participants in the intervention group showed greater improvements in dietary quality score than participants in the control group ($\beta = 0.71$; 95%CI: 0.09; 1.33) after follow-up. Having a nutritional goal at baseline had a moderating effect on the effectiveness of the BGI program on dietary quality (p-interaction $= 0.01$), and stratified results showed that the favorable effect of the intervention on dietary quality was stronger for participants without a nutritional goal at baseline (no nutritional goal: $\beta = 1.46$; 95%CI: 0.65; 2.27 vs. nutritional goal: $\beta = -0.24$; 95%CI: −1.17; 0.69).

Conclusions: The BGI program was significantly effective in improving dietary quality among preselected people with T2DM compared to care as usual. This effect was

stronger among participants without a nutritional goal at baseline. A possible explanation for this finding is that persons with a nutritional goal at baseline already started improving their dietary intake before the start of the BGI program. Future studies are needed to elucidate the moderating role of goalsetting on the effectiveness of the BGI program.

Keywords: healthy diet, self-management, diabetes mellitus type 2, randomized controlled trial, effect modifier, goals, patient education as topic

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) and its complications largely contribute to the global disease burden, making T2DM one of the leading causes of global deaths (1). Complications of T2DM comprise an increased risk of neuropathy, retinopathy, and nephropathy (microvascular), and cerebrovascular-, ischemic heart-, and peripheral vascular diseases (macrovascular) (2). The main drivers in the global T2DM epidemic are lifestyle related factors, including obesity, a sedentary lifestyle, and an unfavorable diet (1). This highlights the importance of managing T2DM and prevent or delay complications, which can be achieved through good cardiometabolic control (3).

Good cardiometabolic control in T2DM can be accomplished by pharmacological treatment and/or lifestyle modification, with improving physical activity levels and dietary quality as main components (3). Improving a person's dietary quality can optimize glucose levels. High-quality diets (i.e., adequate consumption of whole grains, fruits, nuts, fibers, vegetables, and legumes, moderate alcohol consumption, and low consumption of saturated fats, oils, salts, meat products, and sugar), contribute to T2DM prevention and management (4, 5). An important element in achieving good cardiometabolic control is the self-management of people with T2DM (6). However, for many people with T2DM it is difficult to incorporate self-management into their daily lives. Therefore, diabetes self-management education programs, defined as a continuous process intended to facilitate knowledge, skills, and abilities that are needed for diabetes self-management (7), are recognized as essential elements in T2DM care.

Thoolen et al. (8) developed the self-management education program "Beyond Good Intentions" (BGI), which specifically targets initiation and maintenance of self-management. The BGI program was developed using a comprehensive theoretical framework based on theories of self-regulation and proactive coping (8). The BGI intervention was previously found to be effective in reducing cardiovascular risk after 12 months in newly detected people with T2DM, regardless of medical treatment (9). Further research into the long-term effectiveness of the BGI program in a preselected group of people with T2DM (with diagnosed T2DM for up to 5 years) showed no evidence for significant improvement in BMI, cardiovascular risk factors, quality of life, or diabetes self-management behavior after two-and-a-half years follow-up in the ELDES study (10). However, the (long-term) effectiveness of the BGI program on improving dietary quality has not yet been evaluated. Previous studies indicate that self-management programs can improve dietary quality in the short term, however, few studies have studied changes in dietary quality on the longer term (11). Therefore, this study aimed to evaluate the effect of the BGI program in the ELDES study on diet quality among a preselected group of people with T2DM after two-and-a-half years follow-up.

METHODS

Study Design

The study had a parallel randomized controlled trial (RCT) design with a two-and-a-half years follow-up time, and was conducted according to the CONSORT guidelines for experimental designs (12). The study was approved by the Medical Ethical Committee of the University Medical Center Utrecht and was registered at the Dutch Trial Register (Netherlands Trial Register NTR5530/NL5405).

Participant Recruitment, Selection, and Randomization

In the Netherlands, there are ∼115 care groups that offer disease management programs for people with a chronic disease, including people with T2DM. The care groups are responsible for the primary care and for the prevention of complications and symptoms in people with T2DM (13). Of all the people with T2DM, 85% are treated by general practitioners (GPs) in practices close to their homes (14). Three care groups with 43 general practices (either single or group-handed practices) and 89 GPs agreed to participate. In the period between 2014 and 2016, people with T2DM were recruited from care groups in the Dutch city Eindhoven. The participating GPs determined the eligibility of people with T2DM based on the electronic medical records. Individuals were eligible to participate if they were (1) aged between $\geq$18 and $\leq$75 years, and (2) diagnosed with T2DM between 3 months and 5 years. An invitation letter and response card were sent to all eligible people. If applicable, they were further informed about the BGI program through a telephone conversation with a member of the research team. When the potential participant was sufficiently informed and fully understood the information, written informed consent was obtained where after preselection was started.

The preselection was conducted to select those people with T2DM who might benefit from the BGI program. Selection was based on individual's self-management capabilities, and absence of severe anxiety and/or depression (as this should be addressed first), using the validated Self-Management Screening (SeMaS) questionnaire (15). The patient's GP was informed about the

results of the SeMaS. Selection procedures are described in more detail elsewhere (16).

Eligible individuals (n = 1,590) were enrolled in the study if they consented to participate and replied to the SeMaS questionnaire (n = 119). Patients were excluded based on the results of the SeMaS questionnaire or had an insufficient cognitive performance, or inadequate knowledge of the Dutch language (n = 11), resulting in a study population of n = 108. During the two-and-a-half years follow up, one participant died, one moved outside the study area, 21 participants did not respond to the second questionnaire, and 12 discontinued the BGI intervention (**Supplementary Figure 1**).

The 108 preselected people with T2DM were randomized (1:1) based on computer-generated random numbers, with sealed, opaque, sequentially numbered allocation envelopes. The coordinating research center (Julius Center, UMC Utrecht) allocated all preselected individuals to the intervention group (BGI program) (n = 56) or the control group (care as usual) (n = 52), based on a random number corresponding to one of the groups. Participants who were attending the BGI program could not be blinded for the treatment allocation since they knew that they were attending an extra program besides care as usual. Similarly, nurses who were trained to give the BGI program were not blinded. However, the researcher who performed the outcome measurements was blinded.

TABLE 1 | Beyond Good Intentions program overview.

Program component	Description
Individual session	• One session • Duration: 30 min • Participants: participant and trained nurse • Discussed: participant's knowledge, experiences, and attitudes regarding T2DM management • To do: set personal goals to improve diabetes risk profile before start group session
Group sessions	• Four sessions, biweekly • Duration: 2.5 h each • Discussed: topics relevant to all people with T2DM (including physical activity, healthy diet, medication adherence, and self-management) • To do: formulate, implement, and evaluate pro-active self-management goals
Individual evaluation session	• Two weeks after last group session participants filled out evaluation form, which was discussed in an individual evaluation session
Boosting session	• When: 1 year after first individual session • Discussed: progress in goal attainment over the past months • To do: develop new personal goals for the future

Control: Care as Usual

Participants in the control group received usual diabetes care according to the guidelines of the Dutch College of General Practitioners (12). The GP remains ultimately responsible for the care of people with T2DM. Participants are fully informed about T2DM, various treatment options, and their individual treatment plan. GPs did not offer other diabetes self-management education programs to the participants during the study.

Intervention: Beyond Good Intentions Program

The intervention group received not only care as usual, but also followed the BGI program. The main objective of the BGI program is to help people with T2DM achieve optimal self-management by making them more knowledgeable, proactive, and confident about their disease management. The BGI program lasts 12 weeks and consists of several components. First, a 30-min individual introductory session was held between the participant and a trained nurse, wherein participant's knowledge, experiences, and attitudes regarding T2DM management were discussed and participants were asked to set personal goal(s) for improving their diabetes risk profile before the start of the next session. The individual session was followed by four bi-weekly group sessions of two-and-a-half hours, wherein topics relevant to all people with T2DM were discussed and participants were asked to formulate, implement, and evaluate pro-active self-management goals. Topics that were discussed included physical activity, medication adherence, self-management and a healthy diet. Dietary intake recommendations were based on diabetes-specific dietary guidelines currently used in practice, i.e., limit saturated fat intake, increase unsaturated fat intake, and increase dietary fiber intake (especially form fruits and vegetables) (13, 17). Two weeks after the last group session participants filled out an evaluation form, which was discussed in an individual evaluation session. Additionally, 1 year after the first individual session, a group booster session was scheduled, wherein the progress in goal attainment over the past months was discussed and new personal goals for the future were set. The BGI program is described in detail by Vos et al. (16), and a program overview is summarized in **Table 1**.

Nurse Training

The BGI program was guided by registered nurses (n = 3), specialized in care for people with T2DM. Before the start of the BGI program, the nurses had two 3-h training sessions conducted by a psychologist who designed the original program of BGI, following the train-the-trainer principle. The nurses encouraged the participants in the BGI program to support each other and to gain more self-confidence in collecting information about T2DM themselves.

Dietary Intake and Diet Quality Score

Dietary Intake Assessment

Dietary intake was assessed based on questions derived from two food-based dietary questionnaires; the Kristal food habits questionnaire (FHQ) (18) and the Dutch Fat Consumption Questionnaire (FCQ) (19). The FHQ consisted of 20 questions covering topics regarding participants' approaches to reduce fat intake. The questions were based on a four-point Likert scale, with answer options ranging from "never" to "always," including a "not applicable" option. The FCQ consisted of 39 questions covering seven groups of food products (dairy, bread and

spreads, meat, and cheese for warm dishes, dish-gravy, snacks, fruit, vegetables, and sugar-containing beverages). Participants were asked the frequency and sometimes also the quantity of the foods consumed (e.g., "How many days a week do you eat vegetables"). Questions about the frequency of consumption were based on seven or eight scales with answer options ranging from "never or less than once a month" to "7 times or more each week," Questions about the number of servings a day were based on 4, 6, 8, or 10 answer options, ranging from "not applicable" to "9 times or more a day."

Construction and Scoring of the Dietary Quality Score

The dietary quality score (DQS) used in the current study was based on an existing DQS developed by Nettleton et al. (20), specifically focused on people with T2DM and based on the intake of nine food groups: whole grains, vegetables, fruits, nuts, and fish (favorable food groups), and red and processed meats, snacks, sugar sweetened beverages, and sweets (unfavorable food groups). In the current study, dietary intake data of the FHQ and FCQ were used to develop an adapted version of the DQS. Because the dietary intake data were not completely comparable to the data used by Nettleton et al., two food groups were slightly modified: the "whole grains" food group was changed to "grains," and the "fish" food group was changed to "fish and poultry as a replacement of red meat." These food groups and the questions on which they were based are presented in **Supplementary Table 1**.

In the DQS developed by Nettleton et al., food group scores were divided into population-specific quartiles. Individuals were assigned points based on their quartile rank, where higher scores reflected better DQSs. Favorable food groups were assigned ascending scores (0–3 points); individuals in the highest intake quartile received 3 points. Unfavorable food groups were assigned descending scores (3–0 points); individuals in the highest quartile received 0 points.

In the adapted DQS, food group scores were divided into population-specific quartiles or medians. Food groups divided into median intakes were scored 1 or 2 points, food groups divided into quartile intakes were scored 0.5; 1; 1.5; or 2 points, with higher scores reflecting a better dietary quality (**Supplementary Table 1**). A minimal clinically important difference has not been quantified for the DQS. Favorable food groups were assigned ascending scores and unfavorable food groups were assigned descending scores. Most food groups were based on a single dietary intake item, however, the "red and processed meat" and "sweets" food groups were composed of multiple dietary intake items. For these food groups, each dietary intake item was separately distributed in population-specific quartile or median intakes and scored based on these distributions, where after the scores of these items were summed and divided by the number of items per food group. The total DQS was calculated as the sum of the food group scores, resulting in a total DQS ranging from a theoretical minimum of 6.5 to a theoretical maximum of 18 points on a continuous scale, where higher scores reflected a better dietary quality.

Sociodemographic and Lifestyle Variables

Sociodemographic and lifestyle information was assessed at baseline (T0) and after two-and-a-half years follow-up (T1). Age, sex, paid employment status (yes/no), marital status (married/ divorced/widow or widower/ never married), currently having a nutritional goal (yes/no), dietary intake, and physical activity (hours per day light to heavy activity) were assessed using self-reported questionnaires at T0 and T1. Educational level (low/ intermediate/ high education) was retrieved from the self-reported SeMaS questionnaire. In addition, glycated hemoglobin (HbA1c), systolic blood pressure (SBP), lipid profile [low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, total cholesterol, and triglycerides], smoking status (current/former/never smoker), and height and weight of the participants were retrieved from the electronic medical records of the GP. Body Mass Index (BMI: kg/m^2) was calculated from the height and weight stated in the GP electronic medical records.

Potential Effect Modification by Nutritional Goals

Having a nutritional goal was identified as a potential effect modifier, based on clinical plausibility and previous literature (21). For example, a systematic review showed that participants who set goals prior to a diabetes self-management intervention improved their glycemic control after the intervention (22). A possible explanation for this finding might be that people who set goals have a higher motivation to improve their glycemic control (23). Furthermore, participants that set a nutritional goal may be more focused on their diet and have more nutrition knowledge. Persons with more nutrition knowledge are more likely to consume healthier diets (24). Therefore, it is plausible a different effect of the BGI program on DQS could be expected for participants with a nutritional goal compared to those without a nutritional goal.

Statistical Analysis

Baseline participant characteristics were described using descriptive statistics. Continuous variables were described as means and standard deviations (SD) when normally distributed, or medians and interquartile range (IQR) when non-normally distributed. Categorical variables were reported as frequencies and percentages.

For the DQS construction, the intake of food groups was divided into population-specific quartiles or medians with the use of the "Visual binning" option, which is a tool to assist the researcher in transforming continuous variables into categorical variables. The difference in DQS between baseline (T0) and follow-up (T1) measurement was calculated as the DQS at T1 minus the DQS at T0. In a similar manner, differences in food group scores between baseline and follow-up were calculated as the food group score at T1 minus the food group score at T0. Linear regression analyses were performed according to the intention-to-treat principle to examine the effect of the BGI intervention on DQS and food group scores between T0 and T1, presented as the change in DQS for the intervention group compared to the control

TABLE 2 | Participant characteristics in original and imputed data, split by intervention and control group.

Characteristics	Data after multiple imputation (n = 108)		Original data (n = 108)			
	Intervention (n = 56)	Control (n = 52)	Intervention		Control	
			n		*n*	
Age (years)	62.89 ± 8.30	61.71 ± 7.44	56	62.89 ± 8.30	52	61.71 ± 7.44
Sex, male	27 (48.2)	33 (63.5)	56	27 (48.2)	52	33 (63.5)
Educational level			56		52	
Low	15 (26.8)	16 (30.8)		15 (26.8)		16 (30,8)
Intermediate	20 (35.7)	17 (32.7)		20 (35.7)		17 (32.7)
High	19 (33.9)	16 (30.8)		19 (33.9)		16 (30.8)
Other	2 (3.6)	3 (5.8)		2 (3.6)		3 (5.8)
Marital status, married	36 (64.3)	40 (76.9)	55	36 (64.3)	51	40 (78.4)
Paid employment	16 (28.6)	22 (42.3)	55	16 (29.1)	51	21 (41.2)
Nutritional goal at baseline[a], yes	26 (46.4)	25 (48.1)	47	26 (46.4)	42	25 (48.1)
Smoking status			56		52	
Current	4 (7.1)	6 (11.5)		4 (7.1)		6.11.5)
Former	31 (55.4)	22 (42.3)		31 (55.4)		22 (42.3)
Never	21 (37.5)	24 (46.2)		21 (37.5)		24 (46.2)
BMI, kg/m^2	29.52 ± 4.85	30.07 ± 4.55	55	29.58 ± 4.87	52	30.07 ± 4.55
HbA1c, mmol/mol	49.14 ± 7.36	49.79 ± 8.69	54	49.13 ± 7.47	52	49.79 ± 8.69
SBP, mmHg	131.45 ± 13.43	133.35 ± 14.47	55	131.87 ± 13.17	52	133.35 ± 14.47
Lipid profile, mmol/l						
LDL cholesterol	2.60 ± 0.84	2.37 ± 0.83	55	2.60 ± 0.85	52	2.37 ± 0.83
HDL cholesterol	1.27 ± 0.28	1.18 ± 0.37	49	1.26 ± 0.27	47	1.19 ± 0.36
Total cholesterol	4.60 ± 0.89	4.14 ± 0.92	49	4.58 ± 0.89	47	4.09 ± 0.88
Triglycerides	1.60 (1.13; 2.08)	1.60 (1.13; 2.08)	55	1.60 (1.20; 2.10)	52	1.60 (1.20; 2.08)
Physical activity, hours per week	10.88 (5.44; 23.25)	12.00 (3.56; 24.00)	53	10.50 (5.00; 22.38)	47	13.50 (3.75; 24.00)
Dietary quality score[a]	12.83 ± 1.71	12.91 ± 1.97	48	12.83 ± 1.71	49	12.91 ± 1.97

Data are n (%), mean ± Standard deviation (SD), or median [interquartile range (IQR)], data of imputation number 15 are presented for the data after multiple imputation.
[a]Nutritional goal at baseline (yes/no) was not imputed: Intervention (n = 47), Control (n = 42); Diet quality score was not imputed: Intervention (n = 48), Control (n = 49).

group and adjusted for baseline values of dietary quality. Effect modification by nutritional goals was examined by adding a product term "intervention*nutritional goal" to the regression model. If this interaction was significant, analyses were repeated and results on the effect of the BGI intervention on DQS was shown separately for those with and without a nutritional goal.

As a sensitivity analysis, a non-response analysis was conducted to examine potential differences between baseline characteristics of participants who had missing data on the dietary intake questions (non-respondents) and participants who had complete data on the dietary intake questions (respondents). Missing data were imputed (n = 15 imputations) using the multiple imputation procedure in SPSS with the predictive mean matching method (25), with the exception of the nutritional goal and dietary quality questions. Because results were similar in original and imputed data (**Table 2**), results of the main analyses were described after the multiple imputation procedure. All statistical analyses were performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, N.Y., USA). A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Subject Characteristics

Most baseline participant characteristics were similar between the intervention and control group (**Table 2**). Participants had a mean age around 62 years and were overall well-controlled. The DQS at baseline was comparable between the intervention and control group [intervention: 12.8 (± 1.7); control: 12.9 (± 2.0)]. By chance, the control group had a larger percentage of participants that were male (intervention: 48.2%; control: 63.5%), married (intervention: 64.3%, control: 76.9%), and currently employed (intervention: 28.6%; control: 42.3%; **Table 2**).

Effect of the BGI Program on Dietary Quality

Change in DQS after the intervention according to intention-to-treat analyses is shown in **Table 3**. Forty-eight participants had missing data for at least one of the dietary intake questions that determine the total DQS. Therefore, data on change in DQS were available for 60 participants. Total DQS significantly improved for the intervention group compared to the control group after the intervention period (β = 0.71, 95%CI = 0.080; 1.33, p =

TABLE 3 | Change in dietary quality and dietary quality components after the intervention for the intervention group relative to the control group (intention to treat analysis).

	Change in dietary quality for the intervention group compared to the control group β[a]	95% Confidence Interval
Total dietary quality score		
	0.71	0.080 to 1.33*
Individual dietary quality components		
Grains	−0.057	−0.28 to 0.17
Fish	−0.017	−0.20 to 0.17
Snacks	−0.073	−0.29 to 1.17
Nuts	0.094	−0.12 to 0.31
Fruits	0.23	0.015 to 0.44*
Vegetables	0.18	−0.016 to 0.37
Meat	0.074	−0.039 to 0.19
Sweets	−0.065	−0.29 to 0.16
Sugar containing beverages	0.068	−0.032 to 0.17

[a]*Coefficients are adjusted for baseline values of dietary quality/ individual component scores and indicate the change in DQS for the intervention group compared to the control group. *P < 0.05.*

0.028), indicating that participants in the intervention group had a 0.71 points higher DQS change after the intervention compared to the control group. Of the individual components, only fruit intake significantly improved after the intervention period (β = 0.23, 95%CI = 0.02; 0.44, $p = 0.033$). The components vegetables and nuts also improved after the intervention period, although not significantly, while for the other components minimal changes were observed (**Table 3**).

Sensitivity and Subgroup Analyses

Most baseline characteristics were comparable between respondents ($n = 60$) and non-respondents ($n = 48$) to the dietary intake questions (**Supplementary Table 2**). Non-respondents to the dietary intake questions generally had a slightly higher BMI compared to respondents in both the intervention and control group. Compared to respondents, non-respondents in the control group had a slightly higher mean SBP. Further, they more often had a nutritional goal, and more often were male (**Supplementary Table 2**).

Having a nutritional goal at baseline was found to have a moderating effect on the effect of the intervention on DQS (p-interaction$n = 0.01$), and stratified results showed that the favorable effect of the intervention on DQS was stronger for participants without a nutritional goal at baseline (β = 1.46; 95%CI: 0.65; 2.27 vs. −0.24; 95%CI: −1.17; 0.69) (**Figure 1**).

DISCUSSION

People with T2DM who followed the BGI program showed greater improvements in DQS than those only receiving care-as-usual after two-and-a-half years follow-up. This result was mainly driven by an increased fruit consumption. The favorable effect of the BGI program on DQS was stronger for participants without a nutritional goal at baseline.

A systematic review by Norris et al. (11) shows that self-management education in people with T2DM generally has a positive influence on dietary intake. For example, the study by Glasgow et al. (26) including 206 people with diabetes aged 62 years on average, showed a positive effect of a self-management education program on reducing fat and energy intake after 3 months compared to care as usual. However, most reviewed studies had a short follow-up (≤1 year) and did not take into account total dietary quality (11). Elaborating on these previous studies, our study is among the first to demonstrate longer-term effectiveness of a self-management education program on improving dietary quality. We found an improvement in DQS of ∼0.7 units after participation in the BGI program compared to the control group (care as usual). To illustrate the clinical relevance of these findings, the observed difference in DQS should be compared with the assigned points for each food group: individuals were assigned 0,5; 1; 1,5; or 2 points for each food group with higher scores indicating better adherence to the dietary guidelines. Our finding of a 0.7 difference in the DQS between the intervention and control group is comparable to a 0.5 to 1 point increase for one food group. For example, an individual who consumed snacks more than one time a week (0.5 points) decreased their snack consumption to once every 2 or 3 weeks (1 point) or once a month (1.5 points).

An unexpected finding is the stronger positive effect of the program on DQS in participants without a specific nutritional goal. According to the goal-setting theory, defining goals facilitates behavior change by guiding individuals' devotion and effort which promotes persistence to overcome barriers, and increases self-efficacy for self-management in general (27). A systematic review by Fredrix et al. (22) showed that participants who set goals prior to a diabetes self-management education program improved their glycemic control after the intervention, suggesting that goal-setting could be a beneficial strategy for improving glycemic control. Collaborative goal-setting when receiving medical care for diabetes can improve glycemic control through greater perceived self-management competence and an increased level of trust in the physician (28). Furthermore, a study including 54 overweight people with T2DM with diagnosed T2DM ≥ 1 year, and at least one additional risk factor for CVD, showed that nutritional goal setting within a self-management intervention improved dietary quality, assessed using the Healthy Eating Index 2010 (29). Based on these results one would expect that the intervention would be more effective among those with a nutritional goal at baseline, whereas we found the opposite.

