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Digital technology in the management and prevention of diabetes

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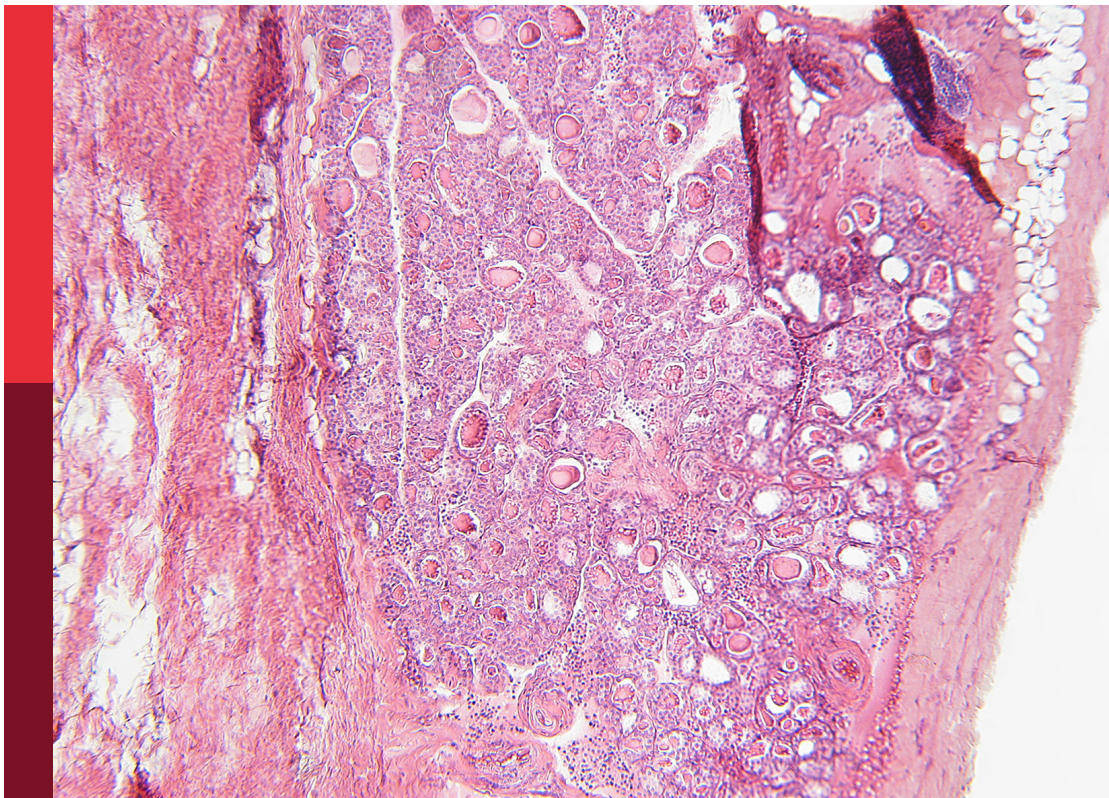

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Digital technology in the management and prevention of diabetes

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Editorial: Digital technology in the management and prevention of diabetes

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KEYWORDS

digital technology, diabetes, management in health, telemedicine, remote rehabilitation

Editorial on the Research Topic
Digital technology in the management and prevention of diabetes

The rapid advancement of digital technologies has transformed the landscape of healthcare, particularly in the management and prevention of chronic diseases (1–3). Digital tools offer unprecedented opportunities to improve patient outcomes through better monitoring, individualized care, and more efficient communication between patients and healthcare providers. In this Research Topic, *Digital Technology in the Management and Prevention of Diabetes*, we bring together cutting-edge research exploring the application of digital tools in the field of diabetes care including 8 original research, 1 perspective article and 1 systematic review. These ten manuscripts featured in this Research Topic represent a diverse range of topics, from artificial intelligence-driven diagnostics to mobile health interventions, all of which highlight the promise of technology in revolutionizing diabetes care.