A possible explanation might be that some people with T2DM already started improving their dietary intake after diagnosis. This hypothesis is in line with the results of a previous study among 144 newly diagnosed people with T2DM in the Netherlands, which showed that these people had an unfavorable fat intake at time of diagnosis compared to the general population, but adapted to a more favorable fat intake shortly after diagnosis and maintained this more favorable intake for 4 years (30). It might be that participants who were already more focused on their diet were also more likely to set a

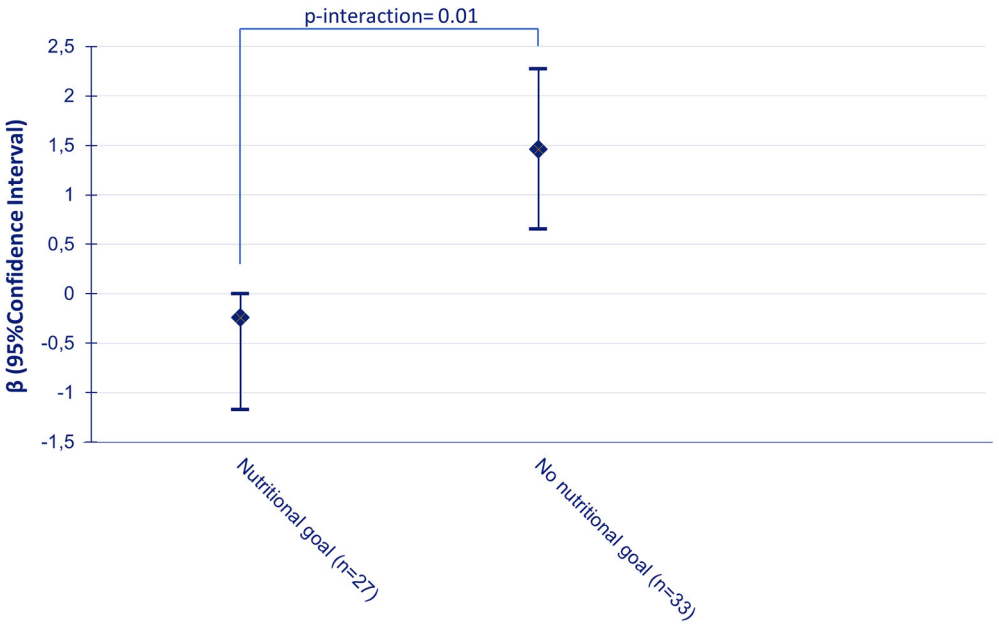

FIGURE 1 | Change in dietary quality score for the intervention group relative to the control group between baseline and follow-up according to nutritional goalsetting at baseline, adjusted for baseline values of dietary quality.

nutritional goal, even though they already improved their diet upon diagnosis, which would leave less room for improvement in DQS following the intervention. Because the current study lacked data on the exact time of diagnosis, future studies are warranted to further explore this hypothesis.

To the best of our knowledge, this study is the first to assess longer-term effectiveness of a self-management education program on improving dietary quality among preselected people with T2DM. The results of this study need to be interpreted in the context of its strengths and limitations.

Our study is strengthened by its design. Randomized controlled trials (RCTs) are viewed as the golden standard for studying cause-effect relations (31). However, even in RCTs, missing data can lead to biased results and thereby threaten validity of inferences (32). Therefore, we applied multiple imputation (25), a recommended method for dealing with missing data in RCTs (32). However, for nutritional goal and dietary intake data it cannot be assumed that data are missing at random (MAR) which is an important assumption to justify imputation. Therefore, for these variables only observed data was used (32).

Some methodological considerations regarding the DQS construction in our study need to be discussed. Deviating from the score of Nettleton et al., we did not distinguish whole grain from refined grain products, because this data was not available. Because whole-grain products have health benefits that are lacking in refined grain products, and because only whole-grain products are protective of T2DM (33), it would have been preferred to include only whole-grain products in our DQS (34). Furthermore, the fish food group deviated from the original score as poultry was included. Although this is not completely comparable to the original DQS, both fish and poultry consumption are considered favorable, and red meat unfavorable components in most DQSs (34). In line with current national dietary guidelines, we based our DQS on the intake of food groups instead of individual nutrients, because persons consume a combination of several foods instead of individual nutrients, and because this takes into account interactions of nutrients within food products (35). Although this approach does not take into account heterogeneity in for example nutritional values within food groups, using food groups is the preferred approach for DQS construction in the context of public health promotion (35). Further, we chose to use population-specific percentile (median and quartile) cut-offs, which do not necessarily reflect healthy intake levels, but enabled a good discriminatory power for each food group (34, 35). Although it may have been useful for the interpretation of the results of the current study, no minimal clinically important difference in DQS could be quantified because there is insufficient scientific evidence to support such a quantification. However, to illustrate the clinical relevance of our results demonstrating a difference in improvement in DQS of 0.7 units after participation in the BGI program, the observed difference in DQS should be compared with the aforementioned assigned points for each food group [i.e., a 0.7 difference in the DQS between the intervention and control group is comparable to a 0.5 to 1 point increase for one food group, such as decreasing the consumption of snacks from more than one time a week (0.5 points) to once every 2 or 3 weeks (1 point) or once a month (1.5 points)].

Several variables included in the current study were retrieved from GP electronic medical records, which limits biases generally associated with self-reporting such as social desirability bias (36). Our primary outcome measure (dietary quality) was, however, assessed based on self-reported dietary intake data. These data were collected using food frequency questionnaires (FFQs), which is the most commonly used data collection tool for determining dietary quality together with 24-h recall and dietary records (37). Although widely accepted, FFQs have some limitations, such as their limited amount of included food items, and sensitivity to measurement error (38). As stated above, self-reporting of dietary intake is prone to social desirability bias (36). Additionally, participants in the intervention group may have reported more favorable intakes because they knew that they were receiving nutritional education.

Lastly, the inclusion rate of the current study was low (7.5%), which may have been attributable to the recruitment by invitation letter rather than recruitment by personal invitation, and the time and effort required from participants in the intervention group (10). In addition, although most characteristics were comparable between responders and non-responders, some differences were observed. Therefore, the results of this study may not be generalizable to the total population of people with T2DM.

In conclusion, the BGI program was effective in improving DQS among preselected people with T2DM after two-and-a-half years follow-up and could therefore contribute to good cardiometabolic control in people with T2DM. The favorable effect of the BGI program on DQS was stronger for participants without a nutritional goal at baseline, possibly because participants that had set a nutritional goal before the start of the study were already more focused on their diet and had already started improving their diet, leaving less room for improvement in DQS following the intervention. Future studies are needed to elucidate the moderating role of setting a nutritional goal on the effectiveness of the self-management education program on DQS, and to evaluate whether the BGI program is also effective in improving DQS among different subgroups of people with T2DM, such as those with comorbidity or poorly controlled T2DM.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethical Committee of the University Medical Center Utrecht. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GR was the principle investigator of the trial. RV was the trial coordinator. JK, RV, and LV were involved in drafting the statistical analysis plan. LV drafted the manuscript, in close collaboration with JK and RV. All authors read, edited, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.583125/full#supplementary-material

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BRIEF RESEARCH REPORT
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Insulin Therapy in Type 2 Diabetes Is Associated With Barriers to Activity and Worse Health Status: A Cross-Sectional Study in Primary Care

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Introduction: Many individuals with type 2 diabetes mellitus (T2DM) experience "psychological insulin resistance". Consequently, it could be expected that insulin therapy may have negative effects on psychological outcomes and well-being. Therefore, this study compared health status and psychosocial functioning of individuals with T2DM using only oral antihyperglycemic agents (OHA) and on insulin therapy (with or without OHA).

Materials and Methods: In this cross-sectional study, we used baseline data of a cluster randomized controlled trial conducted in 55 Dutch general practices in 2005. Health status was measured with the Short Form (SF)-36 (scale 0–100) and psychosocial functioning with the Diabetes Health Profile (DHP, scale 0-100). To handle missing data, we performed multiple imputation. We used linear mixed models with random intercepts per general practice to correct for clustering at practice level and to control for confounding.

Results: In total, 2,794 participants were included in the analysis, their mean age was 65.8 years and 50.8% were women. Insulin-users (n = 212) had a longer duration of T2DM (11.0 versus 5.6 years) and more complications. After correcting for confounders and multiple comparisons, insulin-users reported significantly worse outcomes on vitality (SF-36, adjusted difference -5.7, p=0.033), general health (SF-36, adjusted difference -4.8, p=0.043), barriers to activity (DHP, adjusted difference -7.2, p<0.001), and psychological distress (DHP, adjusted difference -3.7, p=0.004), all on a 0-100 scale.

Discussion: While previous studies showed similar or better health status in people with type 2 diabetes receiving insulin therapy, we found that vitality, general health and barriers to activity were worse in those on insulin therapy. Although the causality of this association cannot be established, our findings add to the discussion on the effects of insulin treatment on patient-reported outcomes in daily practice.

Keywords: type 2 diabetes, insulin, oral antihyperglycemic agents, health status, psychosocial functioning

INTRODUCTION

Insulin therapy may be essential for many patients during the course of type 2 diabetes mellitus (T2DM) (1). While insulin has greater efficacy to lower glycated hemoglobin (HbA1c) compared to oral antihyperglycemic agents (OHA) (2), still many individuals with T2DM are reluctant to start insulin therapy. This "psychological insulin resistance" includes fear of hypoglycemia and weight gain, fear for injections and feelings of guilt and failure (3–8). Consequently, it could be expected that insulin therapy may have negative effects on psychological outcomes and well-being.

Nevertheless, studies in patients who had recently initiated insulin therapy, showed either positive (9–15) or no effects (16–22) on health status and well-being. In contrast, studies in patients who had been using insulin for a longer period found a negative association between insulin therapy and health status (23–25). A recent observational longitudinal study showed that at baseline and during follow-up, individuals with stable insulin therapy had the lowest health status (physical component scale); those who initiated insulin therapy had an unaltered health status (26). These studies however, had methodological limitations: the number of insulin-users was small (25), the selection of confounders was data-driven (24), or there was no adjustment for potential confounders (26).

The aim of this study was to compare health status and psychosocial functioning between individuals with T2DM using only OHA and those using insulin therapy with or without OHA in a real-life context in a mixture of individuals who recently initiated insulin and those using insulin for a longer period of time. Our study adds to the body of existing knowledge and in our opinion deals with methodological limitation of prior studies.

MATERIALS AND METHODS

Study Design, Setting, and Population

In this observational cross-sectional study we used baseline data from a cluster randomized controlled trial (RCT) conducted in 55 general practices in the Netherlands (27). It investigated the effects of a diabetes care protocol (27). Participants were recruited in 2005. All registered T2DM patients were eligible to participate, but those with a short life expectancy, unable to visit the general practice, receiving diabetes treatment at hospital outpatient clinics (secondary care), or those refusing to participate were excluded. For the purposes of the current study, we also excluded T2DM patients who did not use blood glucose lowering medication, but only had a lifestyle advice. The University Medical Centre Utrecht ethics committee approved the original study; patients provided written consent.

Data Collection

The following participants' characteristics were registered on electronic patient files: age, sex, diabetes duration, systolic blood pressure (SBP), body mass index (BMI), HbA1c, lipid profile, level of education, ethnicity, microvascular complications, and macrovascular complications. Systolic blood pressure and body mass index (BMI) were assessed by the practice nurse. HbA1c and lipid profile were measured in local laboratories. Level of education was categorized into low (primary school, pre-vocational education), intermediate (higher general continued education, preparatory scholarly education, middle-level applied education), or high (university of applied science, research university). Ethnicity was categorized into Western-European or other. Microvascular complications were defined as presence of retinopathy (assessed by fundus screening), neuropathy (assessed by feet examination), and/or presence of nephropathy (urine albumin to creatinine ratio >2.5 mg/mmol for men and >3.5 mg/mmol for women, and/or an estimated glomerular filtration rate < 60 ml/min/1.73m2). Macrovascular complications were classified as present if angina pectoris, myocardial infarction, or cerebral infarction was recorded. Medication use was recorded by Anatomical Therapeutic Chemical codes. Insulin use was also identified based on ATC-codes (28).

Questionnaires

Practice nurses handed out questionnaires to the participants, who completed these at home and returned them in a postage paid envelope to the research center. When the questionnaires were not returned within three months, participants received a reminder. For the current study, we used the Short Form-36 (SF-36) and the Diabetes Health Profile (DHP-1). Participants completed the SF-36 and the DHP-) before the intervention from the original cluster RCT took place.

The SF-36 is a 36-item questionnaire which assesses health status, encompassing nine dimensions: physical functioning (10 items), limitations due to physical difficulties (role physical, four items), bodily pain (two items), general health (six items), vitality (four items), social functioning (two items), limitations due to emotional difficulties (role emotional, three items), mental health (five items), and health change (one item). Items are rated on a 2–6-point Likert scales. For each of these dimensions, scores were transformed to a scale ranging from 0 to 100, with higher scores indicating better health (29).

The DHP-1 is a 32-item questionnaire which assesses the impact of diabetes on psychosocial functioning. It comprises three dimensions: psychological distress (14 items, e.g., dysphoric mood, feelings of hopelessness), barriers to activity (13 items on activity restriction due to diabetes, e.g., avoiding going out when blood glucose is on the low side) and disinhibited eating (five items measuring response of emotional arousal and external food cues, e.g., lack of eating restraint). Items are rated on a 4-point Likert scale ranging from 0 ("never" or "not at all") to 3 ("very often" or "very much") (30). For each dimension, scores were transformed to a scale ranging from 0 to 100, where 100 indicates no dysfunction.

Analysis

Since missing data may lead to imprecision and biased results, we performed multiple imputation to handle missing data. Characteristics of participants with any missing value on the SF-36 or DHP-1, and those with complete data are shown in

Supplementary File 1, suggesting data are missing at random. Under the missing at random assumption, we created 10 imputed datasets with 70 iterations (see **Supplementary File 2** for the full imputation strategy). Rubin's rule was used to combine the multiple imputed estimates (31).

Differences between participants using only OHA and those using insulin (with or without OHA) were analyzed with t-test for continuous variables and χ^2 test for categorical variables. To investigate the patient-reported outcomes (SF-36 and DHP) we used linear mixed models with random intercepts per general practice to correct for clustering at practice level. First, a univariable analysis was performed in which only the patient-reported outcome and insulin use were taken into account. Afterwards we conducted multivariable analyses corrected for confounders. We pre-specified the following confounders: sex, age, diabetes duration, ethnicity, level of education, microvascular and macrovascular complications, BMI, SBP, HbA1c, and LDL-cholesterol. Sex, ethnicity, microvascular, and macrovascular complications were entered as binary variables; level of education as a categorial variable. Age, diabetes duration, BMI, SBP, HbA1c, and LDL-cholesterol were entered as continuous variables. Assumptions of the models were assessed in each imputed dataset using residual analysis. A p-value <0.05 was considered to be statistically significant. The p-values from the multivariable analysis were corrected for multiple comparisons by the Holm-Bonferroni Sequential Correction method (32). We used RStudio version 1.0.143 for the statistical analyses and mice 3.3.0 package for multiple imputation (31).

RESULTS

Of the 3,979 eligible participants, 548 refused to participate and 40 failed to participate for unknown reasons. The final study population therefore consisted of 3,391 participants. Of these 3,391 participants, 597 did not use glucose lowering medication and were excluded (see **Figure 1**). The remaining 2,794 participants had 34.2% missing values with regard to the outcomes, distributed among 48.4% of the participants, and 6.4% missing values concerning the confounders, distributed among 52.7% of the participants.

The majority of the participants on insulin therapy (n = 212) also used OHA (59.4%); 86 out of 212 patients (40.6%) did not use OHA. **Table 1** shows that patients who received insulin therapy had a longer diabetes duration, were more often women, and had more microvascular and macrovascular complications. Glycemic control was worse and BMI was higher in insulin-treated patients. **Supplementary File 3** gives an overview of the types of insulin used by the study population. More than half of our population used pre-mixed insulin (see **Supplementary File 3**).

Table 2 shows the results of both the univariable and the multivariable linear mixed models. In the univariable analyses, before adjustment for confounding, individuals treated with insulin (with or without OHA) scored statistically significantly worse on nearly all SF-36 and DHP scales. In the univariable analyses, there were no associations between insulin use and health change (SF-36) and disinhibited eating (DHP). After adjustment for confounding, individuals treated with insulin (with or without OHA) reported statistically significantly worse outcomes on six scales of the SF-36 questionnaire: physical functioning, social functioning, role physical, mental health, vitality and general health. With regard to the DHP, patients treated with insulin (with or without OHA) scored statistically significantly lower on DHP barriers to activity and DHP psychological distress (i.e., more dysfunction). Residual analysis showed no deviation from distributional assumptions and no heteroscedasticity. After correcting for multiple comparisons, the associations between insulin use, and vitality and general health (SF-36), and those between insulin use and barriers to activity and psychological distress (DHP) remained statistically significant (**Table 2**).

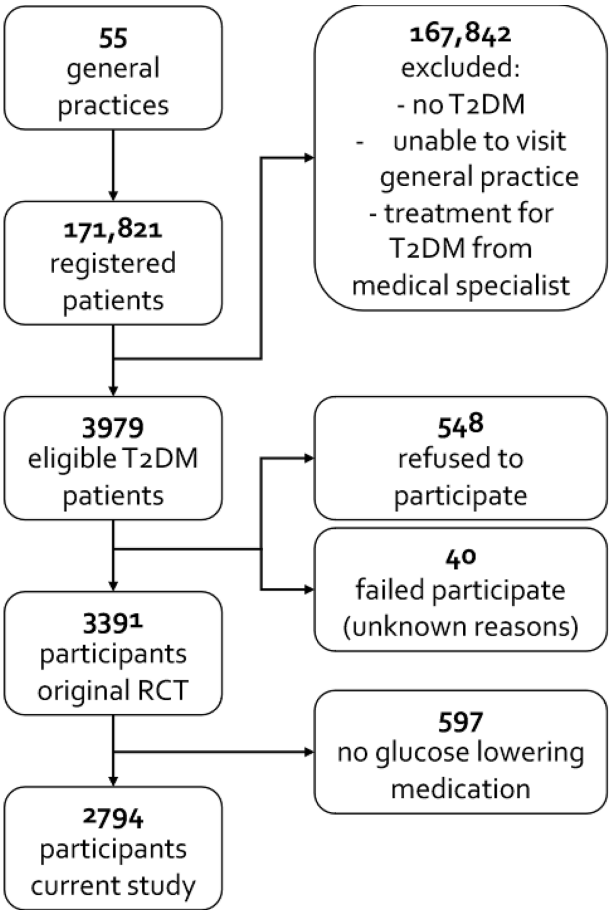

FIGURE 1 | Flowchart. T2DM, type 2 diabetes mellitus.

DISCUSSION

Summary of Findings

Individuals with T2DM who use insulin reported worse vitality and general health, more psychological distress and more

TABLE 1 | Characteristics of type 2 diabetes patients treated in primary care using only oral antihyperglycemic agents or using insulin with or without oral antihyperglycemic agents.

	OHA only (n = 2582)	Insulin ± OHA (n = 212)	P-value
Sex: female (n (%))	1297 (50.2)	123 (58.0)	0.035
Age (years)	65.7 (11.1)	67.1 (11.1)	0.064
Duration diabetes (years)	5.6 (5.9)	11.0 (6.7)	<0.001
Ethnicity: western European (n (%))	2,399 (92.9)	201 (94.8)	0.321
Education (n (%))			0.060
Low	1,731 (67.0)	143 (67.5)	
Medium	624 (24.2)	55 (25.9)	
High	227 (8.8)	14 (6.6)	
Microvascular complications (n (%))	903 (35.0)	107 (50.5)	<0.001
Macrovascular complications (n (%))	441 (17.1)	49 (23.1)	0.033
Body mass index (kg/m^2)	30.0 (5.3)	30.9 (5.4)	0.031
Systolic blood pressure (mmHg)	148.8 (21.4)	149.4 (21.6)	0.690
HbA1c (mmol/mol)	54.0 (12.8)	62.1 (12.9)	<0.001
HbA1c (%)	7.09 (1.17)	7.83 (1.18)	
LDL cholesterol (mmol/l)	2.72 (0.94)	2.63 (0.94)	0.167

All data are given in mean (SD), unless stated otherwise.
HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; n, number; OHA, oral antihyperglycemic agents; SD, standard deviation.

TABLE 2 | Patient reported outcomes of type 2 diabetes patients using only oral antihyperglycemic agents or using insulin with or without oral antihyperglycemic agents.

	OHA only (SD) (n = 2582)	Insulin ± OHA (SD) (n = 212)	Unadjusted difference (95% CI)	P-value	Adjusted difference (95% CI)*	P-value	Adjusted p-value**
Short Form (SF)-36 (scale ranging from 0 to 100, with higher scores indicating better health)							
Physical functioning	70.4 (37.0)	61.5 (33.3)	-8.9 (-13.4 to -4.3)	<0.001	-5.7 (-10.0 to -1.3)	0.011	0.076
Social functioning	82.4 (39.5)	75.7 (32.9)	-6.7 (-11.2 to -2.2)	0.003	-5.8 (-10.4 to -1.1)	0.016	0.095
Role physical	69.0 (56.6)	57.3 (52.2)	-11.7 (-19.0 to -4.5)	0.002	-8.6 (-15.8 to -1.3)	0.021	0.104
Role emotional	78.0 (55.0)	68.9 (53.3)	-9.2 (-16.7 to -1.7)	0.018	-6.4 (-14.4 to 1.7)	0.123	0.435
Mental health	75.7 (31.6)	70.2 (23.0)	-5.5 (-8.5 to -2.5)	<0.001	-4.5 (-7.8 to -1.3)	0.006	0.052
Vitality	62.4 (29.8)	55.0 (27.5)	-7.4 (-11.2 to -3.6)	<0.001	-5.7 (-9.5 to -2.0)	0.003	0.033
Bodily pain	78.4 (40.6)	72.8 (36.2)	-5.6 (-10.4 to -0.8)	0.024	-4.0 (-8.8 to 0.9)	0.109	0.435
General health	59.5 (33.1)	53.3 (24.5)	-6.2 (-9.4 to -2.9)	<0.001	-4.8 (-8.1 to -1.5)	0.005	0.043
Health change	50.2 (30.8)	48.9 (26.3)	-1.3 (-4.9 to 2.3)	0.477	0.3 (-3.4 to 3.9)	0.892	1.000
Diabetes Health Profile (DHP) (scale ranging from 0 to 100, where 100 indicates no dysfunction)							
Barriers to activity	86.8 (33.1)	78.6 (19.8)	-8.2 (-10.8 to -5.7)	<0.001	-7.2 (-9.9 to -4.6)	<0.001	<0.001
Psychological distress	87.9 (21.0)	84.1 (13.9)	-3.8 (-5.6 to -1.9)	<0.001	-3.7 (-5.8 to -1.7)	<0.001	0.004
Disinhibited eating	72.2 (30.2)	70.3 (28.2)	-1.9 (-5.7 to 1.9)	0.339	-1.0 (-4.9 to 3.0)	0.629	1.000

CI, confidence interval; n, number; OHA, oral antihyperglycemic agents; SD, standard deviation.
**Adjusted for: sex, age, diabetes duration, ethnicity, level of education, microvascular and macrovascular complications, BMI, systolic blood pressure, HbA1c, and LDL-cholesterol.*
***P-values from multivariable analysis adjusted for multiple comparisons by the Holm-Bonferroni Sequential Correction method.*

barriers to activity in comparison with patients using only OHA, independent of sex, age, diabetes duration, ethnicity, level of education, microvascular and macrovascular complications, BMI, systolic blood pressure, HbA1c, and LDL-cholesterol.

Implications of Findings

With regard to the SF-36, the statistically significant differences can be considered clinically relevant, when the often suggested minimal important differences (MID) ranging from 3–5 points are taken into account (33). Taking the MIDs for the DHP-18 (developed from the DHP-1) into account, only the difference for barriers to activity was both statistically significant and clinically relevant (34).

Although we cannot ascertain a causal relationship between insulin use, and health status and psychosocial functioning, the findings of this study imply that it is important to make a well-considered decision about the initiation of insulin. Further, it is recommended to include patient-reported outcome measures in future trials comparing glucose lowering medication, insulin or different insulin regimens, keeping the duration of insulin therapy for the latter in mind.

Comparison With Existing Literature

Previous studies with positive or neutral effects on patient-reported outcomes were conducted in the context of starting insulin therapy rather than continued use (9–22). Most studies were of observational nature – either cross-sectional or longitudinal (both retrospective and prospective studies). These observational studies always face the difficulty of dealing with confounding factors and questions about causal inference. For cross-sectional studies like ours, making causal inferences is even harder since there is no longitudinal aspect. An RCT deals with confounding factors – both measured and unmeasured confounding. Unfortunately, most RCTs have a short follow-up

duration, which makes it impossible to make inferences on long term effects. Only one RCT specifically investigated quality of life after insulin initiation (11). The authors of this RCT randomized T2DM with poor glycemic control into one group with early insulin initiation and one group with adjustment of OHA. They found that quality of life improved in both the group of groups, but significantly more in the insulin group. The follow-up duration in this study was only 24 weeks. The association of the start of insulin therapy with improved health status and psychosocial functioning might be the effect of the diminishing symptoms of hyperglycemia. Our study was conducted in a different context, in a mixture of individuals who recently started using insulin and those using it for a longer period of time. We were unable to take duration of insulin therapy into account, but we adjusted for diabetes duration. Longer disease duration may be associated with a higher number and more serious diabetes-related complications and with longer insulin use. Multiple complications are important determinants of impaired health status, which underpins the importance of taking them into account (35). After adjustment for the occurrence of complications, most patient-reported outcomes remained worse in the insulin group, which makes our findings more robust.

Comparable to our study, two other studies conducted in the same context showed negative effects on perceived health status. A Dutch primary care-based study of 1,348 T2DM patients found that insulin therapy was associated with a worse health state (23). The other study found that individuals on insulin therapy with good metabolic control had a lower quality of life compared to those on OHA with poor metabolic control (25). As in our study, the duration of insulin therapy was unknown in these studies.

Two Australian cohort studies by the same authors studied the association between insulin use and health status cross-sectionally as well as longitudinally (both four years follow-up, in 1,290 (24) and 930 (26) T2DM patients). Both studies found that at baseline the insulin-treated individuals had a worse health status compared to non-insulin treated patients, and that the initiation of insulin therapy did not alter health status (subsamples of 38 (24) and 85 (26) patients). The most recent study also found that among those on stable insulin therapy, health status was lowest at all time-points during follow-up (26). The authors conclude that the burden of disease – diabetes duration, worse glycemic control, and higher number of complications – rather than insulin use determines health status (26). Interestingly, we adjusted for these factors and still found a lower health status among those using insulin.

Strengths and Limitations

Our large sample size is a strength of the study. Due to the cross-sectional design, no causal associations between insulin use and patient-reported outcomes can be assumed. The participating practices were representative for primary care centers in the Netherlands, and the same applies to our study population. However the practices were self-selected, which might reflect special interest in improving diabetes care; extra emphasis on diabetes care might cause better results on patient-reported outcomes (27). Our participants were all treated in primary care. In the Netherlands, patients are referred to an internal medicine specialist or endocrinologist in secondary care when adequate glycemic control cannot be achieved or when problems occur that are beyond the scope of the primary care physician. Since in general, patients treated in secondary care have a higher disease burden, the results of our study may not be fully generalizable to patients treated in secondary care.

Since individuals on insulin therapy might have a different stage of disease and disease severity, we corrected for multiple confounders. Unfortunately, data on duration of insulin therapy were not available, while it could be an important effect modifier. We considered including an interaction term for diabetes duration * insulin use, as a proxy for insulin therapy duration. However, as this interaction term would not have been able to differentiate between an individual with a diabetes duration of ten years who started insulin 3 months ago, and an individual with a diabetes duration of ten years who started insulin 9 years ago, we decided this could lead to bias, and hence omitted this interaction. Moreover, we were unable to take type of insulin regiment into account. While type of insulin was registered, we could not differentiate between basal, mix of basal-prandial insulin schemes with sufficient certainty. This was unfortunate, since type of insulin regimen appears to influence quality of life.(Polonsky 2014) Also, novel OHA, e.g., SGLT2 inhibitors, and other agents, e.g., GLP-1 agonists, have emerged since the data were collected. These novel agents might influence the psychological well-being of individuals with T2DM. For example, semaglutide compared with insulin glargine statistically significantly improved the role-emotional and general health domains of the SF-36 but not on other SF-36 domains (36). Nevertheless, even nowadays millions of people all over the world start with insulin therapy instead of GLP-1 receptor agonists or SGLT2 inhibitors. This makes our current study relevant, despite the older data. Moreover, acceptability of insulin therapy may have changed too since the data were collected. We have not analyzed the outcomes for the three groups, i.e., (1) insulin only (2) OHA only and (3) insulin+OHA for two main reasons. In the Dutch Guideline for General Practitioners, as in many other (inter)national guidelines, it is advised to continue OHA when initiating insulin therapy. This means that the "insulin only group" is a group that either does not receive the appropriate therapy, or is a group for which the guideline is abandoned on purpose. In the latter case, reasons to do so are severe side effects from OHA, or chronic kidney disease. Comparing this group to, e.g., the "insulin+OHA group", there are many unmeasured confounders for which we cannot correct with the available data. Functional decline, distress, and depression are strongly associated with exposure level. We cannot ignore the exposure level, even if it is a cross-sectional study. However, we decided not to use depression as a confounder, since it is even more likely that it is an intermediate factor in the causal pathway. Lastly, residual or unmeasured confounding might still be present.

Conclusion

While shortly after insulin initiation health status may be uninfluenced or positively influenced, we found that in the real-life context, in a mixture of individuals who recently

initiated insulin and those using insulin for a longer period of time, vitality, general health, and barriers to activity were worse in those on insulin therapy. Although the causality of this association has not been established, our findings once again stress the need to balance the beneficial effects of insulin therapy against the possible negative effects on patient-important outcomes in daily practice.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data sharing upon request. Requests to access these datasets should be directed to r.c.vos@lumc.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The University Medical Center Utrecht ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GR and MA designed the current study. Data were collected by FC and analyzed by AMB. Both MA and AMB wrote the manuscript. All authors contributed to the interpretation of data and to the discussion, reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.573235/full#supplementary-material

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The Quebec Diabetes Empowerment Group Program: Program Description and Considerations Regarding Feasibility and Acceptability of Implementation in Primary Health Care Settings

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Introduction: Diabetes is a highly prevalent chronic disease that frequently coexists with other medical conditions and implies a high burden for patients and the healthcare system. Clinicians currently are challenged to provide effective interventions that are both multidisciplinary and empower patient self-care. The Diabetes Empowerment Group Program (DEGP) was developed with the aims of fostering patient engagement in diabetes self-care through the lens of empowerment and to support the empowerment of patients with diabetes by providing multidisciplinary group-based care. This research's objectives were to: (1) develop a comprehensive description of the DEGP for potential adopters, and (2) explore the factors influencing the feasibility and acceptability of implementing it in other healthcare settings in Montreal.

Methods: A qualitative descriptive study was conducted, following a participatory approach. Data were obtained from: (1) semi-structured interviews with 14 patients who participated in the pilot program; (2) from semi-structured group interviews with patient partners, healthcare professionals, and other stakeholders from 4 Montreal family medicine groups, and (3) discussions among the participatory research team during various knowledge translation activities. Inductive content analysis of the data was performed.

Results: The DEGP identified seven key elements: medical visit, continuity of care, group-based dynamics, multi-disciplinarity, clinician facilitation, patient-centered agenda, and a theoretical framework of empowerment. The content and organization of the group visits were conceived to address each of these four domains. The empowerment framework comprises four domains of self-care: emotional (attitude), cognitive (knowledge), behavioral (skills), and relational (relatedness). Factors impacting the feasibility and acceptability of implementing the DEGP in other primary care settings were identified.

Discussion: The DEGP fits within the discourse around the need for more patient-centered programs for people living with diabetes, following a more comprehensive empowerment model. This research could facilitate the development or adaptation of similar programs in other settings.

Keywords: diabetes mellitus, family practice, patient-centered care, qualitative research & analysis, self-care, diabetes knowledge, self-efficacy

INTRODUCTION

Diabetes Mellitus is among the most prevalent chronic diseases and represents a major burden for health care systems, primary health care services, and patients. It is estimated that 3.4 million people in Canada (9.3% of the population) live with diabetes (1). Furthermore, 22% of the population is estimated to be prediabetic (2). Given that almost 80% of diabetes care occurs at the primary care level, adequate diabetes management in the primary care setting is essential (3).

Diabetes management and lifestyle changes recommended in the Diabetes Canada 2018 Clinical Practice Guidelines may be difficult for many patients. Furthermore, the complexity of managing diabetes can be overwhelming for patients and primary care providers. In Canada, medical care for people with diabetes generally comprises individual physician visits, with referral to specialists and allied professionals as needed. In accordance with current initiatives to foster evidence-based and patient-centered medicine, Diabetes Canada recommends a multidisciplinary approach that includes physicians, nurse practitioners, nurses, pharmacists, dieticians, and psychological health workers to support individuals managing their diabetes (3). Evidence also suggests that diabetes management is improved when patients are empowered and engaged in self-care (4, 5). Therefore, two key elements can be identified in this expert recommendation: (1) the provision of care by a multidisciplinary clinical group and (2) increase a person's control over his/her medical condition.

In response to these diabetes care needs, The Diabetes Empowerment Group Program (DEGP) was developed and piloted at Santé Kildare, a Family Medicine Group (FMG) in Montreal, Canada. The pilot aimed to assess the feasibility of the DEGP and refine it using participant feedback. Three cohorts of 6–8 patients (21 in total) living with diabetes (type 1 or type 2) or pre-diabetes participated in 6 sessions over the course of 3 months. It was conceived as a collaborative multidisciplinary patient-centered program that aims to stimulate patient empowerment and enable the development of a community of individuals who support one another.

Effective knowledge translation strategies are needed to support its implementation throughout Montreal. Knowledge translation is reinforced by using a robust, scientific process to develop a detailed description of the intervention that speaks to potential adopters and identification of the factors that impact its implementation. Two of these factors include the feasibility and acceptability of implementing the intervention at other sites and by other stakeholders.

This research's objectives were to: (1) develop a comprehensive description of the DEGP for potential adopters, and (2) explore the factors influencing the feasibility and acceptability of implementing it in other healthcare settings in Montreal. The knowledge generated by this research is expected to support the implementation and adaptation of similar patient-centered diabetes empowerment programs in other healthcare settings.

METHODS

Study Design

A qualitative descriptive study design (6) with a participatory research approach (7) was used for both study objectives. A participatory approach was used whereby knowledge users' inclusion in the research process supported the generation of relevant and meaningful knowledge, and the translation of this knowledge into practice. Collaboration between researchers and non-academic stakeholders supports the generation of more meaningful knowledge and more effective knowledge translation (7, 8). The research team consisted of: three researchers from the Department of Family Medicine of McGill University, a family physician (DEGP physician), a nurse practitioner (DEGP nurse), and three patient partners. The three patient partners had been participants in the DEGP pilot (9). All members of the research team collaborated throughout the entire research process, including: the definition of objectives, data collection, data analysis, and dissemination of results (10).

Data Collection

Data collection took place between 2015 and 2017. Data were obtained from three main sources. The description of the DEGP was informed by: semi-structured interviews were conducted with patients who had participated in the 2015 DEGP pilot; and data generated by the research team's ongoing reflection on the program during the development of knowledge translation tools. Perceptions regarding the feasibility and acceptability were identified using group interviews with patient partners and healthcare providers.

Description of the DEGP

Regarding semi-structured interviews, all 21 patients who had participated in the pilot were approached to participate in interviews. Fourteen of these patients agreed to participate. The interview guide was developed inductively by the research team. Questions posed to patients emphasized their perceptions of the program and recommendations for improvement. Interviews were recorded and transcribed.

The research team's reflection also informed the program's description throughout the development of knowledge translation tools such as logic models, program implementation guides, manuscript preparation, patient recruitment brochure creation, and scientific conference presentation. The DEGP physician, the DEGP nurse, and the three patient partners had been involved in the pilot. As the research was conducted, more detailed reflections on the program came to light. These reflections were documented in personal notes and meeting minutes.

Exploration of Feasibility and Acceptability

Factors influencing the feasibility and acceptability of implementing a similar or adapted group program were elicited from 3 group interviews. The group interview discussions included patient partners, healthcare providers (physicians and nurses), allied health professionals (kinesiologist, dietician, pharmacist) and administrators (clinic managers and clinic coordinators, quality improvement coordinator) from 4 primary care family medicine clinics in Montreal (Santé Kildare, Herzl Family Practice Center, CLSC Cote-des-Neiges, CLSC Parc-Extension). One of three patient partners participated in each of the group interviews. The group interview guide was developed by the research team using a hybrid approach. The questions emphasized the feasibility and acceptability of implementing the DEGP in different settings. The Diffusion of Innovations framework informed the initial questions (11). The research team then added additional questions to address the research objectives and elements specific to the DEGP. The DEGP physician facilitated the group interviews, and two observers took detailed notes. The interviews were audio-recorded and transcribed.

Analysis

Inductive thematic analysis (12) was performed on the patient interview transcripts and meeting notes to draw out key elements of the DEGP. A trained research assistant identified initial codes representing sub-themes. The research team generated additional sub-themes. The themes and sub-themes and were used in the construction of a description of the DEGP. This description led to the generation of a logic model to explain desired outcomes of interest to various stakeholders.

Considerations for implementation in other settings was coded using a hybrid approach (13) (deductive and inductive), using Greenhalgh et al.'s Diffusion of Innovations in Health Organizations framework (11) to establish broad themes and assign emergent sub-themes to these. The research assistant identified initial codes representing sub-themes. The sub-themes were discussed, validated, categorized, and interpreted by the research team. The research team discussed these themes and sub-themes in relation to Greenhalgh et al.'s Diffusion of Innovations in Health Organizations framework. This led to the description of acceptability and transferability of the DEGP in other Montreal settings presented below.

Ethics

Ethics approval was obtained from the McGill University Faculty of Medicine Institutional Review Board. All research team members and all participants in the individual and group interviews provided written consent before participating.

RESULTS

Description of the Diabetes Empowerment Group Program (DEGP)

The DEGP was conceived as a series of group medical visits with a fixed cohort of 6–8 patients. Meetings take place twice a month for the first 8 visits, then for one year thereafter (or longer if there is interest) meetings are held on a monthly basis. The group is facilitated by a family physician or nurse practitioner and another allied health professional. A broad theme is discussed at each visit (**Table 1**). The sessions, however, are open-ended and flexible in order to promote participation and pertinent discussion. The facilitator's role is key to help guide conversation and provide factual information as needed. The purpose of discussions is to share experiences, increase knowledge, teach skills, foster mutual support, and promote a greater sense of control over one's health.

Reflection and discussion of the DEGP contributed to the identification of seven key principles that characterize this intervention. These elements comprise: (1) medical visit, (2) continuity of care, (3) group-based dynamic, (4) multidisciplinary collaborative team, (5) facilitation by clinicians, (6) patient-centered agenda, and (7) based on an empowerment framework. Those interested in implementing this intervention should address each element and consider how they may be adapted according to their setting's resources and context. The following briefly describes how each principle was considered a key advantage of the intervention compared to standard diabetes medical care in the pilot program at Sante Kildare.

Medical Visit

Each of the DEGP meetings is considered a formal medical visit. In the pilot program, the DEGP involved up to 8 patients at once. An advantage of this program is that clinicians can spend as much time with the group as they would in individual visits, except the time spent with each patient is increased.

Continuity of Care

The DEGP involves a fixed cohort of patients and clinician facilitators. Compared to a drop-in approach, this program better ensures continuity with healthcare providers, facilitates a cumulative curriculum, and fosters social support networks among patients.

Group-Based Dynamic

Group visits have been recognized as a powerful tool for growth and change (14–16). They facilitate exposure to multiple perspectives, mutual support, encouragement, and feedback in a safe environment. Groups enhance self-management education and skills-building. Group visits also reinforce messages that are received in individual visits. Modeling, peer problem solving, and

TABLE 1 | Examples of discussion topics by DEGP visit.

Visit/Theme (2 h)	Discussion Topics	Possible Tools
Group visit 1 - Introduction to the program Facilitators: Family Physician and Nurse	• Introductions • Structure of the program • Confidentiality • Empowerment construct • Personal experience living with diabetes • Beliefs and values related to diabetes	• Ice breakers • Empowerment framework illustration • Describe your diabetes path • Write down fears and challenges related to diabetes
Group visit 2 - Understanding Diabetes Facilitators: Family Physician and Nurse	• What is diabetes? • "Pathophysiology" of my disease • Symptoms of hyperglycemia and hypoglycemia • Checking my sugars	• Illustrations of organs and body systems • Glucometer demonstration • Tools for tracking sugars • Write down challenges related to hypo or hyper-glycemia
Group visit 3 - Lifestyle habits (part 1): food and nutrition Facilitators: Family Physician, Nurse and **Dietician**	What is safe to eat, what to avoid and why?	• Portion sizing • Balanced plate • Food labels • Field trip to grocery store • Online resources • Collective kitchen • Restaurant choices
Group visit 4 - Medications Facilitators: Family Physician, Nurse and **Pharmacist**	• How my medications work • Side effects • Medication compliance	• Resources • Illustrations and videos of medication action • My diabetes journal
Group visit 5 - Foot care Facilitators: Family Physician, Nurse and **Podiatrist**	• My feet and their importance • Foot health • What does a podiatrist do?	• Individual foot exam • Shoe exams • Resource to buy appropriate footwear
Group visit 6 - Lifestyle habits (part 2): physical activity and exercise Facilitators: Family Physician, Nurse and **Exercise specialist** or **physical trainer**	• Physical activity and exercise • Consequences of sedentary lifestyle • Making exercise a regular part of my day	• Podometer • Community resources • Demonstrating/teaching exercises • Exercise prescription • Online resources

social support may also reduce perceived barriers to change in attitudes and behaviors.

Multidisciplinary Collaborative Team

Comprehensive care involves different health professionals working together in a mutually respectful manner, acknowledging the value of each other's discipline-specific skills, training, attributes, and contribution to diabetes care. During the pilot project, the multidisciplinary team consisted of a physician, nurse, pharmacist, nutritionist, podiatrist, and health coach. Other professionals may be invited based on the theme of the discussion.

Facilitation by Clinicians

The clinician facilitates the discussion, as opposed to lecturing. The facilitators draw on their experience using counseling skills, such as active listening and motivational interviewing, to encourage open and collaborative discussion. The facilitators ensure that every participant is engaged in discussion by asking open-ended questions, gently inviting less-talkative participants to contribute, and steering the conversation when one topic or one individual dominates the discussion.

Patient-Centered Agenda

Although each visit has a general theme, it is important that the information discussed be of interest and relevant to the participants (**Table 1**: Examples of discussion topics by DEGP visit). In order to maintain a patient-centered agenda, guest presenters and facilitators adjust the content of the discussion based on questions and concerns raised by participants. No formal, didactic presentation is given at each visit; however, the presenter may prepare topics of discussion or activities that may (or may not) be used depending on patient interest. This is often more enjoyable and requires preparation for the guest presenters.

Content Based on Empowerment Framework

The concept of empowerment has been proposed as a framework for engaging patients in self-care (17). The DEGP was developed around the theoretical framework of psychological empowerment, developed by Zimmerman (18) and adapted by Christens (19), comprising four components: attitude, knowledge, behavior, and relatedness.

Attitude includes the individuals' beliefs about themselves, including self-efficacy, perceived competence and control, and motivation. *Knowledge* refers to an individual's understanding of

their community and includes critical awareness, understanding of causal factors, skills, and resource utilization. *Behavior* refers to the actions they take to effect change, such as: community involvement, skills development, organizational participation, and coping behaviors. Finally, *relatedness* refers to the psychological aspects of interpersonal interaction that underlie effective psychological empowerment. These include: collaborative competence, bridging social divisions, facilitating others' empowerment, mobilizing networks, and passing on a legacy.

Additional Knowledge Translation Activities Supporting the Description of the DGEP

Understanding of the DEGP, in terms of its constituent elements and more nuanced features, was further refined throughout the knowledge translation (diffusion and dissemination) processes. These activities helped develop a more elaborate description of the intervention as they provided opportunities for the research partners to reflect collaboratively with particular groups of stakeholders in mind.

First, the research team developed a logic model (**Table 2**). The logic model delineated four key values at the foundation of the program, each targeting different stakeholder groups: patient autonomy (patients), interdisciplinarity (clinicians), equity (administrators, community organizers, and decision-makers), and quality assurance (researchers). Participants representing the different stakeholder groups were involved throughout the participatory research process to ensure that the program and/or knowledge developed through the research addressed these groups' specific needs. In the logic model, different outputs were conceived for each group, based on the needs they identified throughout the process.

TABLE 2 | Proposed model guiding the knowledge translation of the DEGP.

Rationale	To provide a health care service that will improve patients' control over their diabetes.		
Values	Patient autonomy	Interdisciplinarity	Health equity and quality assurance
Target audience	Patients	Clinicians	Administrators, community organizations, and other decision-makers
Primary objective	To offer a health care service that will improve patients' sense of empowerment in relation to their diabetes.		
Secondary objectives	To ensure that the program meets the needs of patients with diabetes and diabetes care providers	To ensure that patients, clinicians, and other stakeholders are involved in the development and implementation, and evaluation of the program	To ensure that the program is feasible, integrated, and cost effective in our health care system
Intervention	Participatory research on the Diabetes Empowerment Group Program and development of knowledge translation outputs		
Knowledge translation activities	Collaborative development of: DEGP content Recruitment material Empowerment assessment tool (MEA-D) Facilitation of DEGP sessions	Collaborative development of: DEGP content Training material Program evaluation (i.e., MEA-D, clinical outcomes) Facilitation of DEGP sessions	Participate in: Aligning program objectives with institutional and health policy objectives Program evaluation (i.e., definition of clinical outcomes, cost effectiveness, feasibility)
Resources	Patient partner and participatory research support Remuneration for patient partnership	Participatory research and quality improvement support Interdisciplinary partners Flexibility regarding schedules and care delivery	Identification of population needs to improve diabetes outcomes Identification of resources available to allocate toward diabetes care programs (funding for material and human resources) Administrative support for the DEGP Research support for program evaluation
Outputs	Recruitment strategies among peers Empowerment assessment tool (MEA-D) Social and civic mobilization of patient partners	Implementation guide Empowerment assessment tool (MEA-D) Evidence of clinical markers of diabetes control Enhanced culture of collaboration with patients and other stakeholders	Evidence of improved diabetes management and population engagement measures Evidence of satisfaction among patients and health care providers Enhanced culture of collaboration with patients, clinicians and researchers

Through their collaborative involvement in the research, patient partners would develop recruitment material; clinicians would develop recruitment, training material, and implementation guides; administrators would provide resources to support the program's implementation and evaluation; researchers would help ensure the knowledge generation processes followed rigorous standards.

Second, in support of the evaluation of the DEGP, the research team developed and validated the McGill Empowerment Assessment - Diabetes (20). This measure of empowerment related to diabetes self-care addresses the four domains of Christens' (19) empowerment framework: attitude, emotion, behavior, and relatedness. In their development of this assessment tool, the team was prompted to reflect on the various theoretical dimensions of empowerment and how the DEGP addresses them.

Third, the patient partners involved in the program and research project developed recruitment material targeting people living with diabetes from the community. Specifically, the patient partners worked with a graphic designer to develop a recruitment brochure. This activity deepened the research team's understanding of what the program means to people living with diabetes. The reflection informing this brochure led to the patient partners co-authoring a commentary on their participation in the DEGP and this research (9).

Finally, various aspects and stages of this research were presented at scientific conferences or described in scientific manuscripts. These helped tailor messages to clinicians and researchers. They drew out the lessons learned from having developed and implemented the DEGP, and having conducted collaborative, practice-based research involving researchers, clinicians, and patient partners.

Considerations of Acceptability and Feasibility

Several key considerations emerged from the discussions regarding the acceptability and feasibility of implementing or adapting the DEGP (**Table 3**). Informed by Greenhalgh's Diffusion of Innovations framework (11), these considerations are categorized according to: characteristics of the DEGP, system characteristics, setting (health institution) characteristics, and adopter/participant (patient, clinician, and administrator) characteristics. These are elaborated below.