Specifically in this Research Topic, Lv et al. developed interpretable machine learning models based on three weighted diversity density (WDD)-based algorithms to diagnose type 2 diabetes mellitus (T2D) using physical examination indicators. The algorithms demonstrated strong predictive performance with inclusion of algorithms tolerant to missing values made the models robust and applicable for broader use in clinical settings. Peleg et al. developed and validated the questionnaire of digital tool use for diabetes to assess the type, number, and frequency of digital tools used by patients with T2D. A mixed-methods approach was used, including qualitative phone surveys of T2D patients, endocrinologists, and technology experts to develop the questionnaire, followed by a quantitative phase involving 367 participants. The questionnaire was found to be valid and reliable in identifying digital tools used for T2D self-management, despite variations in factor structures between ethnic groups. The study provided a standardized method for evaluating digital tool use and could be adapted for other illnesses by modifying specific

instructions and wording. Matboli et al. developed a machine learning-based model to identify key features that influence drug responses in the treatment of T2D using medicinal plant-based drugs and a probiotics drug. The drugs effectively reduced liver inflammation, insulin resistance, and improved lipid profiles and kidney function biomarkers, particularly at higher doses. The machine learning model identified 13 molecular features, 10 biochemical features, and 20 combined features. This model highlighted the potential of machine learning in identifying therapeutic targets related to T2D pathogenesis. Yang et al. explored the impact of remote resistance exercise programs delivered via a smartphone application on skeletal muscle mass among elderly patients with T2D. After the intervention, there was a significant increase in skeletal muscle index (SMI) for both males (31.64 to 33.25 cm^2/m^2) and females (22.72 to 24.28 cm^2/m^2). Improvements were also observed in skeletal muscle cross-sectional area (SMA), radiodensity (SMD), and intermuscular adipose tissue (IMAT). The study demonstrated that remote resistance exercise programs delivered via smartphone are effective in increasing skeletal muscle mass in elderly patients with T2D. Yuan et al. also used the same platform to compare the effects of tele-rehabilitation with conventional face-to-face rehabilitation for patients with T2D and heart failure with preserved ejection fraction (HFpEF) in a real-world setting. A total of 90 patients using tele-rehabilitation were matched with 90 patients receiving face-to-face rehabilitation. Both groups showed significant improvements in short physical performance battery (SPPB) scores, 6-minute walk distance, gait speed, and quality of life (EQ-5D-5L) from 3 to 6 months after rehabilitation. There were no significant differences in functional outcomes or quality of life between the two groups. The study concluded that tele-rehabilitation is non-inferior to face-to-face rehabilitation and was well-accepted by patients, suggesting it could be a viable alternative to conventional rehabilitation programs among this specific population. Fundoiano-Hershcovitz et al. evaluated the relationship between depression, walking activity, and blood glucose (BG) levels in a cohort of 989 users with T2D and prediabetes by using the Dario digital health platform. Users with self-reported depression had higher BG levels compared to those without depression. Depression was significantly associated with a lower average number of steps per month, and the number of steps predicted the next month's average BG adjusting for depression. Walking activity mediated the effect of depression on BG levels. These findings suggest that regular walking can help mitigate the negative impact of depression on BG control in individuals with T2D and prediabetes, supporting the integration of walking into treatment protocols as a simple and effective intervention. Su et al. compared the effects of different intensities of aerobic exercise delivered by a smartphone application-based program on glycemic control, pain relief, and functional outcomes in patients T2D and knee osteoarthritis (KOA) in a randomized trial setting. A total of 228 patients were randomized into three groups: high-intensity, moderate-intensity, and regular rehabilitation programs. After six months, the high-intensity group showed a significantly greater reduction in HbA1c levels compared to the other groups. However, while all groups saw improvements in pain and quality of life as measured by the KOOS subscales, there were no significant differences between the intensities of exercise in terms of pain relief or functional improvement. All groups also experienced reductions in BMI, but these reductions were not statistically different across the groups. The findings suggested that high-intensity aerobic exercise offers superior glycemic control but does not provide additional benefits over moderate-intensity or regular rehabilitation programs for pain and functional outcomes in KOA patients. Koçkaya et al. gathered opinions from specialized physicians on current diabetes management through an online questionnaire and in-person discussion sessions at the Diabetes Innovation Summit 2023. According to the respondents, around 60% of diabetes patients followed multiple daily injections (MDI), with 62% using blood glucose monitors (BGM), 31% using intermittent-scanning continuous glucose monitors (isCGM), and 23% using continuous glucose monitors (CGM). Physicians expressed concerns about misleading HbA1c results and challenges in achieving TIR targets despite CGM use. The present study highlights that physicians are generally supportive of utilizing new technology, while it is a long journey to improve the concepts of using technologies in public.