Characteristics of the DEGP

One of the key factors facilitating DEGP's acceptability is its alignment with best practice recommendations. The program follows a multidisciplinary approach, as recommended by Diabetes Canada, and emphasizes the patients' role in self-care.

The program was also developed according to a relatively comprehensive empowerment framework, comprising four dimensions: knowledge, skills, attitudes, and relatedness. The relational aspect was highlighted as one of the major advantages of the DEGP over other offered diabetes care services.

> *I liked when you were talking about empowerment. To me, the biggest barriers are the guidelines. This is somebody else's rule… and I spend all the... I don't look at the actual person; I look at a whole bunch of numbers. And I think it's actually harmful. Like you say, the disease is theirs – or the reality is theirs, and their life is theirs, and they have to… This has to be part of their life, or they're not going to continue it. There has to be something in it for them. If they are going to tell you what are the costs of whatever you are asking or suggesting to them – I think they are more likely to do this in a group. (Family physician)*

This program provides a dynamic space to learn and share from each other, where patients' priorities and concerns are taken into account.

> *It's so different than in individual appointments; and hearing of everybody's different perspective… And we had time. So these conversations didn't have to be blunted and really short. And I think probably some of those more complex ideas, about being an individual and having to manage your diabetes within your life that's different than someone else's life - there is just more space for it… (Nurse practitioner)*

System Characteristics

One of the major perceived barriers to implementing the DEGP was the existence of government-mandated chronic care programs targeting persons with diabetes. The interview subjects expressed reservations about investing additional resources or adapting current resources to develop and implement innovations such as DGEP.

> *I think it would be a shame if we weren't able to take advantage of some of the great things that have come out of your program, but how to incorporate it into what exists already, in terms of a focus on what components of empowerment – how can we introduce that into some of the structure of the program we have already? How can we introduce that into the classes? How can we learn from that, how can we make the program better? (Continuous quality improvement Coordinator)*

Governments differ according to their preference for centralized or decentralized decision-making structures. More centralized power tends to leave less room for deviation or innovation, and health services may, as a consequence, fall short of meeting the needs of particular populations (21, 22). The Quebec Ministry of Health had recently enacted changes to the governance structure of regional health authorities and family medicine groups' operations, which left clinicians feeling overwhelmed.

> *Right now there are so many changes, and people are a bit overwhelmed with everything. So getting something new right now—anything, even if it's a wonderful idea—I'm not sure how it will get received. The people, we know… in the media, everybody says… I could feel it from the people I worked with. It's like… "Not another thing, please!" - (Academic family medicine group Program Director)*

Changes in legislation can shift priorities toward different activities, whereby health care providers and patients must negotiate new avenues for addressing their own priorities.

TABLE 3 | Considerations for feasibility and acceptability of implementing the DEGP.

Themes	Details	Considerations
Innovation characteristics		
	Based on empowerment framework	Ability to develop activities that promote enhanced knowledge, skills, attitudes, and relatedness among patients.
	Aligns with best practice recommendations	Multidisciplinary services: are patient centered, promote self-care and are situated within the Patient Medical Home
System characeristics		
	System readiness for innovation	• Existence of similar programs and perceptions about the quality of services provided • Culture of program assessment, quality improvement, and innovation is fostered • Leadership, expertise, and change management support
	Sociopolitical context	• Health care user (patient) power and influence in health care services • Centralization vs. decentralized health care policy • Incentives and mandates align with DGEP objectives
	Knowledge translation	Diffusion and dissemination of experiences and new knowledge through institutional and primary care research networks
	Expectations regarding health professionals' roles	Flexibility regarding health professionals' (physicians, nurses, and other allied health professionals) domain of practice and remuneration
	Agility responding to populational needs	• Readiness and capacity of healthcare system to respond to populational needs and gaps in current diabetes services: • Decision making devolves to front line teams • Interventions conceived around populational needs • Strong primary care health care foundation and advocacy
Setting characteristics		
	Capacity to allocate material and human resources	• Flexibility regarding clinician schedules • Administrative support • Available Space for group meetings
	Culture of innovation	• Staff's training and experience with innovation and implementation • Identification and promotion of clinical change champions and early adopter of practice changes
	Multidisciplinary health professional team	• Promotion of patients' sense of belonging within Patient Medical Home • Links to community services and ability to collaborate and remunerate community professionals
Adopters/participants		
Patients		
	Perceived value	• Dissatisfaction with existing services • Perceived value of group medical visits • Understanding of empowerment • Patient desire to actively engage in content and development of services offered • Perceived benefit of group visits
	Recruitment and retention	• Motivation to engage with others and commit to extended number of visits • Clear objectives of group program • Perceived benefit of participation in DGEP • Reaching orphan patients • Capacity to devote time
Clinicians		
	Perceived value	• Need for improvement of existing services • Understanding of empowerment • Perceived benefit of facilitator role and collaborative group dynamic
	Recruitment and retention	• Dedicated time, resources and adequate remuneration • Perception of patient benefit • Enjoyment of participation
Administrators		
	Perceived value	• Relative advantage over existing programs or ability to integrate with current services • Perceived value of patient engagement

It's all about leadership. It's all about somebody committed, and in a leadership position, and getting people on board—which is the idea of it, but in our restricted circumstances, we also really have the practical issue of limitation of personnel at all levels. (Family physician)

Other important system-level factors reported by the participants that constrain innovation are remuneration and performance incentives and disincentives. In Quebec, physicians are self-employed and bill the provincial government for their services. Physicians are primarily remunerated *via* fee-for-service in primary care settings, with an additional sum based on client enrollment (23). In cases where physicians are concerned about meeting the client enrollment requirements, nurses and allied health professionals could play a more prominent role in delivering the program.

Setting Characteristics

Based on experience conducting the DEGP pilot, requisite material, and human resources to run the program were identified. Space, where the group meetings are to be held, is needed. The program also demands some administrative work, such as: contacting patients who had expressed interest in participating, identifying availability, and establishing a schedule. In addition, flexibility regarding clinicians' schedules may be needed to work around the interested patients' availability (possibly in the evenings and weekends).

At our [family medicine group] I think it would be very feasible to implement the program, because we already have a nutritionist who just started; we have 5 new nurses, I think their schedules are still open. We're open on Saturdays and Sundays. So if we were to want to have the meetings on weekends, we would have a space upstairs... (Nurse practitioner)

The staff's training and experience innovating and successfully implementing programs were also considered major assets. Change management is considered an important factor in successful implementation in health care settings (24, 25). In settings that foster a culture of innovation and continuous quality improvement, the staff has cultivated knowledge and skills to evaluate needs, mobilize resources, and modify existing practices.

What we're trying to do with [continuous quality improvement] right now, is to try to make our decisions about what we—where we focus our efforts, where we focus our resources and time is based on solid data and evidence for the efficacy of whatever it is we're going to work toward. So that's what we're trying to shift toward right now – as a philosophy for the entire clinic, as a strategic approach to how we use our resources. So I could tell you that would weigh very heavily in how we try to decide how we move forward with any type of initiative right now. I don't think that was the case before; but it's certainly something we are trying to move toward now. (Continuous quality improvement coordinator)

Finally, at the practice level, another asset to DEGP implementation is its alignment with the Patient Medical Home model, which emphasizes multidisciplinary care and links to community services. Settings that embrace multidisciplinary care have a more developed and refined practice of inter-professional collaboration.

Patients

The DEGP requires a sufficient number of people living with diabetes who are willing and able to commit 2 h of their time, on occasion, to group visits. Attracting potential participants implies that they perceive some value in what the program offers, such as engagement with others living with diabetes or playing a greater role in determining the discussions' content.

There are definitely people who are afraid of group settings. They only want their doctor, it's a private matter; "No one sees my file, and I'm not going to start talking to anybody else about whatever problems I have." (Patient partner)

It also implies that they understand their condition as something requiring some attention.

The young pre-diabetic, they are not very interested… Very often they don't even want to see a dietician, or a kinesiologist; and the dropout rate is quite high. Because they don't feel… I mean they're young… They don't feel sick; they say, "Well, why should I come and spend time? I know what to do." But they just don't do it. So I think it might be a barrier to recruit these people into groups. For those who are on active treatment, I think maybe it's a different story; they feel they are sicker, because they have to take pills. But with the pre-diabetics especially, we have a hard time. (Family physician)

It was suggested that clinicians could target more homogeneous groups, including those who would not typically attend standard cardiometabolic prevention programs, patients with lower literacy levels, specific cultural or marginalized groups, or uncontrolled or newly diagnosed patients.

I'm wondering too if in your groups you had people from similar cultures; because even things like food, right, it's so cultural. You have people who eat rice for each of their meals, and large amounts. I find it hard – I'm not going to tell someone to cut out… I mean, I know it's a lot of the dietician's role as well, but still; food is a huge factor, so if patients were able to help each other. (Nurse Practitioner)

The patient partners suggested that recruitment may be more successful if they receive an invitation from their primary health care professional directly and get the opportunity to discuss the potential benefits of this kind of program. Scheduling was considered an important challenge by the participants, which could limit certain populations' capacity to attend depending on the time selected.

We definitely had more retired patients; we did do an evening as well to try to accommodate; but it was true that even though we made the evening accommodating, it was the more difficult one, still. (DEGP Nurse)

Another major concern we had with the cardio-metabolic program when I was involved with it was getting your younger

working diabetic to come to so many meetings. Because many of them have a young family; they work full-time, they work downtown. There is no parking here. And it was a huge barrier. It really was. We tried evening classes, we… We really tried various things; and they were like, "But it's too late, I'm tired at the end of a work day." (Family physician)

Retention of participants was also considered an important element of implementation planning. The high retention rate of the DEGP seemed, to the discussants, to suggest that the relational and patient-centered focus of the DEGP and the fixed-cohort structure may have improved patients' commitment to the program.

After the first meeting, I was hooked. I think my neighbor was too. The idea that you're not there in a… lecturing sense, listening to someone go on. You're actually participating, or you're talking. Or somebody would say, "Hey I've got that problem too, and this is how I dealt with it." And it's more… you're drawn into it more, and you learn more. And there's more… buy-in, if you like, in participating, rather than sitting there and being lectured to or being instructed. (Patient partner)

The patients' perceived benefit of their participation in the program reportedly motivated their desire to return and continue to engage in self-care. One of the patient partners explained that their interactions with others in the DEGP made a profound, lasting impression on them: "a good group stays with you for life."

Furthermore, to ensure better retention, it was suggested that the facilitators provide the participants with clear objectives and regularly solicit the participants for feedback, as was done in the pilot program.

Health Professionals

Considerations were raised regarding the attraction of facilitators and allied health professionals to the program. The DEGP physician and nurse were initially interested in developing the DEGP to address shortcomings of existing services and create a fun, engaging, and collaborative space for health care professionals and patients to discuss living with diabetes, the challenges people face, and the strategies they have put in practice. This collaborative, multidisciplinary, patient-centered approach appeared to appeal to the health professionals who participated in the group interviews.

I think the concept is wonderful; and I think a lot of patients that we see, as it was said, it's as if we're lecturing them. And most of the time I find myself saying, "I don't want to be lecturing you when I'm saying those things, but it's really important." It might be just things that I'm saying, and they're like, "Okay, okay, I've heard this a million times before." But the fact that they're in a room with other people sharing the same disease and condition! (Pharmacist)

As with the patients, the health professionals' perceived benefit (including the perceived need to improve existing services) and their enjoyment of participation would increase their likelihood of participating in subsequent sessions and/or groups. As the visits were longer and more frequent than individual visits, the clinician-patient therapeutic alliance was more quickly and easily developed. In addition, the close collaboration with fellow health professionals further increased their satisfaction. The patient-centered agenda and group dynamic brought about topics that were more pertinent and meaningful for patients. The clinicians noted that the topics brought up by patients were some that they might never have considered discussing (e.g., shame in carrying a diabetes diagnosis, perception of physician attitudes, cultural barriers, or political views on diabetes care). The clinicians who participated in the pilot reported that they found that the open interaction made the visits more gratifying.

Potential barriers reported by clinicians included the availability of adequate resources, the capacity to dedicate time and remuneration. Support of an administrative coordinator is recommended to assist with the program's coordination, including recruitment, contacting patients, and group visit logistics. Regarding time, the DEGP was considered more feasible in settings where clinicians had time and flexibility in their practices to take part in programs such as this. Working in clinics with experience in championing innovations or a stronger culture of innovation and partnership with patients was considered an asset. Physician remuneration may represent a challenge in some settings. However, where physicians cannot apply a group billing code and are remunerated according to a fee-for-service model, they may bill for individual medical consultations since the meeting consists of a formal medical visit. Group facilitation, however, need not necessarily be conducted by a physician. As mentioned above, where physicians' remuneration is more challenging, nurses and allied health professionals could play a more prominent role.

Administrators

To support the implementation of the DEGP, it was suggested that administrators be provided evidence that this program is more effective than existing programs.

They [administrators] are very big on indicators. "Show us why this is a good program to adopt." (Nurse manager)

Developers of novel interventions often face the challenge of needing to provide evidence of effectiveness, with limited capacity to conduct pilot studies. Consequently, especially when budgets are restricted, many new programs are developed top-down rather than bottom-up.

Interview facilitator to interview subjects: "From your experience at your individual sites, what was helpful in starting new initiatives? […] What were some of the elements that actually made things happen?"
Continuous quality improvement coordinator: "Well, top-down mandates…"
Family Physician: "Being dictated from the top! Literally being told: this is what we're doing."

The initial, small-scale pilot's primary aim was to assess the feasibility of DEGP. Given the pilot's scale, causal claims about its cost-savings or its improvement of diabetes or self-care outcomes could not be established. In order to

demonstrate the effectiveness of the DEGP, a larger, sufficiently-powered pilot will need to be conducted. While data on its effectiveness is unavailable, the participants suggested that attracting select administrators may be achieved by highlighting that perceptions of the program are favorable and that it is considered an improvement over existing interventions, in concept, since the DEGP was conceived to address some of their shortcomings. For instance, the pilot's 90% retention rate suggests that the program may be more attractive to patients than the current government-mandated Cardiometabolic Program in Quebec, which was found to have a retention rate of <60% (26).

DISCUSSION

Trustworthiness

Regarding the trustworthiness of the results generated through this research, data sources and participatory processes speak to the credibility of findings (27, 28). The description of the DEGP was informed by discussions with the healthcare providers and patients involved in the pilot. In addition, the interview guide was collaboratively developed by the participatory research team, which includes researchers, clinicians, and patient partners. The triangulation of data further contributed to the credibility of the findings. Discussions with patients and healthcare providers from other settings enabled a deeper understanding of the program and a description that encompasses diverse perspectives and addresses different understandings.

Another key consideration is the transferability of the findings to other settings (28). We described the major themes regarding the feasibility and acceptability of implementing the DEGP that emerged from discussions with patient partners and healthcare professionals from three different settings in Montreal. As above, the triangulation of data from interviews with the DEGP team and healthcare providers from other settings helped ensure a more comprehensive description of the program, which incorporates a variety of healthcare providers' perspectives. Therefore, we expect that the present description of DEGP might inform the implementation of this program or its adaptation in Quebec and internationally.

Future Directions

The DEGP is a novel, patient-centered program for people living with diabetes that emphasizes multidisciplinary collaboration, group dynamics, and relational aspects of self-care. We provided a detailed description of the DEGP and identified key factors pertaining to the feasibility and acceptability of its implementation or adaptation in other healthcare settings. We hope that the present research drives improvements to current programs and the development of the DEGP in other settings. To further support its implementation and adaptation, we are currently developing an implementation guide, which will provide more concrete and practical recommendations. We also developed and validated a measure of empowerment (MEA-D McGill Empowerment Assessment -Diabetes) (20), which will better enable an assessment of participants' needs prior to the program, and measurement of change following the program. We plan to disseminate these documents and tools across Quebec and Canadian research networks.

Further pilot research is needed, using a larger cohort, in order to demonstrate the effectiveness of the DEGP in terms of health outcomes, cost savings, and validated measures of empowerment. Once the DEGP is implemented or adapted in other healthcare settings, we also plan to explore further the usefulness of the conceptual table (**Table 3**), for clinical practice stakeholders, in addressing the feasibility and acceptability of implementing the DEGP or other group-based primary care practice innovations. Additional developments of this program may include: involvement of patient partners in facilitation, development, and evaluation; evaluating the feasibility of DEGP implementation in diverse settings and populations; and the inclusion of psychosocial outcomes, as is increasingly prominent in evaluating the effectiveness of diabetes programs.

CONCLUSION

The DEGP is an innovative, patient-centered medical care program conceived to educate and motivate diabetes self-care in a collaborative environment. It responds to recommendations from Diabetes Canada for a multidisciplinary approach in support of patients' management of their diabetes. It addresses some of the shortcomings of existing programs by emphasizing the relational impact of group activities and patient engagement in the program content, following a collaborative, multidisciplinary framework. Patients expressed appreciation for the opportunity to share and learn with patients and health care providers alike. Clinicians expressed interest in integrating elements of the DEGP into existing diabetes self-care programs, if provided adequate resources. Administrators appeared favorable toward this novel program, in concept, but explained the challenge of allocating material and human resources without sufficient evidence, and expressed reticence in supporting programs that lie outside ministerial or institutional priorities. The participatory research process broadened the participants' understanding of the DEGP and the needs of different stakeholders. This research provides a detailed description of the DEGP and insight on the factors that may impact the feasibility and acceptability of implementing similar group-based primary care interventions in other settings.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because The institutional review board has not granted permission to share this data (interview transcripts). Requests to access the datasets should be directed to Fanny Hersson-Edery, fanny.hersson-edery@mcgill.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by McGill University Faculty of Medicine Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FH-E prepared the manuscript and all authors revised and approved the final version. All authors contributed to the conception and design of the study as well as data collection, analysis, and interpretation of results.

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Effect of SGLT2 Inhibitors on Type 2 Diabetes Mellitus With Non-Alcoholic Fatty Liver Disease: A Meta-Analysis of Randomized Controlled Trials

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Objective: Clinical trials showed that sodium-glucose cotransporter 2 (SGLT2) inhibitors can improve non-alcoholic fatty liver disease (NAFLD). In this work, a meta-analysis of randomized controlled trials was conducted to evaluate the effect of SGLT2 inhibitors on type 2 diabetes mellitus (T2DM) with NAFLD.

Methods: PubMed, Embase, Web of Science, and Cochrane Libraries were used for the systematic literature review to determine eligible studies. A randomized effect model was adapted to perform a meta-analysis on these eligible studies to estimate the combined effect sizes. Differences were expressed as the weighted average difference (WMD) of the continuous results and the 95% confidence interval (CI).

Results: Ten randomized controlled trials with 573 participants were included. SGLT2 inhibitors significantly reduced the levels of alanine transaminase (WMD -5.36 [95% CI: -8.86, -1.85], p = 0.003) and Aspartate Transaminase (WMD -2.56 [95% CI: -3.83, -1.29], p <0.0001). In terms of body composition, liver proton density fat fraction (WMD -2.20 [95% CI: -3.67, -0.74], p = 0.003), visceral fat mass area (WMD -20.71 [95% CI: -28.19, -13.23], p <0.00001), subcutaneous fat areas (WMD -14.68 [95% CI: -26.96, -2.40], p = 0.02) were also significantly reduced.

Conclusion: SGLT2 inhibitors can remarkably reduce hepatic enzymes, hepatic fat and improve body composition. Thus, they may become a new treatment option for NAFLD.

Systematic Review Registration: PROSPERO, identifier CRD42020215570.

Keywords: sodium-glucose cotransporter 2 inhibitors, type 2 diabetes mellitus, liver proton density fat fraction, visceral fat mass area, non-alcoholic fatty liver disease

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease, and its prevalence continues to increase worldwide. T2DM and NAFLD have a close relationship, and approximately 80% of patients with type 2 diabetes mellitus (T2DM) have NAFLD (1). NAFLD is a complication and a risk factor of T2DM. Its pathogenesis is complex, including insulin resistance (a common key

factor in T2DM and NAFLD), oxidative stress, and mitochondrial dysfunction (2), which causes non-alcoholic steatohepatitis (NASH) to aggravate insulin resistance. Insulin resistance is a common key factor in the occurrence of T2DM and NAFLD (3, 4). NAFLD is usually accompanied by various complications, such as cardiovascular disease and chronic kidney diseases (5, 6), thereby seriously affecting the life expectancy of patients with T2DM. Therefore, early intervention and treatment of T2DM with NAFLD are required. Given the lack of approved drug therapies for NAFLD, medicines for related complications such as diabetes are being investigated for possible liver-related benefits. Although the insulin sensitizer pioglitazone can play a antihyperglycemic role and improve liver function, it is used cautiously in clinical practice because of its problematic safety in long-term use and side effects such as weight gain and edema (7).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are novel oral antihyperglycemic drugs that have received attention due to their unique mechanism of inhibiting glucose reabsorption in the proximal renal tubules and increasing urinary glucose excretion (8). This type of antihyperglycemic method does not depend on insulin and reduces body weight (9). Clinical trials reported that SGLT2 inhibitors can improve NAFLD and reduce Aspartate Transaminase (AST) and liver fat in patients with T2DM and NAFLD (10). However, contrary opinions have been held in some studies (11). The previous studies summarized the effects of SGLT2 inhibitors on hepatic fat and hepatic enzymes, but failed to assess the effects on liver fibrosis. Therefore, whether SGLT2 inhibitors affect liver fibrosis requires further discussion. Newer, larger sample and longer term studies with relatively complete data need to be included, and the preliminary conclusion needs to be updated. For this purpose, we once again reviewed trials on SGLT2 inhibitors to reach a more comprehensive and reliable conclusion.

METHOD

Search Strategy

Related articles as of July 2020 were searched from PubMed, Embase, Web of Science, and Cochrane libraries by using the following subject terms: (Sodium-Glucose Transporter 2 Inhibitors OR SGLT2 Inhibitors OR SGLT 2 Inhibitors OR SGLT2Inhibitors OR Sotagliflozin OR Dapagliflozin OR Empagliflozin OR Canagliflozin OR Luseogliflozin OR Ipragliflozin OR Canagliflozin OR Ertugliflozin OR Gliflozins) AND (Non-alcoholic Fatty Liver Disease OR NAFLD OR Nonalcoholic Fatty Liver Disease OR Fatty Liver, Nonalcoholic OR Fatty Livers, Nonalcoholic OR Liver, Nonalcoholic Fatty OR Livers, Nonalcoholic Fatty OR Nonalcoholic Fatty Liver OR Nonalcoholic Steatohepatitis OR Nonalcoholic Steatohepatitides OR Steatohepatitides, Nonalcoholic OR Steatohepatitis, Nonalcoholic), no language restrictions. Two reviewers (Xinyue Xu and Li Guo) independently selected the relevant articles according to the title and abstract and then screened the full text to determine whether it meets the inclusion or exclusion criteria. References to all eligible trials, meta-analyses, and related reviews were also reviewed to avoid missing any articles. All search results were downloaded into EndNote (version X9, Thomson Reuters, Philadelphia, PA, USA) to eliminate duplication, and the searched citations were merged to simplify the screening process.

Eligibility Criteria

All randomized controlled clinical trials (RCTs) evaluating the effects of SGLT2 inhibitors on patients with T2DM and NAFLD were included in the meta-analysis. Inclusion criteria were as follows: (a) the population was patients with T2DM and NAFLD aged 18–75 years; HbA1c: 6%–12%, fatty liver confirmed by imaging examination (ultrasound or computed tomography); and alcohol intake should not exceed 140 g/week for women and 210 g/week for men. Other causes of liver disease (such as viral hepatitis, autoimmune hepatitis, and primary biliary cirrhosis) were excluded. (b) Therapeutic intervention includes various types of SGLT2 inhibitors, and the control group has sufficient information about baseline and post-treatment in the study report, such as glycosylated hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), homoeostasis model assessment of insulin resistance (HOMA-IR), alanine transaminase (ALT), Aspartate Transaminase (AST), fibrosis 4 (FIB-4) index, liver proton density fat fraction (PDFF), visceral fat area (VFA), subcutaneous fat areas (SFA), and body weight. (c) The full text was provided, and the study was designed as a randomized controlled trial. Exclusion criteria includes the following: (a) animal studies; (b) pregnant or breastfeeding women; (c) non-randomized controlled trials; and (d) reviews, conference abstracts, reviews, meta-analysis, incomplete article results, and case reports.

Data Extraction and Assessment for Study Quality

The following relevant data were extracted from each study: first author, year of publication, sample size, intervention (type and dose of SGLT2 inhibitors), drug in the comparison group, follow-up time, and patient baseline information.

Two reviewers (Xinyue Xu and Li Guo) independently assessed the quality of RCTs using the Cochrane Risk of Bias Tool, which included the following seven criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), reporting bias selective reporting (reporting bias), and other biases (certain biases not indicated above but influence the results). As per the recommendations of the Cochrane Handbook, each project was evaluated as a "low risk," "high risk," or "unclear risk" risk of bias.

Statistical Analysis

RevMan 5.4 software provided by Cochrane was used for analysis, and the measurement data were all presented as mean and standard deviation (SD). Outcomes were compared using weighted mean difference (WMD), and 95% confidence interval (CI) was used for each effect. I^2 statistics was used to assess the heterogeneity of the studies. Studies with an I^2 statistic of

25%–50% were considered as low heterogeneity, those with an I^2 of 50%–75% as moderate heterogeneity, and those with an I^2 of > 75% as high heterogeneity. Random effects models were used in all studies. According to the characteristics of the study, subsequent subgroup analysis or sensitivity analysis was conducted to explain the reasons for heterogeneity. Forest plot was drawn by RevMan defaults to adverse events. When the 95% CI horizontal line of a study does not intersect the forest plot invalid line and falls to the left of the invalid line, it can be considered that the mean of the indicator in the SGLT2 inhibitor group was less than that in the control group, that is, the experimental factors in the SGLT2 inhibitors group reduced the occurrence of adverse events. Hence, the experimental factors were beneficial and effective. P values of less than 0.05 were considered statistically significant.

RESULTS

Literature Search

The literature search identified 439 studies, 95 of which were from PubMed, 145 from Embase, 66 from the Cochrane Library, and 133 from the Web of Science. A total of 196 duplicate papers were excluded, 104 papers were removed based on title and abstract, and from 139 studies were evaluated further, 129 studies were excluded for the following reasons: (a) non-RCT studies (n=35), (b) conference abstracts (n=66), (c) incomplete trial results (n=26), (d) exclusion due to more than 1000 subjects to avoid overweighting (n=1), and (e) duplication of data (n=1). The final 10 eligible studies were included in the final meta-analysis (10–19). **Figure 1** describes the study selection flowchart in detail.

Study Characteristics and Quality Assessment

The included research characteristics are shown in **Table 1**. The articles presented 10 trials involving 573 subjects (295 SGLT2 inhibitors subjects and 278 control subjects) published between 2017 and 2020. Four multicenter studies were included, and five were from Japan, four studies were from Germany, South Korea, Sweden, India, the remaining one study was conducted at 87 centers in Germany, the Czech Republic, Hungary, Mexico, Poland, Romania, Russia, Sweden, the UK and the United States. Many types of SGLT2 inhibitors were included in the intervention group, including empagliflozin (two studies), dapagliflozin (five studies), Ipragliflozin (three studies), and Luseogliflozin (one study). One study used empagliflozin or dapagliflozin. For the control group, the intervention drugs were as follows: metformin, pioglitazone, sitagliptin, and Glucagon-like peptide-1 receptor agonist, glimepiride. The duration of follow-up ranged from 12 weeks to 52 weeks. Urinary tract infections were reported in three studies, hypoglycemia was reported in one study, and arthralgia in large joints was reported in one study. Four studies reported no serious adverse effects, and three studies reported no adverse events. In summary, the SGLT2 inhibitors were safe. According to the Cochrane Risk Bias Tool, all studies are parallel grouping studies with high quality. Quality assessment results for the included studies are summarized in **Figure 2**.

Effect of SGLT2 Inhibitors on Glycemic Indices

Glycosylated Hemoglobin A1c

Nine RCTs reported HbA1c levels in 242 SGLT2 inhibitors users and 197 non-users. Compared with other antihyperglycemic drugs, SGLT2 inhibitors were more likely to reduce HbA1c, but the difference was not statistically significant (WMD-0.16 [95%CI: -0.38, 0.06], P = 0.16). I^2 = 91%, heterogeneity was greater, and no heterogeneity analysis was conducted because the two groups were not statistically different (**Figure 3**).

Fasting Plasma Glucose

In 9 RCTs, a pooled study of 439 participants showed that SGLT2 inhibitors were likely to reduce FPG, but no statistical difference was observed between the two groups (WMD -4.32 [95% CI: -9.74, 1.09], p = 0.12). The results are highly heterogeneous (P <0.00001, I^2 = 77%) (**Figure 3**).

Homeostatic Model Assessment of Insulin Resistance

Six studies evaluated the effects of SGLT2 inhibitors on HOMA-IR. Overall analysis showed that SGLT2 inhibitors did not significantly reduce HOMA-IR compared with other antihyperglycemic agents (WMD -0.39 [95%CI: -1.06, 0.28], P = 0.26). These findings suggest that SGLT2 inhibitors are not superior over other drugs in improving insulin resistance. Significant heterogeneity was observed between studies (P < 0.00001, I^2 = 88%) (**Figure 3**).

High evidence RCTs in this meta-analysis revealed that SGLT2 inhibitors reduced the HBA1c, FPG, and HOMA-IR levels. However, some studies included other effective antidiabetic drugs, thus influencing the final data analysis and resulting in high heterogeneity in the meta-analysis.

Effect of SGLT2 Inhibitors on Liver Functions

Alanine Transaminase

Nine RCTs reported ALT levels in 268 SGLT2 inhibitors users and 213 non-users. The meta-analysis showed that SGLT2 inhibitors significantly reduced the ALT levels in patients with NAFLD compared with other drugs (WMD -5.36 [95% CI: -8.86, -1.85], p = 0.003). Significant heterogeneity was found between studies (p < 0.00001, I^2 = 90%) (**Figure 4**).

Aspartate Transaminase

Eight RCTs reported AST levels in 252 SGLT2 inhibitors users and 197 non-users. The meta-analysis showed that SGLT2 inhibitors significantly reduced the AST levels in patients with NAFLD (WMD -2.57 [95% CI: -3.84, -1.30], p < 0.0001). Moderate heterogeneity was observed between studies (p = 0.03, I^2 = 54%) (**Figure 4**).

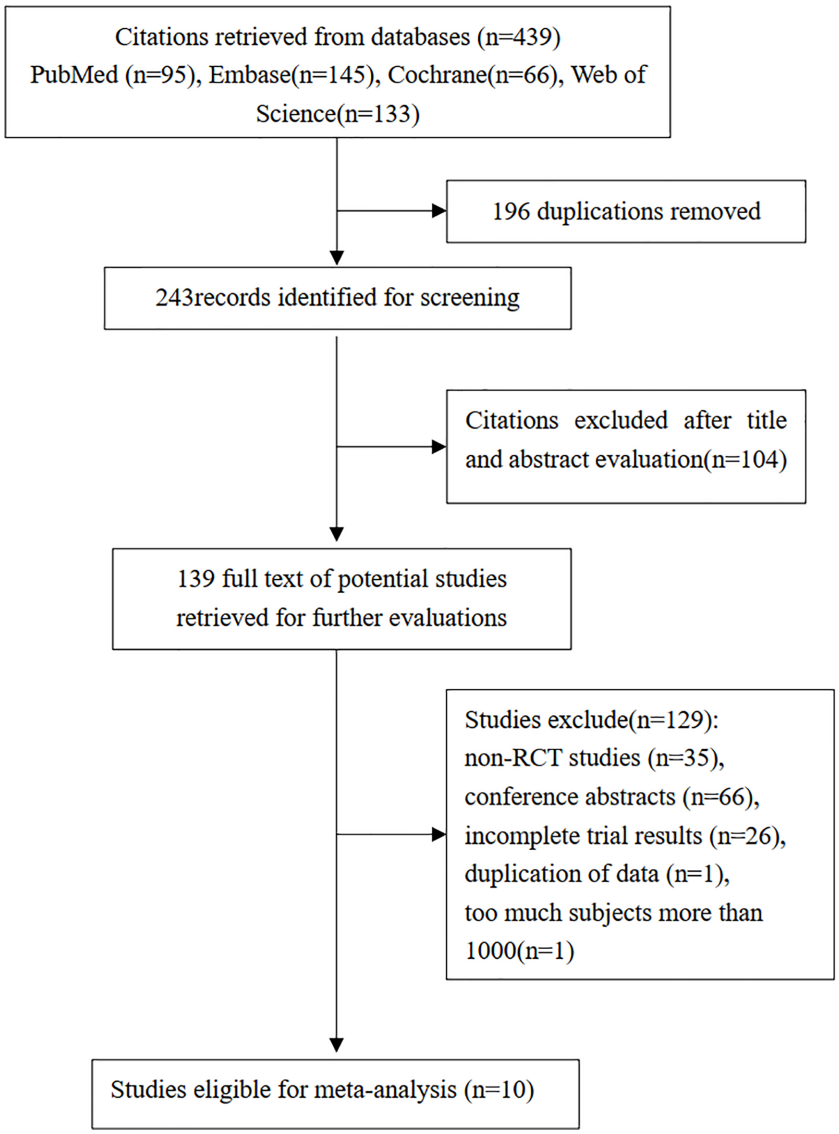

FIGURE 1 | Summary of study identification, inclusion, and exclusion.

Fibrosis-4 Index for Liver Fibrosis

Three RCTs evaluated the effect of SGLT2 inhibitors on FIB-4. Compared with other antihyperglycemic drugs, SGLT2 inhibitors can significantly reduce FIB-4 (WMD -0.06 [95% CI: -0.10, -0.02], p = 0.0010). No heterogeneity was observed between studies (p = 0.88, I^2 = 0%) (**Figure 4**).

These randomized controlled trials strongly support the use of SGLT2 inhibitors to reduce ALT and AST levels and improve liver fibrosis in patients with T2DM and NAFLD.

Effect of SGLT2 Inhibitors on Body Composition

Body Weight

Eight RCTs reported the weight of 226 SGLT2 inhibitors users and 181 non-users. Compared with other antihyperglycemic drugs, SGLT2 inhibitors can significantly reduce body weight (WMD -3.02 [95% CI: -4.57, -1.47], p = 0.0001). Significant heterogeneity was found between studies (P < 0.00001, I^2 = 98%) (**Figure 5**).

Proton Density Fat Fraction

PDFF is a quantitative biomarker that is based on MRI and can accurately estimate liver fat content. Three RCTs reported PDFF in 76 SGLT2 inhibitors users and 63 non-users. SGLT2 inhibitors significantly reduced PDFF compared with other antidiabetic drugs (WMD -2.20 [95% CI: -3.67, -0.74], p = 0.003). No heterogeneity was observed between studies (p = 0.44, I^2 = 0%) (**Figure 5**).

Visceral Fat Area

Six RCTs reported the measurement of VFA using DXA in 179 SGLT2 inhibitors users and 142 non-users. The results showed

TABLE 1 | Demographic and clinical characteristics of included studies.

Source	Sample (F)	Age(years)	Duration (years)	Trial Duration	Agent (Daily Dosage)	Comparator (Dosage)
Aso Y (19)	57 (23)	55.0 ± 8.6	NR	24 weeks	Standard-hypoglycemic treatment + dapagliflozin 5 mg	Standard-hypoglycemic treatment
Bando Y (18)	62 (22)	55.1 ± 8.6	9.6 ± 4.5	12 weeks	Continued-hypoglycemic treatment + ipragliflozin 50 mg	Continued-hypoglycemic treatment
Eriksson JW (17)	42 (9)	65 ± 36	6.6 ± 5.1	12 weeks	Dapagliflozin 10 mg	Placebo
Han E (11)	45 (17)	53.9 ± 10.9	9.4 ± 5.8	24 weeks	Metformin + pioglitazone + ipragliflozin 50 mg	Metformin + pioglitazone
Ito D (16)	66 (34)	58.2 ± 10.9	9.1 ± 5.8	24 weeks	Ipragliflozin 50 mg	Pioglitazone 15-30 mg/day
Johansson L (15)	82 (41)	58.0 ± 9.0	6.4 ± 6.0	52 weeks	metformin + saxagliptin 5 mg + placebo + dapagliflozin 10mg	metformin + glimepiride 1-6 mg + placebo
Kinoshita T (10)	98 (45)	59 ± 1	7.2 ± 0.5	28 weeks	Dapagliflozin 5 mg	Pioglitazone 7.5–15 mg/day
Kuchay MS (14)	50 (20)	65.3 ± 6.23	NR	20 weeks	Standard-hypoglycemic treatment + empagliflozin 10 mg	Standard-hypoglycemic treatment
Mittag-Roussou V (13)	39 (19)	57.7 ± 10.9	NR	6 months	Dapagliflozin 5 – 10 mg empagliflozin 10 – 25 mg	Exenatide 10 – 20 μg or liraglutide 0.6 - 1.8 mg or dulaglutide 0.75 - 1.5 mg/week.
Shibuya T (12)	32 (14)	56.5 ± 11.68	9.6 ± 1.0	6 months	Luseogliflozin 5 mg	Metformin 1500 mg/day

F, Female; NR, No report.

that SGLT2 inhibitors significantly reduced VFA compared with other antidiabetic drugs (WMD -23.83 [95% CI: -28.72, -18.95], $p < 0.00001$). Significant heterogeneity was found between studies ($p < 0.0001$, $I^2 = 82\%$) (**Figure 5**).

Subcutaneous Fat Areas

Four RCTs reported the measurement of SFA in 131 SGLT2 inhibitors users and 93 non-users using DXA. The results showed that SGLT2 inhibitors significantly reduced SFA compared with other antidiabetic drugs (WMD -14.68 [95% CI: -26.96, -2.40], $p = 0.02$). Significant heterogeneity was noted between studies ($p < 0.00001$, $I^2 = 95\%$) (**Figure 5**).

These randomized controlled trials provide a strong support for the use of SGLT2 inhibitors to reduce weight, liver fat, VFA, and SFA in patients with T2DM and NAFLD.

Sensitivity Analyses and Subgroup Analyses

Sensitivity analyses were performed to identify the sources of heterogeneity. When pioglitazone was excluded from the control group, the heterogeneity was significantly reduced. For example, in AST analysis, when the three RCTs of Han, Ito, and Kinoshita were excluded, the heterogeneity changed from 54% to 0%. In the weight analysis, when these three RCTs were excluded, the heterogeneity changed from 89% to 0%. Therefore, further subgroup analysis was performed based on the differences in the control group. The results suggested that SGLT2 inhibitors reduced the AST levels in patients with NAFLD and had superior effect over pioglitazone (WMD -1.28 [95% CI: -2.23, -0.33], $p = 0.008$) and metformin (WMD -3.80[95% CI: -5.07, -2.53], $p < 0.00001$) (**Figure 6**). In terms of weight reduction, SGLT2

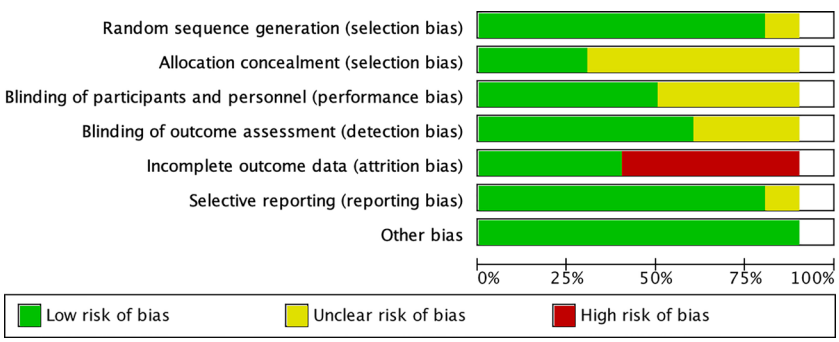

FIGURE 2 | Quality evaluation chart of included studies.

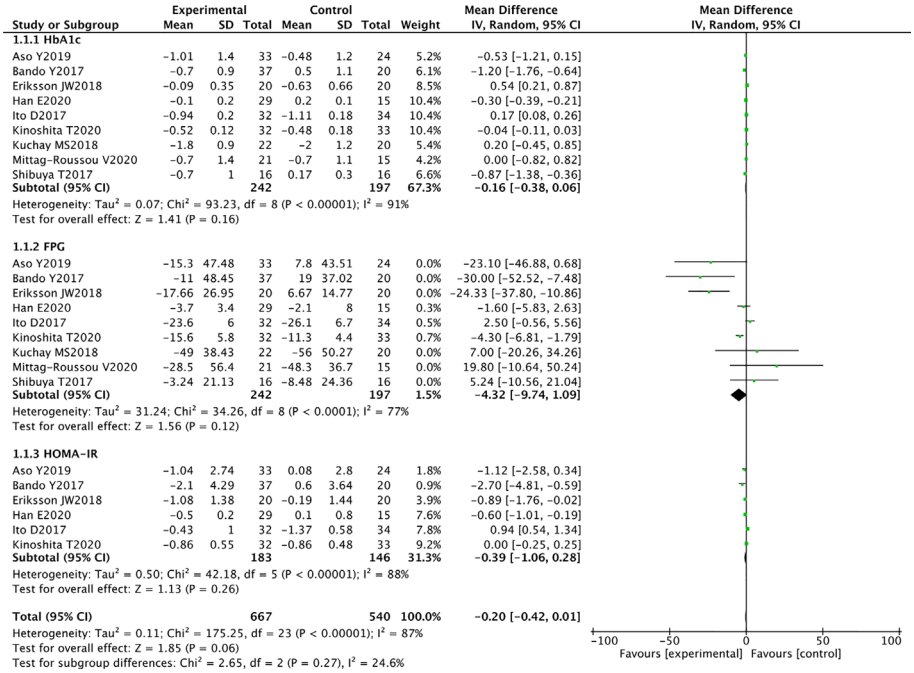

FIGURE 3 | Meta-analysis of the effect of SGLT2 inhibitors on glycemic indices compared with the control group.

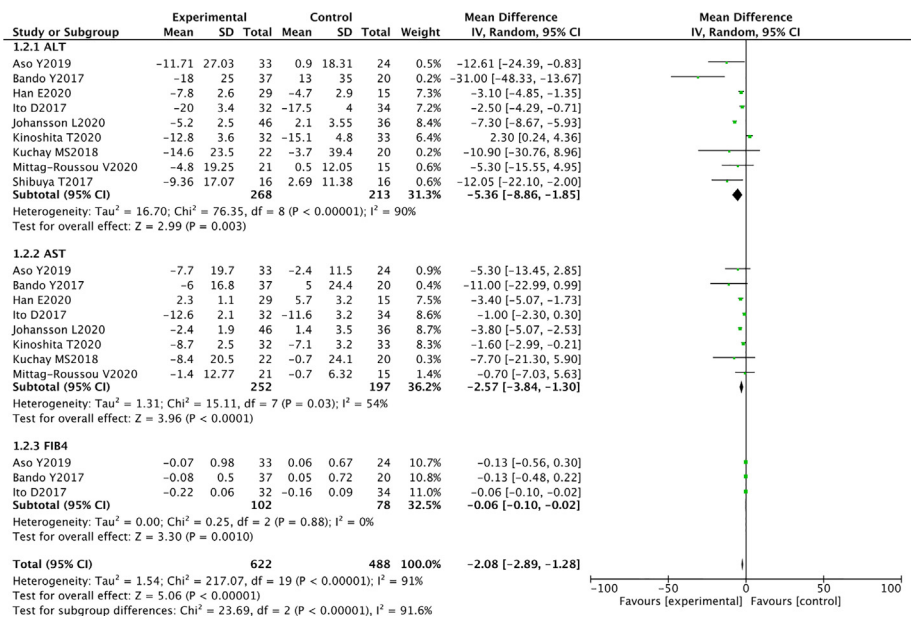

FIGURE 4 | Meta-analysis of the effect of SGLT2 inhibitors on liver function compared with the control group.

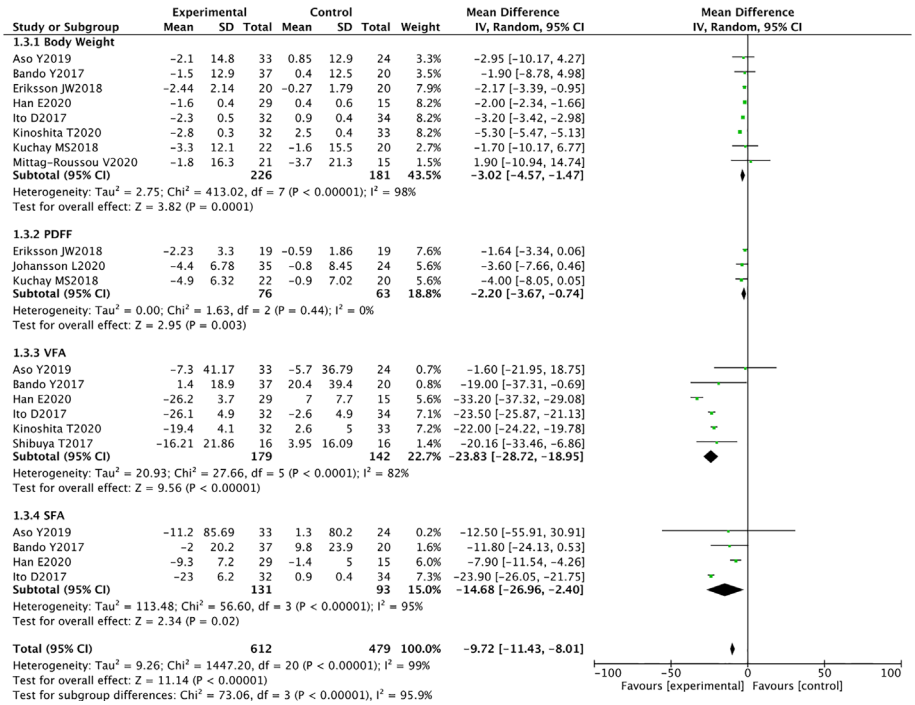

FIGURE 5 | Meta-analysis of the effect of SGLT2 inhibitors on body composition compared with the control group.

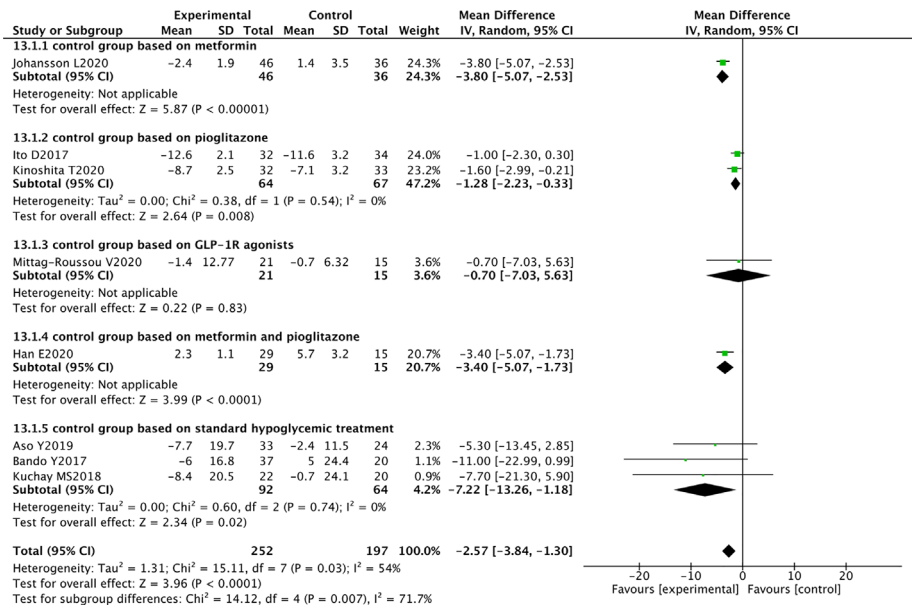

FIGURE 6 | Meta-analysis of AST level comparisons between SGLT2 inhibitors and the control group based on the control.

inhibitors were superior over pioglitazone (WMD -4.25 [95% CI: -6.31, -2.19], p < 0.0001) (**Figure 7**).

Publication Bias

Given that only 10 RCTs were included in this meta-analysis, the number of articles was small, and publication bias tests were not performed.

DISCUSSION

This meta-analysis of 10 RCTs aimed to evaluate the effect of SGLT-2 inhibitors in patients with T2DM and NAFLD. The ability of SGLT-2 inhibitors to control glycemia and improve fatty liver was investigated. Results showed that SGLT-2 inhibitors were superior over other antihyperglycemic drugs used in these RCTs in improving liver enzymes, reducing liver fat, reducing body weight, and improving liver fibrosis. No statistically significant differences were found in their activities of lowering blood glucose or improving insulin resistance.

As a chronic disease, NAFLD has become an important health problem. NAFLD, coronary heart disease, hypertension, and atherosclerosis are metabolic syndromes with insulin resistance as their common mechanism. T2DM combined with NAFLD further disrupts glucose metabolism and increases the incidence of NASH. The coexistence of high glucotoxicity and lipotoxicity substantially increases the incidence of diabetic macrovascular events and accelerates the transformation of fatty liver into cirrhosis and even liver cancer. NAFLD is often accompanied by oxidative stress, dyslipidemia, inflammation, and insulin resistance. Therefore, its treatment should focus on correcting these disorders.

SGLT2 inhibitors positively affect chronic diseases, including diabetes, obesity, cardiovascular disease (20), and kidney disease (21). This meta-analysis confirmed that SGLT2 inhibitors can reduce liver fat, lower ALT, AST, and FIB-4 levels and alleviate NAFLD. Animal experiments revealed that SGLT2 inhibitors can improve fatty liver by reducing lipid production, enhancing insulin resistance, and alleviating endoplasmic reticulum stress (22). However, the pathophysiological mechanisms of these effects on NAFLD are controversial. The tissue characteristics of NAFLD are predominantly hepatic lipid accumulation, which is caused by an imbalance between hepatic triglyceride synthesis and fatty acid oxidation (23). SGLT2 inhibitors induce a metabolic shift from carbohydrate oxidation to fatty acid oxidation, thus possibly prevent lipid accumulation by increasing fatty acid oxidation in adipose tissues and the liver. In addition, they can reduce energy by excreting glucose in the urine (24). This energy loss may promote β-oxidation in liver and visceral fat, induce liver fat metabolism, and reduce VFA. The latter decreases the transport of fatty acids from adipose tissues to the liver, corrects hyperinsulinemia, and increases adiponectin levels. The adenosine monophosphate-activated protein kinase pathway is activated by adiponectin, which inhibits fat formation and accelerates the oxidation of fatty acids in the liver (25). The main pathological status of patients with NAFLD is insulin resistance (3), Excessive insulin levels promote lipogenesis, leading to liver steatosis. SGLT2 inhibitors lower the blood glucose and gradually correct hyperinsulinemia (26) while improving insulin resistance and reducing hepatic lipogenesis. Additional pathogenesis of NAFLD includes oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum homeostasis. SGLT2 inhibitors directly inhibited the enhanced expression of dipeptidyl peptidase-4 in the liver (19), reduced the plasma FGF21 levels (27, 28), and improved the mitochondrial function or reduced endoplasmic reticulum stress in the liver.

Pioglitazone can reduce hepatic enzymes and hepatic fat. In this meta-analysis, SGLT2 inhibitors were superior in reducing AST compared with pioglitazone, and the difference was statistically significant. Pioglitazone may also increase VFA, SFA, and body weight, which is not conducive to the long-term prognosis of patients with NAFLD (10). This meta-analysis

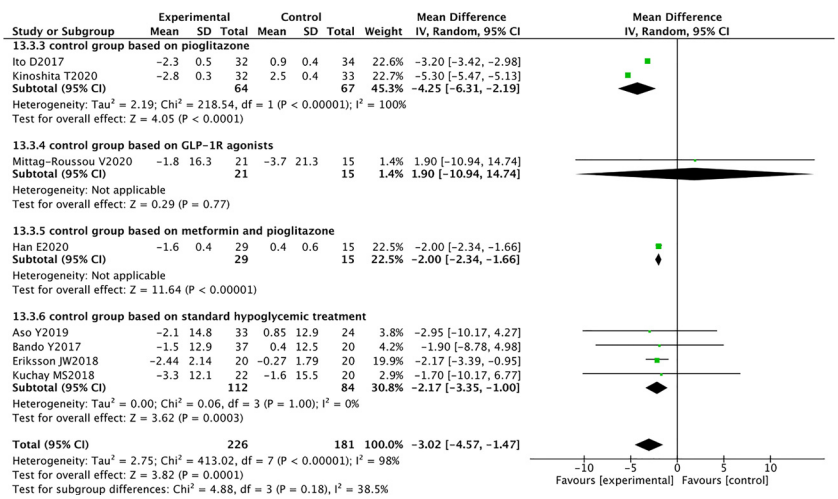

FIGURE 7 | Meta-analysis of body weight level comparisons between SGLT2 inhibitors and the control group based on the control.

showed that compared with glucagon-like peptide-1 receptor (GLP-1R) agonists, SGLT-2 inhibitors can improve AST. However, the difference was not statistically significant. Only one study and the small number of subjects included in this study severely limited our ability to analyze the differences between SGLT-2 inhibitors and GLP-1R agonists in affecting the liver (13). Moreover, the use of GLP-1R agonists is limited due to their disadvantages such as severe gastrointestinal discomfort and the need for subcutaneous injections.

This meta-analysis showed that SGLT2 inhibitors were not superior over other antihyperglycemic drugs in lowering blood glucose but effectively improved NAFLD. Considering the mechanism of SGLT2 inhibitors on NAFLD, they may not be dependent on lowering blood glucose to improve fatty liver. This finding may provide a new idea for the treatment of NAFLD patients without T2DM.

The highlight of this meta-analysis was the comprehensive evaluation of the effects of SGLT2 inhibitors on patients with T2DM and NAFLD in terms of blood glucose control, improvement of liver enzymes, and influence on body composition. This work provided evidence for the use of SGLT2 inhibitors in these patients. However, the following are the limitations of this article: (a) only a few randomized controlled trials met the conditions, and most RCTs have small sample sizes and thus produce insignificant results. Additional RCTs are needed to further validate the current results. (b) The majority of the RCTs included in this study were from Asia. Ethnic differences and Asian-specific lifestyles may have influenced the results. (c) The included studies had short follow up periods with the longest at only 52 weeks. In addition, the long-term prognosis for SGLT2 inhibitors is unclear, thus requiring continued follow-up. (d) NAFLD diagnosis was based on imaging, and no histological examination was conducted. Therefore, the effect of SGLT2 inhibitors on T2DM with NAFLD was not histologically evaluated.

CONCLUSION

For non-alcoholic fatty liver disease, SGLT2 inhibitors are more effective in reducing AST, ALT, FIB-4, PDFF, VFA, SFA, and weight levels than other antihyperglycemic drug; however, their decreasing effect on HbA1c, FPG, and HOMA-IR levels was not superior over other antihyperglycemic drugs. The improvement of NAFLD by SGLT2 inhibitors provides a new treatment option for patients with T2DM and NAFLD.

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.

AUTHOR CONTRIBUTIONS

QW designed the study and reviewed the manuscript. XX collected the data, analyzed the data, and wrote the manuscript. LG collected the data and analyzed the data. JL contributed to the introduction and reviewed the manuscript. LL designed the study and contributed to the introduction and the discussion. All authors contributed to the article and approved the submitted version.

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The Effects of Vitamin D Supplementation on Metabolic and Oxidative Stress Markers in Patients With Type 2 Diabetes: A 6-Month Follow Up Randomized Controlled Study

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Vitamin D deficiency could play an important role in the pathogenesis of type 2 diabetes mellitus (T2DM) as it may alter several crucial processes in the development of diabetes and its complications, such as pancreatic insulin secretion, peripheral insulin resistance, persistence of systemic „sterile" inflammation and immune activation. Vitamin D may also have an antioxidant effect through the inhibition of free radicals generation. The reported study was designed with eligible consecutively recruited patients with T2DM on standard metformin therapy (n=130), randomized in 1:1 ratio, considered to have undergone Vitamin D supplementation according to the guidelines proposed by the Endocrine Society, or to have continued with metformin only. The potential benefit was monitored through the influence on glycemia level, glycated haemoglobin (HbA1c), insulin resistance index (calculated as homeostatic model assessment; HOMA-IR), Castelli Risk Index I and Tryglicerides/Thiobarbituric acid-reactive substances (TG/TBARS) Index in a 6-month follow up period. Our study indicates that oral daily doses of vitamin D improve HbA1c levels over the 3-month and 6-month period, followed by a significant decrease in advanced oxidation protein products levels over the 3-month period when higher vitamin D doses are given. The effect of vitamin D on HOMA-IR index, malondialdehyde levels and TG/TBARS index was not statistically significant. Further investigation should consider defining the doses of vitamin D in patients with T2DM which may attenuate the oxidative stress risk, the risk of metabolic syndrome and the risk of related cardiovascular events.

Keywords: vitamin D supplementation, HbA1c, insulin resistance, oxidative stress, type 2 diabetes

INTRODUCTION

During the past years there has been a growing interest in extra-skeletal effects of vitamin D since it has been discovered that vitamin D receptors are expressed not only in tissues related to bone metabolism, but also in many other tissues, such as brain, prostate, breasts, immune cells etc. (1, 2). This has linked vitamin D to many chronic diseases, such as cancer, heart disease, metabolic syndrome, prediabetes, diabetes, inflammatory and autoimmune diseases (3, 4).

Patients with type 2 diabetes mellitus (T2DM) usually have a lack of vitamin D but it is still unknown whether this is a coincidence or whether low levels of vitamin D may contribute to the disease appearance. Recent studies have suggested that vitamin D deficiency could play an important role in T2DM pathogenesis through altering several crucial processes in the development of diabetes and its complications: pancreatic insulin secretion, peripheral insulin resistance, down-regulation of the insulin receptor gene, systemic „sterile" inflammation and immune activation (3, 5). Besides hyperinsulinemia and hyperglycaemia, T2DM is a condition characterized by an increased formation of free radicals and a decreased antioxidant capacity. Some experimental studies have shown that vitamin D may have an antioxidant effect followed by the inhibition of free radicals generation, consequent lipid peroxidation and oxidative modification of other biomolecules (6). Due to the abovementioned effects, vitamin D supplementation has been proposed as a possible therapeutic tool for T2DM to optimize glycaemic control and to prevent the occurrence of complications (7).

Despite the promising data from observational studies, vitamin D supplementation trials have yielded inconsistent results. Some of them have reported a significant reduction of fasting blood glucose (FBG) and glycated haemoglobin (HbA1c) while others have shown no statistically significant improvement in vitamin D group vs. placebo (7–10). These results should be interpreted with caution because most of the trials included small heterogeneous groups of patients in different stages of disease with suboptimal doses of vitamin D, various ways of administration, lifestyle habits, dietary habits, age, ethnicity, season of the year, location and climate conditions (5, 7).

Moreover, little or no research has determined any long-term effect of vitamin D supplementation in T2DM patients with co-administration of the standard pharmacological regimen, by using daily doses of vitamin D according to the available guidelines (11). Therefore, the study reported was aimed at determining whether vitamin D supplementation in T2DM patients, who underwent standard metformin therapy, may have a benefit through the influence on insulin resistance, Castelli risk index I and oxidative stress markers, in a 6-month follow up randomized controlled study.

PATIENTS AND METHODS

Study Design and Participants

A prospective, randomized, controlled open-label study was conducted in a summer-winter period (overall trial start date 02.04.2018; overall trial end date 15.12.2018.) in Primary Health Care Center Podgorica, Montenegro. The study was conducted according to the Declaration of Helsinki and Good clinical Practice guidelines. Ethical approval was obtained by the Ethical Committee of Primary Health Care Center in Podgorica (Ethical Committee of Primary Health Care Center in Podgorica, ID number 05/01-E.K.-5989/1) and all participants provided a written informed consent. Study was also registered on ISRCTN registry platform (02.12.2019. ID number ISRCTN25609316). In the region, Mediterranean climate prevails, at latitude 42°, where regular diet is characterized by Mediterranean eating habits, which may reflect a basal vitamin D level.

A sample size was determined according to the key variable HbA1c of previous study (12) considering $\alpha = 0.05$ and statistical power $1\text{-}\beta = 0.8$. The calculated sample size was 49 patients per group. Out of 560 pre-screened T2DM patients, 150 met the eligibility criteria. Allowing the drop-out rate of 30%, a total of 130 participants (65 in each group) were enrolled, ≥ 30 years of age, diagnosed with T2DM according to American Diabetes Association (ADA) 2011 criteria (13), who had good metabolic control (HbA1c ≤ 7%), who were treated with metformin and were given lifestyle advice.

The exclusion criteria were as follows: the use of vitamin D supplements and any diabetes pharmacotherapy other than metformin 6 months prior the study; the use of drugs that affect the metabolism of vitamin D; the presence of severe anemia; a chronic liver or kidney failure; alcoholism, pregnancy; malabsorption; urolithiasis; hypercalcemia; body mass index (BMI) ≥ 40 kg/m2 and the presence of acute or chronic inflammatory conditions.

Outcomes

The primary outcome of the study was change in insulin resistance and glycemic control measured by the homeostasis model of assessments (HOMA-IR) and glycemic parameters (FBG, HbA1c). The oxidative stress parametres [malondialdehyde (MDA) and advanced oxidation protein products (AOPP)] and inflammation markers [C-reactive protein (CRP)] were considered secondary outcomes. Furthermore, alteration of vitamin D levels over time, blood pressure, lipid profile, BMI, calcium total (Ca), calcium ionized (Ca ++) and atherogenic risk were also considered as secondary outcomes.

Intervention

The eligible participants recruited consecutively were randomly assigned to two groups in 1:1 ratio. The Serum level of 25(OH)D (marker of vitamin D status) was measured at baseline in all participants. Half of the patients (n=65) were randomly prescribed vitamin D3 therapy and continued their prescribed metformin therapy for 6 months, while the other group (n=65) continued their prescribed metformin therapy only. The dosing was carried out according to the Endocrine Society's clinical practice guidelines as for the vitamin D baseline levels (10). The supplements were given in the form of Vigantol oil drops (Merck KGaA, 0.5 mg/ml, one drop equals 500 IU). The participants in the first group who were vitamin D deficient [defined as serum levels of 25(OH)D ≤ 50 nmol/L] were asked to take 50 000 IU of

vitamin D3 weekly (equal to 15 drops of vitamin D supplement-Vigantol oil daily) during the first 3 months and 14 000 IU weekly (4 drops daily) for the next 3 months. The participants in the same group whose 25(OH)D levels were > 50 nmol/L were asked to take 14 000 IU weekly (4 drops daily) until the end of the study. The study protocol is shown in **Figure 1**. At the screening visit, data about participant's level of physical activity, sun exposure and average dietary intake of vitamin D of three consecutive days were also reported. Every participant received a table with a list of food containing vitamin D and was advised not to alter the usual dietary amounts of vitamin D. All participants also agreed not to change physical activity and sun exposure patterns while enrolled. The compliance was carefully controlled by the medical staff. The Patients whose diabetes therapy has changed during the study period were excluded. The report involved clinical and laboratory analyses of data through the 3- and the 6-month assessment period. All supplements were provided to the patients by the authors themselves through the medical staff. Supplement adherence was assessed at the end of every month by returning the empty bottles of Vigantol oil. In the Metformin + Vitamin D group, a total of 16 patients were excluded (Six with assigned regimen of 50 000 IU+14 000 IU, and 10 with assigned regimen of 14 000 IU): 1 patient was diagnosed with pancreatic tumor, 1 developed urticaria-like skin lesions after taking first dose of supplement and reaction was classified as moderate, 5 patients did not take the supplement regularly and 9 patients changed diabetes medication. In the Metformin group all 65 patients completed the study successfully.

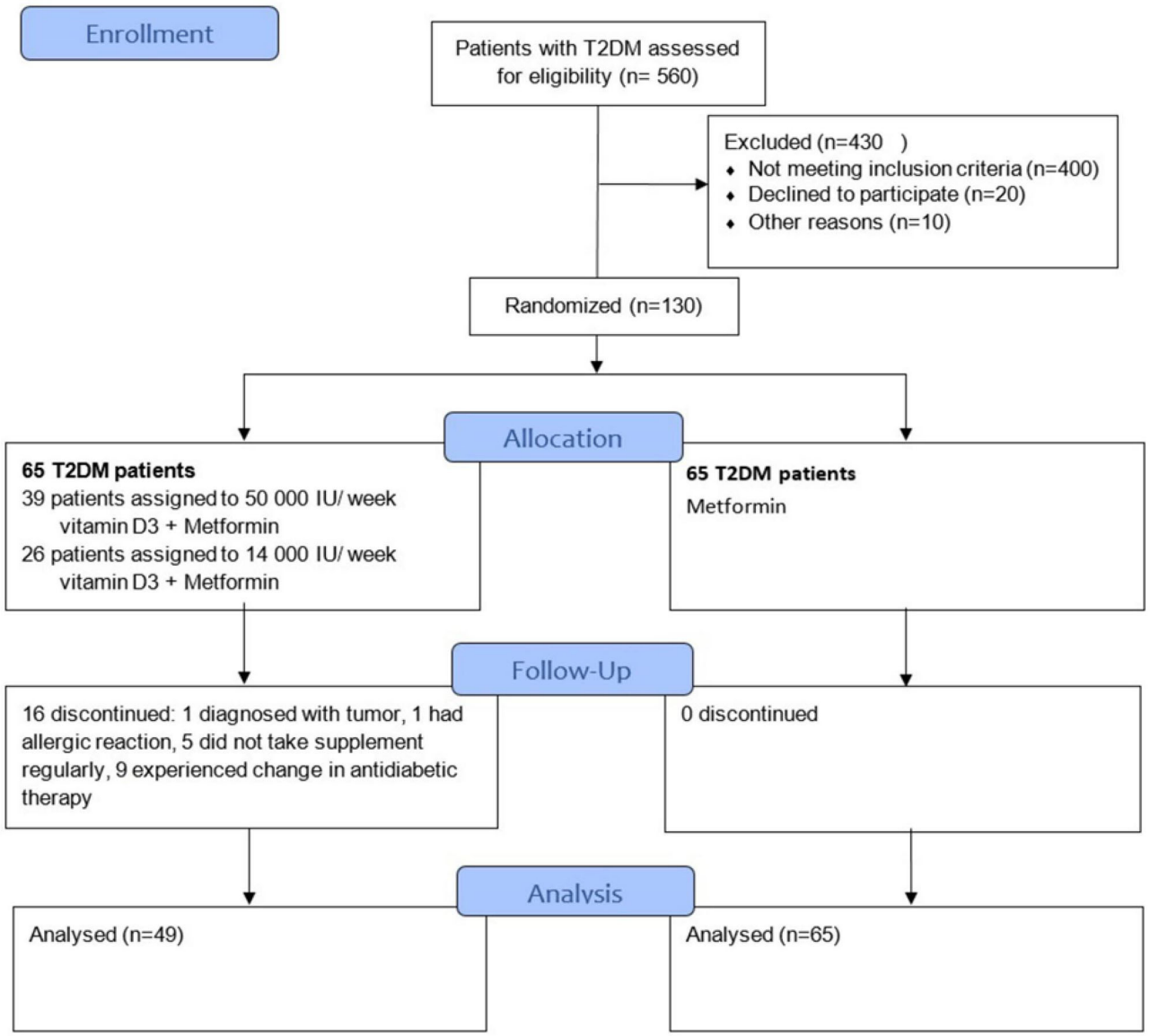

FIGURE 1 | Participant flowchart and study design.

Follow Up and Outcome Measurements

All participants were subjected to anthropometric measurements and laboratory tests at baseline, 3 and 6 months of intervention. Body height in centimeters was measured without shoes using a wall-mounted stadiometer. Body weight was measured in wearing light clothes and without shoes on electronic (digital reading) scales previously calibrated with a possible error of ± 100g. BMI was calculated as kg/m^2. Waist circumference (WC) was measured while standing and with clothes on using the non-stretchable tape positioned parallel to the floor over the umbilicus. Systolic (SBP) and diastolic blood pressure (DBP) were measured in a seated position after 10 minutes of rest with an electronic blood pressure monitoring device (Microlife's BP A150-30 AFIB). Two measurements were done one minute apart and the average value was used.

Blood Samples

Samples were drawn from venous blood early in the morning after 12 hours of overnight fasting. Serum levels of FBG, creatinine, total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG) and Ca were measured using standard enzymatic procedures (Roche Cobas 6000 c 501, Mannheim, Germany). Ca ++ was determined using the ion-selective method on an electrolyte analyzer [Roche Diagnostics AVL 9180 Electrolyte Analyzer (AVL 9180, Roche, Japan)].

Serum CRP level was determined by immunoturbidimetric method (Roche Cobas 6000 c 501, Mannheim, Germany).

For HbA1c, blood was used with K2EDTA anticoagulants and it was determined immunoturbidimetrically (Roche Cobas 6000 c 501, Mannheim, Germany).

Fasting insulin (FI) and 25(OH)D serum levels were measured by electrochemiluminescence using commercial Roche tests on the Cobas 6000/e601 automated analyzer (Roche Diagnostics, Mannheim, Germany). This is a competitive electrochemiluminescence assay which employs a vitamin D binding protein as capture protein, for the quantitative determination of total 25-OH vitamin D in human serum and plasma. According to the manufacturer's instruction measuring range is 3 to 70 ng/mL (7.5 - 175.0 nmol/L), functional sensitivity 4.01 ng/mL (10.0 nmol/L) (CV 18.5%), within-run precision: < 15 ng/mL: SD ≤ 1 ng/mL > 15 ng/mL: ≤ 6.5%, intermediate precision: < 15 ng/mL: SD ≤ 1.7 ng/mL > 15 ng/mL: ≤ 11.5%.

Lipid peroxidation was measured in plasma and expressed as the Thiobarbituric acid-reactive substances (TBARS) biomarker malondyadehide (MDA). The mean recovery was 90% (SD ± 2%), the CV was 4% (14). The TG/TBARS index was used to monitor the ratio between the potentially oxidizable substrates-polyunsaturated fatty acids of circulating triglycerides and their oxidized counterparts-lipid peroxides.

Advanced oxidation protein product level (AOPP) was measured in serum spectrophotometrically, expressed as chloramine-T equivalents. Before the analysis, plasma samples were diluted in 1:10 ratio (15). In order to avoid turbidity interference with lipids and drugs, plasma samples were previously treated with 2 mol/L magnesium chloride ($MgCl_2$) and 4% phosphortungstate dissolved in 0.19 mol/L sodium hydroxide (NaOH), centrifuged at 1000*g* for 20 minutes, and supernatant was used for AOPP analyses (ubaci referencu).

Castelli risk index I was determined through the TC/HDL cholesterol ratio, reflecting cholesterol-related atherogenic risk, characteristic of the metabolic syndrome (16), recently studied as the potential surrogate marker related to the insufficiency of vitamin D and metabolic syndrome (17).

HOMA-IR was calculated by the formula HOMA−IR=FBG (mmol/L)×FI(μIU/L)/22.5 (18).

Statistical Analysis

All normally distributed data were presented as mean ± SD. All data not normally distributed were presented as median and interquartile range. A Student's t test was used to compare the continuous variables between the Metformin + Vitamin D and Metformin group, when the distribution was normal, and Mann-Whitney test when the data have not been distributed normally. Skewed continuous variables were natural log transformed before the analysis. Two way ANOVA for repeated measures was used to monitor parameters over time. Linear regression analysis was used to assess the mean difference between Metformin + Vitamin D and Metformin group after 3 and 6 months (the mean difference is reported as β). All effects were adjusted for gender, baseline age, BMI, FI and HbA1c. The significant p value was set as 0.05 (two-sided). All statistical analyses were performed using R software (version 3.4.3) (R Foundation for Statistical Computing, Vienna, Austria) (19).

RESULTS

Out of 560 pre-screened patients 130 consented to participate in the study. **Table 1** shows baseline demographic characteristics of the study population. Clinical and biochemical parameters were balanced between the groups.

For vitamin D concentration, repeated measures two-way ANOVA revealed significant interaction ($F=75.349$, $p<0.001$), significant effect of group ($F=37.976$, $p<0.001$), and significant effect of time ($F=115.201$, $p<0.001$) (**Table 3**). In Metformin + Vitamin D group 25(OH)D levels increased significantly during intervention period ($p<0.001$). In Metformin group 25(OH)D levels significantly increased during the first 3-month period and then significantly decreased ($p<0.001$ for all) (**Table 2**). After 3 and after 6 months of supplementation, 25(OH)D levels differed significantly between groups ($p<0.001$) adjusted for participants' age, gender and baseline levels of BMI, FI and HbA1c (**Table 4**).

For HbA1c, there are significant effect of group ($F=9.782$, $p=0.037$), and significant effect of time ($F=9.782$, $p<0.001$) (**Table 3**).

In Metformin + Vitamin D group, HbA1c levels decreased significantly after 3 months of supplementation ($p=0.011$) and increased significantly between 3 and 6 month of supplementation ($p<0.001$). Significant difference in HbA1c levels between groups was seen after 3 ($p=0.031$) and after 6 months ($p=0.017$) (**Figure 2**).

For FBG, SBP, MDA, TC, Ca, and Ca ++ repeated measures two-way ANOVA revealed significant effect of time ($p=0.020$,

TABLE 1 | Baseline demographic characteristics of study population.

	Metformin + Vitamin D group N=49		Metformin group N=65		p-value
	N	%	N	%	
Age (years)↓	60.41 (8.5)		63.65 (8.2)		0.044[1]
Male†	36	55.4	21	42.9	0.256[2]
T2DM duration (years)†	4 (5)		6 (5)		0.188[3]
Non smokers†	22	44.9	38	58.5	0.356[2]
Smokers†	12	24.5	12	18.5	
Ex-smokers†	15	30.6	15	23.1	
Creatinine (μmol/L)†	78 (21)		84 (24)		0.082[3]
Vitamin D (nmol/L)†	48.79 (31.63)		58.02 (32.32)		0.095[3]
FBG (mmol/L)↓	7.90 (1.4)		7.92 (1.5)		0.841[1]
HbA1c (%)	6.56 (1.02)		6.74 (0.81)		0.387[3]
FI (μU/L)†	11.25 (7.43)		10.66 (8.92)		0.445[3]
HOMA-IR†	3.67 (2.63)		3.64 (3.22)		0.349[3]
BMI (kg/m2)↓	30.13 (4.6)		29.79 (5.0)		0.834[1]
Body weight (kg)	87.44 (14.1)		89.61 (18.5)		0.488[1]
Ca	2.43 (0.16)		2.48 (0.15)		0.462[1]
Ca ++	1.16 (0.09)		1.15 (0.07)		0.407[1]

Data are presented as ↓ mean (SD) or † median (Interquartile range) or † count, %. [1] t test, [2] Chi square test, [3] Mann-Whitney test. FBG, fasting blood glucose; HbA1c, glycated hemoglobin; FI, fasting insulin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; BMI, Body mass inde;, Ca, total calcium; Ca ++, calcium ionized.

TABLE 2 | Comparison of measured parameters over the 6-month period of vitamin D treatment.

	Metformin + Vitamin D group			Metformin group		
	Baseline	3 month	6 month	Baseline	3 month	6 month
Vitamin D (nmol/L)†	48.79 (31.63)[a,b]	104.70 (30.46)[b,#]	92.24 (20.25)[#]	58.02 (32.32)[c,d,]	67.44 (25.13)[d]	51.77 (23.99)
HbA1c (%)↓	6.56 (1.02)[a]	6.32 (0.69)[b,#]	6.48 (0.70)[#]	6.74 (0.81)[c]	6.66 (0.85)[d]	6.87 (0.92)
FI (μU/L) †	11.25 (7.43)	9.81 (7.04)	11.26 (6.68)	10.66 (8.92)	12.62 (8.30)	11.92 (7.86)
BMI (kg/m2)↓	30.1 (4.6)	30.1 (4.6)	29.7 (7.8)	29.8 (5.0)	25.7 (10.9)	28.8 (6.1)
WC (cm)	103 (11)	103 (11)	104 (11)	105 (11)	106 (10)	105 (11)
HOMA-IR †	3.67 (2.63)	3.63 (3.02)	3.44 (2.89)	3.64 (3.22)	3.42 (2.64)	3.39 (3.37)
FBG (mmol/L)↓	7.87 (2.4)[a,b]	7.28 (1.16)	7.23 (1.26)	7.91 (1.44)	7.97 (1.74)	7.74 (1.49)
SBP (mmHg)↓	136.69 (24)[a]	142.48 (17.33)[b]	136.65 (17.78)	139.48 (19.15)	142.52 (17.33)	141.45 (16.62)
DBP (mmHg)↓	83.19 (12.14)	85.23 (9.03)	83.07 (8.21)	81.28 (10.16)	84.01 (9.91)	84.18 (9.67)
MDA (TBARS) (μM/L)†	3.14 (1.89)	2.97 (1.21)	2.77 (2.38)	3.31 (1.73)[d]	3.17 (1.32)[d]	3.09 (3.97)
AOPP (μM chloramines T equivalents)†	185.74 (146.48)[a]	131.19 (64.64)[b,#]	220.28 (63.73)	176.02 (134.35)[c]	104.56 (67.32)[d]	199.42 (78.28)
CRP (mg/L)†	1.79 (3.02)	1.36 (2.55)	1.61 (2.93)	1.40 (2.06)	1.49 (2.08)	2.13 (3.16)
TC (mmol/L)†	5.26 (1.92)[a]	5.10 (1.72)[b]	5.72 (1.60)	5.40 (1.64)	5.30 (1.14)	5.60 (2.01)
TG (mmol/L)†	1.72 (1.02)	1.41 (0.99)	1.70 (1.08)	1.77 (1.04)	1.90 (1.24)	1.85 (1.40)
HDL (mmol/L)↓	1.35 (0.34)	1.33 (0.31)[#]	1.38 (0.30)	1.26 (0.30)[c]	1.19 (0.26)[d,#]	1.25 (0.34)
LDL (mmol/L)↓	3.36 (1.06)	3.18 (0.98)	3.40 (1.04)	3.41 (1.05)	3.13 (0.90)	3.22 (1.19)
Castelli †	4.00 (2.07)	4.09 (1.75)	3.99 (1.67)	4.52 (2.03)	4.30 (1.57)	4.51 (1.70)
TG/TBARS↓	0.56 (0.32)	0.58 (0.32)	0.55 (0.28)	0.60 (0.30)	0.70 (0.32)	0.62 (0.34)
Ca	2.43 (0.16)	2.44 (0.16)	2.48 (0.15)	2.41 (0.10)	2.41 (0.11)	2.44 (0.09)
Ca ++	1.16 (0.09)	1.22 (0.08)	1.23 (0.10)	1.15 (0.07)	1.21 (0.06)	1.23 (0.18)

Data are presented as ↓ mean (SD) or † median (Interquartile range), In two way ANOVA for repeated measures: In the Metformin + Vitamin D group: p<0.05 [a]vs 3 months, [b]vs 6 months, In the Metformin: p<0.05 [c]vs 3 months, [d]vs 6 months, # between group at specific time point. HbA1c, glycated hemoglobin; FI, fasting insulin; BMI, Body mass index; WC, waist circumference; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; MDA, malondialdehyde; AOPP, advanced oxidation protein products; CRP, C-reactive protein; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TBARS, thiobarbituric acid reactive substance; Ca, total calcium; Ca ++, calcium ionized.

p=0.046, p<0.001, p=0.008, p<0.001, and p<0.001) (**Table 3**), but there was no significant difference between groups during the intervention period.

For BMI, repeated measures two-way ANOVA revealed no significant interaction (F=2.175, p=0.129), significant effect of group (F=4.489, p=0.039), and significant effect of time (F=4.926, p=0.015) (**Table 3**). For DBP, repeated measures two-way ANOVA revealed no significant interaction (F=0.528, p=0.567), significant effect of group (F=4.501, p=0.039), and significant effect of time (F=3.989, p=0.029) (**Table 3**).

For AOPP, repeated measures two-way ANOVA revealed no significant interaction (F=0.098, p=0.907), significant effect of

TABLE 3 | Results of two-way ANOVA for effects of the Time factor and Group factor in the study.

Parameter	Source	F	p value	Partial Eta Squared
Vitamin D	Time	115.201	<0.001	0.526
(nmol/L)	Group	37.976	<0.001	0.267
	time * group	75.349	<0.001	0.420
HbA1c (%)	Time	9.782	<0.001	0.158
	group	3.999	0.048	0.037
	time * group	1.391	0.253	0.026
FI (μU/L)	Time	0.852	0.428	0.008
	Group	0.000	0.992	0.000
	time * group	0.389	0.628	0.008
BMI (kg/m2)	Time	1.479	0.231	0.016
	Group	0.231	0.632	0.003
	time * group	1.597	0.210	0.017
WC (cm)	Time	1.046	0.354	0.013
	Group	2.544	0.115	0.030
	time * group	0.860	0.418	0.010
HOMA-IR	Time	1.049	0.348	0.010
	Group	0.297	0.587	0.003
	time * group	0.694	0.491	0.006
FBG (mmol/L)	Time	3.978	0.020	0.037
	Group	2.304	0.132	0.022
	time * group	2.733	0.070	0.026
SBP (mmHg)	Time	3.233	0.046	0.039
	Group	0.488	0.487	0.006
	time * group	0.862	0.417	0.011
DBP	time	2.881	0.062	0.035
(mmHg)	Group	0.128	0.722	0.002
	time * group	1.264	0.285	0.016
MDA	Time	251.942	<0.001	0.716
(TBARS)	Group	0.021	0.884	0.000
(μM/L)	time * group	0.109	0.865	0.001
AOPP (chloramines	Time	53.710	<0.001	0.496
T equivalents)	Group	4.029	0.047	0.035
	time * group	0.187	0.667	0.002
CRP (mg/L)	Time	0.576	0.528	0.006
	Group	0.184	0.669	0.002
	time * group	1.260	0.282	0.012
TC (mmol/L)	Time	5.009	0.008	0.046
	Group	0.100	0.753	0.001
	time * group	0.355	0.694	.003
TG (mmol/L)	Time	0.342	0.673	0.003
	Group	2.610	0.109	0.025
	time * group	2.509	0.092	0.024
HDL(mmol/L)	Time	4.783	0.009	0.044
	Group	3.919	0.050	0.036
	time * group	1.212	0.300	0.012
LDL(mmol/L)	Time	3.010	0.052	0.031
	Group	0.120	0.730	0.001
	time * group	0.763	0.468	0.008
CASTELI	Time	1.035	0.357	0.010
	Group	1.755	0.188	0.017
	time * group	1.544	0.217	0.015
TG/TBARS	Time	1.751	0.176	0.018
	Group	2.755	0.100	0.027
	time * group	0.683	0.496	0.007
Ca	Time	101.000	<0.001	0.186
	Group	1.757	0.188	0.017
	time * group	0.091	0.763	0.001
Ca ++	Time	18.068	<0.001	0.156
	Group	0.198	0.657	0.002
	time * group	0.170	0.772	0.002

Two-way ANOVA for repeated measures. HbA1c, glycated hemoglobin; FI, fasting insulin, BMI, Body mass index; WC, waist circumference; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; MDA, malondialdehyde; AOPP, advanced oxidation protein products; CRP, C-reactive protein; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TBARS, thiobarbituric acid reactive substance; Ca, total calcium; Ca ++, calcium ionized.

**Interaction.*

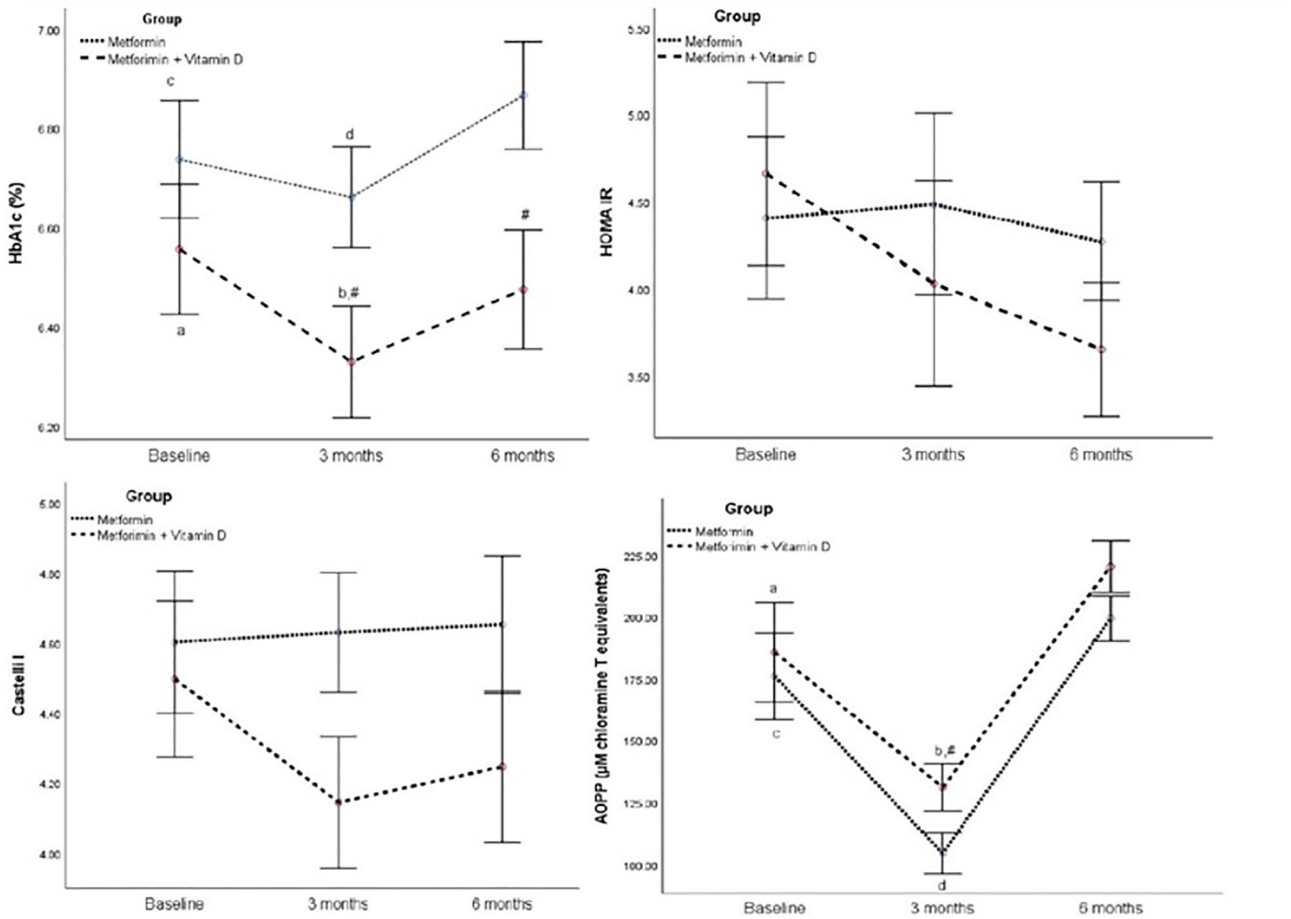

FIGURE 2 | HbA1c, HOMA IR, Castelli I, and AOPP in the follow-up of 6 months between Metformin and Metformin + Vitamin D group. Data are presented mean ± SE, In two way ANOVA for repeated measures: In the Metformin + Vitamin D group: p<0.05 a vs 3 months, [b] vs 6 months, In the Metformin: p<0.05 [c] vs 3 months, [d] vs 6 months, # between group at specific time point.

group (F=4.214, p=0.047), and significant effect of time (F=90.323, p<0.001) (**Table 3**). Significant difference between groups was seen only in 3rd month of intervention time (**Table 4**).

Regarding mean change, regression analysis significant differences between groups were seen in Vitamin D after 3 months (B 42.25 (95%CI 35.43 - 49.98), p<0.001), and after 6 months (B 38.76 (95%CI 31.72 – 45.80), p<0.001). Also, it is demonstrated a significant mean difference of 0.20 mmol/L in HbA1c after 3 months (p=0.050), of 0.24 mmol/L in HbA1c after 6 months (p=0.045).

DISCUSSION

In the present study we have found that the recommended doses of vitamin D significantly decreased the level of HbA1c after 3 as well as after 6 months of vitamin D supplementation in patients with T2DM treated with metformin, compared to the metformin group. The most recent meta-analysis carried out by Hu at al. indicated that vitamin D supplementation had beneficial effects on HbA1c, insulin resistance and FI in the subgroup of subjects with short-term follow-up intervention, but had no effect among those with more than 3 months of intervention (20). Similar results were obtained in the systematic review by Nigil Haroon et al. (21). There are many causes which could support these results. First of all, it should not be ignored that the 6-month period is the time of three seasonal changes, in our case, from summer to winter, when the climate conditions, the amount of clouds and a smaller extent of UV exposure may have a significant influence on the endogenous production of vitamin D. Furthermore, the diet and daily habits may differ significantly in winter, which may contribute to the worsening of the metabolic control. Additionally, the patient's perception of treatment and motivation may have a significant influence on the treatment efficacy. To our knowledge, this is the first study with individual dosing plan for patients regarding 25(OH)D levels according to the Endocrine Society guidelines (11). The daily doses proposed were 7142 IU (50 000 IU weekly) for vitamin D deficient patients and 2000 IU for patients who had

TABLE 4 | Adjusted p values of measured parameters over the 6-month period of vitamin D treatment.

	3 month		6 months	
	Adjusted B (95%CI)	**p-value**	**Adjusted B (95%CI)**	**p-value**
Vitamin D (nmol/L)	42.25 (35.43-49.98)	<0.001	38.76 (31.72-45.80)	<0.001
HbA1c (%)	-0.20 (-0.40- -0.03)	0.050	-0.24 (-0.48- -0.006)	0.045
FI (μU/L)	-0.87 (-4.48-2.75)	0.635	-1.23 (-0.82-1.38)	0.245
BMI (kg/m2)	2.88 (-0.02-5.77)	0.052	1.73 (-1.45 – 4.89)	0.288
WC (cm)	-1.12 (-2.43-0.19)	0.094	-1.32 (-2.82-0.19)	0.086
HOMA IR	-0.70 (-2.24-0.85)	0.372	-0.61 (-1.54-0.33)	0.203
FBG (mmol/L)	-0.59 (-1.08- -0.10)	0.018	-0.38 (-0.85-0.09)	0.116
SBP (mmHg)	1.81 (-4.35-7.97)	0.561	-2.82 (-9.10-3.44)	0.373
DBP (mmHg)	0.87 (-2.63-4.38)	0.622	-1.74 (-5.05-1.57)	0.299
MDA (TBARS) (μM/L)	-0.030 (-0.60-0.54)	0.916	-0.60 (-1.55-0.94)	0.215
AOPP (μM chloramine T equivalents)	38.62 (-13.10-90.34)	0.142	5.93 (-35.42-47.28)	0.776
CRP (mg/L)	-1.40 (-6.50-3.70)	0.588	1.64 (-3.31-0.56)	0.385
TC (mmol/L)	-0.17 (-0.50-0.16)	0.321	0.06 (-0.35-0.48)	0.756
TG (mmol/L)	-0.42 (-0.76- -0.08)	0.019	-0.46 (1.08-0.16)	0.156
HDL (mmol/L)	-0.42 (-1.24-0.39)	0.305	0.04 (-0.03-0.11)	0.270
LDL (mmol/L)	-0.53 (-1.55-0.49)	0.306	0.25 (-0.14-0.64)	0.209
Castelli I	-0.40 (-0.83- -0.05)	0.040	-0.26 (-0.73-0.21)	0.409
TG/TBARS	-0.11 (-0.23-0.01)	0.078	-0.06 (-0.18-0.05)	0.288
Ca	0.18 (-0.02-0.06)	0.369	0.19 (-0.02-0.06)	0.333
Ca ++	0.00 (-0.03-0.03)	0.989	-0.005 (-0.07-0.06)	0.874

B was adjusted for baseline value of specific parameter, age, gender, FI, BMI and HbA1c. HbA1c, glycated hemoglobin; FI, fasting insulin; BMI, Body mass index; WC, waist circumference; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure, MDA, malondialdehyde; AOPP, advanced oxidation protein products; CRP, C-reactive protein; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TBARS, thiobarbituric acid reactive substances; Ca, total calcium; Ca ++, calcium ionized.

25(OH)D levels > 50 nmol/L. This dose of 2000 IU was not sufficient to provide 25(OH)D levels beyond 100 nmol/L, which is believed to be crucial for extra-skeletal effects (22). The same fact could explain why we did not maintain a significant effect of vitamin D on FI and HOMA-IR levels over the six-month period. Talaei et al. showed that the effect of vitamin D on insulin resistance was significant only when the vitamin D concentration was between 100 and 150 nmol/L (22). Since the definition of the optimal vitamin D level remains controversial, vitamin D deficiency would not be the inclusion and standard judgment criterion (23, 24). However, it is possible that vitamin D has beneficial effects only in vitamin D deficient patients especially in those with poor glycaemic control (25, 26). Yet, Krul-Poel et al. found that vitamin D supplementation was not sufficient to improve glycaemic control in patients with well controlled T2DM, but they used intermittent high-dose of vitamin D. They may have an impact on different outcomes compared to daily doses (27, 28).

A meta-analysis that included 17 randomized controlled trials evaluated the effect of vitamin D supplementation on lipid profile in patients with T2DM. Results revealed that vitamin D supplementation had positive effects in vitamin D deficient patients who had received vitamin D intervention for ≤ 12 weeks. Our results also showed that vitamin D had beneficial effect on HDL cholesterol after 3 months of supplementation when there was higher prevalence of vitamin D deficiency in the Vitamin D+Metformin group and higher vitamin D doses were given (29).

The proposed mechanisms of vitamin D beneficial effects may occur on different levels. By acting as an immunomodulator, vitamin D can regulate innate and adaptive immunity, particularly dendritic cell maturation, macrophage differentiation and T-cell proliferation, while decreasing inflammatory response, inflammatory cytokine secretion and apoptosis of beta cells. On the cellular level, it can down-regulate inflammatory and redox sensitive nuclear transcription factor kappa beta (NFκB) (30–33). Vitamin D stimulates insulin secretion by calcium flux-dependent mechanisms (34).

Although we observed decrease in CRP levels in Metformin + Vitamin D group this decrease did not reach statistical significance. The lack of significant difference between groups in our study could be explained by a small sample size.

We also observed significant increase in Ca and Ca ++ levels in both groups during the study period ($p<0.0001$). Still, there was no significant difference between groups in Ca and Ca++ levels. Seasonal changes in sunlight and dietary habits in spite of given recommendations could be the reason for this result.

Oxidative stress is strongly associated with T2DM and plays a key role in insulin peripheral sensitivity and insulin secretory response (6, 35). It is well documented that hyperglycaemia contributes mostly to the generation of the reactive oxygen species (ROS), through glucose autoxidation and consequent non-enzymatic glycation of proteins in T2DM (36, 37). Recent evidence has suggested that Vitamin D can decrease oxidative stress. Meta-analysis performed by Sepidarkish et al. has shown that vitamin D supplementation significantly reduced levels of MDA, a primary biomarker of lipid peroxidation (38, 39). In the same meta-analysis the positive effect on MDA was observed only in subgroups with bi-weekly administration of vitamin D doses that are between 100 000 and 200 000 IU per month. Doses less than 100 000 IU and more than 200 000 IU per month were

under significant effect. Different dosing and different way of administration could be the reason for not having more pronounced effects of vitamin D on MDA levels during our study. Similar results were reported by Eftekhari et al. (40). It is well documented that vitamin D possess the antioxidant potential *in vivo* and *in vitro*, serving as a lipophilic substance, as a membrane and lipoprotein free radical scavenger and antioxidant (41–43). It seems that vitamin D treatment was not a promising approach in improving the AOPP level, most probably because of its lipophilic properties (**Table 2**). Beneficial effect was seen only after 3 month period when higher doses of vitamin D were given. After 3rd month AOPP had the same trend of rising in both groups, which can be attributed to the interaction of drugs present in circulation (most probably metformin) with method, since all samples were made at once, under the same conditions.

Our study had some limitations. Firstly, it was a randomized but not a placebo controlled trial. Levels of 25(OH)D were used as vitamin D status markers, but vitamin D has several forms with different levels of activity (1). Insulin resistance was assessed using HOMA IR instead of hyperinsulinemic-euglycemic clamps, which is proposed as a gold standard (44). Serum 25(OH)D was measured by an electrochemiluminescence immunoassay, not a gold standard method-liquid chromatography mass spectrometry (45). The strengths of our study include its randomized, prospective design; the use of vitamin D status dependent on oral daily doses according to ES guidelines; the study was mediumd and long-term follow-up randomized.

CONCLUSION

Our study has indicated that oral daily doses of vitamin D proposed by ES guidelines reduce the levels of HbA1c over a 3-month and over a 6-month period. Its effect on metabolic control, through the improvement on HOMA-IR, and oxidative stress measured through AOPP improvment might have a promising effect if vitamin D could be maintained in optimal dose. Further investigation would reconsider vitamin D doses in patients with T2DM, which may attenuate the oxidative stress risk, the risk of metabolic syndrome and the related cardiovascular events.

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 Ethical Committee of Primary Health Care Center in Podgorica (ID number 05/01-E.K.-5989/1). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MC contributed in the conception of the work, participated in the study design, and wrote the manuscript. RK contributed in the conception of the work, participated in the study design, and critically revised the manuscript. AK and GK contributed in the conception of the work, performed biochemistry analyses, and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Adding Pay-for-Performance Program to Routine Care Was Related to a Lower Risk of Depression Among Type 2 Diabetes Patients in Taiwan

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Background: Patients with type 2 diabetes (T2DM) often experience depression during treatment, negatively influencing their treatment compliance and clinical outcomes. Recently, the pay-for-performance (P4P) program for chronic diseases, with high-cost and high-risk feature, such as T2DM, has been implemented and has been operational for several years. Nevertheless, its effect on the risk of developing depression among T2DM cases is unknown. This study aims to explore the association of P4P use with the subsequent risk of developing depression among these patients.

Methods: This cohort study used a nationwide health insurance database to identify patients 20–70 years of age newly diagnosed with T2DM who enrolled in the P4P program between 2001 and 2010. From this group, we enrolled 17,022 P4P users and then 17,022 non-P4P users who were randomly selected using propensity-score–matching. Enrolled patients were followed until the end of 2012 to record the occurrence of depression. The Cox proportional hazards regression was utilized to obtain the adjusted hazard ratio (aHR) for P4P use.

Results: During the study period, a total of 588 P4P users and 1,075 non-P4P users developed depression at incidence rates of 5.89 and 8.41 per 1,000 person-years, respectively. P4P users had a lower depression risk than did non-P4P users (aHR, 0.73; 95% Confidence Interval, 0.65–0.80). This positive effect was particularly prominent in those receiving high-intensity use of the P4P program.

Conclusion: Integrating P4P into routine care for patients with T2DM may have beneficial effects on curtailing the subsequent risk of depression.

Keywords: type 2 diabetes, pay-for-performance, depression, cohort study, risk

INTRODUCTION

Depression is a chronic mental disorder that impacts cognitions, moods, behaviors, and physical well-being, thereby affecting quality of life (1). Depression affects approximately 350 million people worldwide and is particularly common among individuals with chronic diseases (2). For example, the association between depression and type 2 diabetes (T2DM) has been recognized for many years. One epidemiological study suggested that at least one-third of people with diabetes suffer from clinically relevant depressive disorders (3). A meta-analysis of 11 studies reported a 24% increased risk of incident depression in people with T2DM, compared to those without T2DM (4). Notably, the combination of diabetes and depression poses critical clinical challenges to the healthcare system. T2DM patients suffering from concomitant depression have an estimated 52% increase ($10,016 vs. $15,155) in annual medical expenses over those without depression (5), and more than double the likelihood of mortality due to poor glucose regulation and poor compliance with diabetes treatments (6). Therefore, an early implementation of effective diabetes management is important to prevent or lessen the susceptibility to depression among such patients (7).

The present standard modality for decreasing depression onset among diabetic patients is the use of anti-depressant medications. Some of these medications, however, may induce adverse side effects such as weight gain and decreased glycemic control (4, 8, 9). In response to this, another option, the pay-for-performance (P4P) program for patients with high-cost and high-risk chronic diseases, has raised attention due to its feature (10). The aim of P4P programs is to establish a complete "patient-centered" co-care model for self-care related to health education, consultation, referral system establishment, and resource linking. Moreover, in order for the patient to stabilize the disease and improve quality of life, it is necessary to actively participate in programs, and regularly follow-up with case management, allowing patients to receive regular visits and evaluate physician-prescribed medications to reduce the development of any complications (11). A growing body of scientific evidence indicates that implementing P4P significantly increases the quality and satisfaction of medical care for diabetic patients (12), and diminishes the burden of disease-generated complications (13, 14). At present, no data are available on the success of P4P in decreasing the risk of depression among T2DM patients. To address this concern, we used a national insurance database to compare depression risks between patients with T2DM who received and who did not participate in the P4P program.

METHODS

Data Source

The Longitudinal Health Insurance Database (LHID) was utilized as the data source in this retrospective cohort study. The LHID is a sub-dataset of the National Health Insurance Research Database (NHIRD) of Taiwan, made up of one million randomly sampled people with over 10 years of available follow-up data. It has been established that these recruited individuals have similar age and sex distributions to the general population of Taiwan because of a multistage stratified systematic sampling method performed by the Bureau of National Health Insurance (NHI) to ensure the representativeness of the sampling (15). This database has been previously used in numerous research reports (16, 17). This database compiled (i) demographic information of enrollees; (ii) health insurance claims data; (iii) diagnostic codes; (iv) contracted pharmacies; and (v) medical examination information on persons under the NHI program. This study was conducted in accordance with the Helsinki Declaration, and was approved by the local institutional review board and ethics committee of Buddhist Dalin Tzu Chi Hospital (No. B10004021-3).

Study Population

Patients 20–70 years of age, newly-diagnosed with T2DM between 2001 and 2010 were identified (**Figure 1**). To ensure the accuracy of diagnoses, patients with T2DM were identified if they had at least three ambulatory or one inpatient claims with the International Classification of Disease, 9th Edition, Clinical Modification (ICD-9-CM) diagnosis code 250 without type 1 diabetes (ICD-9-CM code 2501). A total of 1,540 patients with T2DM were excluded because of previous diagnosis of depression (ICD-9-CM code 296.2, 296.3, 300.4, or 311). In accordance with the rationale in identifying T2DM cases, we only selected participants who had at least three outpatient visits, or at least one inpatient claim due to depression (ICD-9-CM code 296.2, 296.3, 300.4, or 311), dating from 1996, when the computerized claims data from the LHID became available, until the date of cohort entry. Those with a follow-up period <12 months were also excluded ($n = 345$). Overall, we enrolled 63,853 subjects with new-onset T2DM.

Healthcare claim data for all included patients were reviewed to determine whether the P4P model had been used following the onset of T2DM. Patients were considered as P4P users if their claim files were noted with the code of "E4" in the treatment claims after diabetes onset (13), whereas the remaining subjects were classified as non-P4P users. In Taiwan, P4P has been applied to several chronic diseases, including diabetes (13, 14) and schizophrenia (18, 19). P4P has been launched into routine clinical practice since 2001, with the aim of providing holistic care to complex or high-resource patients, particularly those with T2DM (20). This program integrated a multi-component intervention comprised of medical history, evaluation of management plan, diabetes self-management education and periodic laboratory evaluations. These evaluations contained results from blood sugar, hemoglobin A1c (HbA1c), low-density lipoprotein, triglycerides, serum creatinine, urine albumin/creatinine ratio, systolic and diastolic blood pressures, eye examination, and foot examination for initial enrollment visit. Furthermore, several of these examinations, including blood sugar, HbA1c, and systolic and diastolic blood pressures, are performed every 3 months for care visit continuity (20). Taken together, the P4P program is patient-tailored and includes assessments, planning, integration, implementation, and follow-up evaluations of treatment plans via closer collaboration between clinical

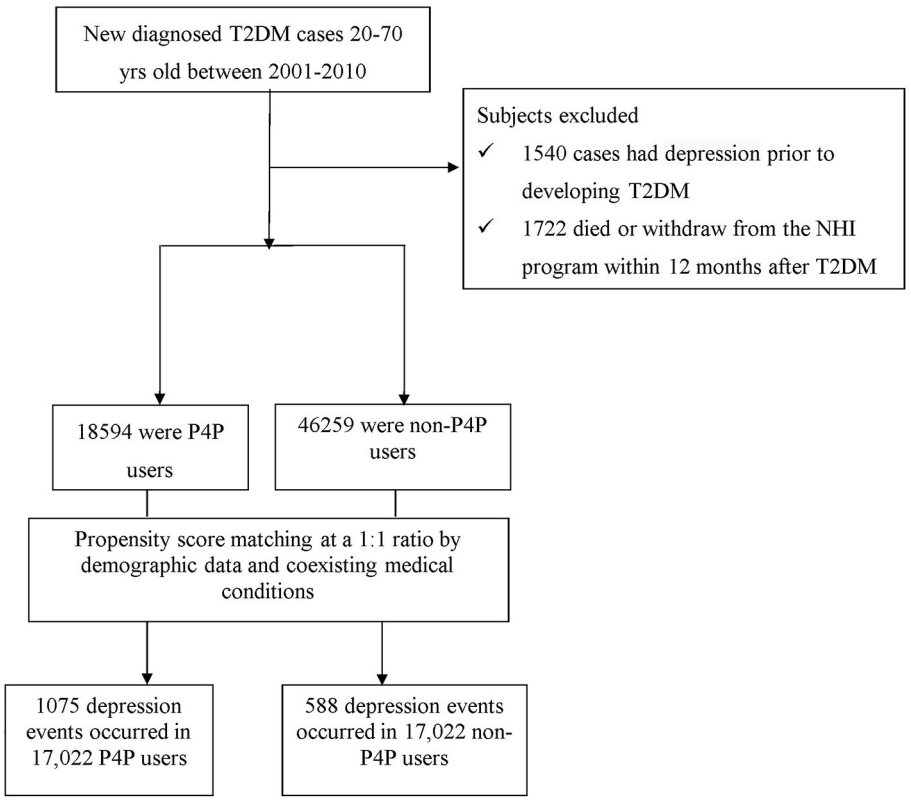

FIGURE 1 | Flow chart of selection and follow up of study subjects.

specialists, such as physicians, certified diabetes educators, and registered dietitians, allowing participants to follow regular visits and healthcare providers to evaluate medication compliance and effect.

In this study, 18,594 patients were categorized as P4P users. A comparison cohort was randomly selected from the remaining insured T2DM cases without the involvement of P4P. To ensure comparability of samples, we utilized the propensity score (PS) with a 1:1 matching method to balance the characteristics between the P4P and non-P4P groups. We used multivariable logistic regression models to estimate PS-value according to all baseline characteristics (listed in **Table 1**) as covariates included in the model. Patients were matched by PS using one-to-one nearest neighbor matching within 0.2 caliper distance, in which, pairs of user and non-user were formed, such that matched subjects have similar values of each propensity. Afterwards, an equal number of P4P and non-P4P patients were analyzed in this study. Additionally, to consider immortal time bias that may bias the results in favor of the treatment group (21), the index date for the follow-up period for non-P4P users was the date of T2DM diagnosis, while that for P4P users was defined as the date of initiation of P4P use. The end date of the follow-up period for both groups was the earliest of the following: (a) a diagnosis of depression; (b) withdrawal from the insurance program; or (c) the date of December 31, 2012.

Definition of Other Covariates

Information on potential confounders included age, sex, monthly income (for estimating insurance payment), the urbanization level of enrollees' residential area, and former comorbidities. Monthly income was separated into three classes (class 1 [lowest income] to class 3 [highest income]). The urbanization level was classified into seven grades, as outlined in a previous study (22), with a higher grade indicating a more urban environment. In this study, we divided urbanization into three levels, namely, high (metropolitan cities), medium (small cities and suburban areas), and low (rural areas). Baseline comorbidities for each subject were determined by individual medical records in the year preceding cohort entry, which included hypertension (ICD-9-CM 401-405), obesity (ICD-9-CM 278.0), stroke (ICD-9-CM 430-438), heart disease (ICD-9-CM 410-429), chronic kidney disease (ICD-9-CM 585), rheumatologic disorders (ICD-9-CM 725-729), and cancer (ICD-9-CM 140-208).

Statistical Analysis

Categorical variables are reported as frequency and/or percentage, and continuous variables are presented as mean with standard deviation (SD). In step one of the analyses, Chi-square test and *t*-test were used to examine the differences in demographic variables and comorbidities between those with and without P4P use. The incidence rate of depression was calculated as the number of cases per 1,000 person-years.

TABLE 1 | Demographic data and selected comorbidities of study subjects.

Variables	Total	Non-P4P users *N* = 17,022	P4P users *N* = 17,022	*p*
Age (year)				0.74
≤50	12,279 (36.1)	6,155 (36.2)	6,124 (36.0)	
>50	21,765 (63.9)	10,867 (63.8)	10,898 (64.0)	
Mean (SD)	53.6 ± 10.1	53.6 ± 10.2	53.6 ± 10.1	0.82
Sex				0.88
Female	16,761 (49.2)	8,388 (49.3)	8,373 (49.2)	
Male	17,283 (50.8)	8,634 (50.7)	8,649 (50.8)	
Monthly income				0.36
Class 1	12,802 (37.6)	6,420 (37.7)	6,382 (37.5)	
Class 2	19,263 (56.6)	9,643 (56.7)	9,620 (56.5)	
Class 3	1,979 (5.8)	959 (5.6)	1,020 (6.0)	
Residential area				0.68
Urban	19,819 (58.2)	9,938 (58.4)	9,881 (58.0)	
Suburban	5,286 (15.5)	2,650 (15.6)	2,636 (15.5)	
Rural	8,939 (26.3)	4,434 (26.0)	4,505 (26.5)	
Comorbidity				
Hypertension	17,849 (52.4)	8,915 (52.4)	8,934 (52.5)	0.84
Obesity	621 (1.82)	315 (1.85)	306 (1.80)	0.69
Rheumatoid	350 (1.0)	239 (1.4)	211 (1.2)	0.18
Heart disease	6,311 (18.5)	3,128 (18.4)	3,183 (18.7)	0.44
Chronic kidney disease	552 (1.6)	337 (2.0)	315 (1.9)	0.38
Cancer	1,215 (3.6)	552 (3.2)	563 (3.3)	0.74
Stroke	2,324 (6.8)	1,206 (7.1)	1,218 (7.2)	0.80

Multivariate Cox proportional hazards regression was then applied to compute the hazard ratio (HR) with 95% confidence interval (CI) of depression risk in association with P4P use. To test the robustness of the relationship between P4P use and subsequent depression risk, we summed the total number of P4P use and categorized P4P usage as low, medium, or high based on the tertile distribution of P4P use. The assumption of proportional hazards was confirmed by plotting the graph of the survival function vs. the survival time and the graph of the log, log (survival), vs. the log of survival time. Statistical analyses were performed using SAS Version 9.3 software (SAS Institute Inc., Cary, NC, USA), with $p < 0.05$ considered significant.

RESULTS

The analysis included data from 17,022 P4P users and 17,022 non-P4P users. Analysis of the distributions of pertinent characteristics between the two groups, including age, sex, monthly income, residential area, and comorbidities, indicates that the two groups were comparable with respect to these characteristics (**Table 1**). The mean age for P4P users and non-P4P users were 53.6 ± 10.2 and 53.6 ± 10.1 years, respectively. The sex ratio was approximately 1:1 between males and females in both cohorts. The majority of participants had monthly income levels of Class 2 (56.6%) and tended to live in more urbanized areas (58.2%). The primary comorbidity in both cohorts was hypertension (52.4%), followed by heart disease (18.5%), and stroke (6.8%).

Among all eligible T2DM subjects, a total of 1,663 first episodes of depression occurred, 1,075 in non-P4P users and 588 in P4P users during follow-up periods of 127820.16 and 99788.27 person-years, respectively. The incidence rate of depression was found to be significantly lower in P4P users than in non-P4P users (5.89 vs. 8.41, respectively, per 1,000 person-years), with an adjusted HR of 0.73 (95% CI: 0.65–0.80) (**Table 2**). Subgroup analysis by low, medium, and high intensity of P4P use further indicated that T2DM patients using P4P at high intensity had a 52% lower risk of depression (95% CI: 0.41–0.58).

We performed an additional stratified analysis by age and sex to determine the effect of P4P on the risk of depression. In general, the use of P4P was associated with a lower risk of depression, regardless of subject's sex or age. Multivariable stratified analysis showed that the likelihood of decreased depression was greater in males than females (adjusted HR: 0.67; 95% CI: 0.58–0.81) (**Table 3**).

DISCUSSION

Findings of this retrospective cohort study indicated that depression risk was lower for T2DM patients who received P4P than for those who did not. Multivariable analysis showed that P4P use was associated with a 73% lower risk of depression among T2DM subjects. High-intensity use of P4P had markedly greater benefits, with a 52% lower risk of depression. As a dose-response relationship is considered strong evidence for a causal relation between exposure level and outcome, this finding suggests that P4P use is indeed successful in decreasing the likelihood of depression. While studies on this issue are scarce, this positive therapeutic effect is consistent with earlier reports and adds to a growing body of evidence regarding the clinical effectiveness of P4P (12–14, 23).

We suggest several potential reasons for the beneficial effect of P4P on depression risk in this study. First, a unique difference between the P4P program and conventional treatment is that the former utilized a highly interactive approach to more actively engage T2DM patients with educational and therapeutic information, throughout the post-implementation period (10, 20). This approach might be beneficial in instituting individually-tailored, need-based strategies for these patients to increase their acceptance of T2DM and ultimately improve their psychological adjustment. Of the studies conducted thus far, some have shown that interventions such as structured self-monitoring of blood glucose, consecutive group-based counseling, and an education program were related to lower risks of depression following T2DM diagnosis (7, 24). Second, the continuity of care embedded in P4P is reported to enable diabetic patients to maintain good metabolic control, especially of their HbA1c levels (25). For diabetic patients, higher HbA1c is thought to correlate with a higher risk of developing depression (26, 27). Previous studies have shown that patients with poorly controlled diabetes commonly had higher levels of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin 1

TABLE 2 | Risk of depression for T2DM patients with and with no use of P4P program.

Patient group	*N*	Events	Person-years	Incidence	Adjusted HR* (95% CI)
Non-P4P users	17,022	1,075	127820.16	8.41	1
P4P users	17,022	588	99788.27	5.89	0.73 (0.64–0.83)
Low intensity	8,497	287	42338.85	6.78	0.85 (0.75–0.98)
Medium intensity	4,425	163	24126.49	6.76	0.84 (0.71–0.97)
High intensity	4,100	138	33322.93	4.14	0.48 (0.41–0.58)

** Model adjusted for sex, age, residential area, monthly income, and comorbidities.*

TABLE 3 | Incidence and depression risk for T2DM patients with and with no P4P use stratified by sex and age.

Variables	Non-P4P users			P4P users			Adjusted HR (95% CI)
	Patients	Person-years	Incidence	Case	Person-years	Incidence	
Sex							
Female	652	62988.59	10.35	372	49585.20	7.50	0.75[Y] (0.65–0.84)
Male	423	64831.57	6.52	216	50203.07	4.30	0.67[Y] (0.58–0.81)
Age							
≤50	347	44602.88	7.78	192	34874.25	5.51	0.74* (0.62–0.89)
>50	728	83217.28	8.75	396	64914.02	6.10	0.73* (0.63–0.87)

[Y] Model adjusted for age, residential area, monthly income, and comorbidities.
** Model adjusted for sex, residential area, monthly income, and comorbidities.*

(IL-1), IL-6, and HbA1c-values (28, 29). These mediators may play important roles in the pathogenesis of neuropsychiatric symptoms, especially depression (30).

Age-and sex-specific analyses showed that P4P provides greater benefits for male subjects. Two reasons may account for this phenomenon. First, women have been shown to be more health-conscious than men and thus may be more likely to pursue treatment at the earliest notice of medical irregularity (31), thereby lessening or moderating the preventive effect of the P4P program in influencing depression onset. In addition, females may benefit from inherent estrogen, which is known to suppress production of the inflammatory cytokines IL-1, IL-6, and TNF-α (32), which may affect the effect of P4P among them.

As previously described in the Methods section, the database used in this study has several strengths, including its representativeness of the entire Taiwanese population and the large sample size that ensured reliable findings. In addition, this study is the first to investigate the relationship between P4P use and depression risk in patients with T2DM by using a longitudinal cohort study design, thus allowing us to robustly examine the relationship between high intensity P4P use and the risk of depression among such patients. Nonetheless, several limitations of this study merit attention. First, the use of secondary health care databases might pose the risk of errors in the coding process. To diminish this potential risk, the disease of interest in this study, namely T2DM, as well as the manifestations of depression and comorbidities, were identified if it ever occurred at a minimum of three outpatient visits, or if, at least, one inpatient admission during the follow-up period was recorded. Additionally, the NHI of Taiwan randomly reviews the charts and audits medical charges to verify the accuracy of claims (15). Moreover, because the coding approach and data availability were similar for the two cohorts, it could be argued that this similarity would only tend to underestimate, rather than overestimate, the magnitude of exposure—disease association. Second, the LHID lacks information on social network relationships, family history, personality attributes, laboratory data, and body mass index. Thus, we used several available comorbidities as surrogates to address these unmeasured confounders. For example, obesity and hypertension were used to substitute for the influence of body mass index and physical inactivity (33). Future research, however, addressing these factors is needed to expand on these preliminary findings. Third, although our study revealed a substantial benefit resulting from the use of P4P for T2DM patients, it must be recognized that these participants were not randomly categorized into users and non-users. Data derived from a retrospective cohort study are generally of lower statistical quality than those derived from randomized trials because of potential biases. Therefore, caution should be exercised when interpreting the findings. A large-scale randomized controlled trial is, therefore, recommended to better determine the efficacious influence of P4P on other psychiatric disorders among diabetic patients.

CONCLUSION

This large-scale cohort study is the first to clarify whether adding the P4P into the routine care process could lessen the subsequent depression risk among T2DM patients. Our results show that the implementation of P4P indeed decreases the subsequent risk of depression by 27%. Notably, we observe an additional positive effect associated with high-intensity P4P for such patients. The current study provides further evidence that the integration of P4P programs into routine disease management may be beneficial for achieving treatment goals and reducing costs for patients with chronic diseases.

DATA AVAILABILITY STATEMENT

The data supporting the conclusion of this study are available from the authors, but the raw data (NHIRD) need to be obtained from the National Health Research Institute of Taiwan through an application process upon approval.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board and Ethics Committee of Buddhist Dalin Tzu Chi Hospital (No. B10004021-3). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

W-CL, HL, H-JH, and T-YT were involved in the study design and drafted the manuscript. W-CL, HL, H-RG, and T-YT contributed to the data analysis and revised manuscript and were responsible for the study conception, design, data analysis, and drafting. W-CL, H-JH, M-CL, and T-YT contributed to the interpretation of data and provided comments on the final draft of the manuscript. M-CL and T-YT provided administrative support and comments on the manuscript drafts. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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