Shomali et al. wrote a piece of perspectives in this Research Topic. They explored critical elements of digital health innovations in diabetes and cardiometabolic care. They also highlighted that digital health technologies, such as CGM, wearable devices, and artificial intelligence (AI), provide real-time data that enable both patients and healthcare professionals to manage diabetes more effectively. The integration of these technologies into everyday life would allow for continuous, personalized care outside of traditional clinical settings. They demonstrated that these innovations enhance self-management, improve patient engagement, and offer more timely interventions, thus improving health outcomes for people living with diabetes.

The only one systematic review and meta-analysis in this Research Topic reviewed and analyzed the effects of whole-body vibration (WBV), a digital technology-based therapeutics on glycemic control in patients with T2D (Fabregat-Fernández et al.). Six randomized clinical trials involving 223 participants met the inclusion criteria for the systematic review, with four of those studies qualifying for the meta-analysis. The meta-analysis demonstrated a positive and significant effect size, indicating a substantial improvement in glycosylated hemoglobin levels among WBV-treated patients compared to control groups. The results suggested that WBV may be beneficial for improving glycemic control in T2D patients.

In conclusion, the manuscripts featured in this Research Topic highlight the transformative potential of digital technologies in diabetes care. However, challenges remain in achieving widespread adoption, particularly in overcoming financial and technological barriers. The findings underscore the need for continued research and the development of accessible, user-friendly technologies to meet the needs of diverse patient populations. As the field advances, digital health innovations are poised to play an increasingly critical role in the prevention and

management of diabetes, paving the way for more efficient and equitable healthcare delivery.

Author contributions

YS: Writing – original draft. XZ: Writing – original draft. GH: Writing – review & editing.

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Conflict of interest

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

Publisher's note

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Identifying diagnostic indicators for type 2 diabetes mellitus from physical examination using interpretable machine learning approach

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Background: Identification of patients at risk for type 2 diabetes mellitus (T2DM) can not only prevent complications and reduce suffering but also ease the health care burden. While routine physical examination can provide useful information for diagnosis, manual exploration of routine physical examination records is not feasible due to the high prevalence of T2DM.

Objectives: We aim to build interpretable machine learning models for T2DM diagnosis and uncover important diagnostic indicators from physical examination, including age- and sex-related indicators.

Methods: In this study, we present three weighted diversity density (WDD)-based algorithms for T2DM screening that use physical examination indicators, the algorithms are highly transparent and interpretable, two of which are missing value tolerant algorithms.

Patients: Regarding the dataset, we collected 43 physical examination indicator data from 11,071 cases of T2DM patients and 126,622 healthy controls at the Affiliated Hospital of Southwest Medical University. After data processing, we used a data matrix containing 16004 EHRs and 43 clinical indicators for modelling.

Results: The indicators were ranked according to their model weights, and the top 25% of indicators were found to be directly or indirectly related to T2DM. We further investigated the clinical characteristics of different age and sex groups, and found that the algorithms can detect relevant indicators specific to these groups. The algorithms performed well in T2DM screening, with the highest area under the receiver operating characteristic curve (AUC) reaching 0.9185.

Conclusion: This work utilized the interpretable WDD-based algorithms to construct T2DM diagnostic models based on physical examination indicators. By modeling data grouped by age and sex, we identified several predictive markers related to age and sex, uncovering characteristic differences among various groups of T2DM patients.

KEYWORDS

diabetes, diabetes diagnosis, diabetic prediction, diagnostic indicator, health informatics, interpretable machine learning

1 Introduction

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes mellitus (DM), whose pathogenesis is that the cells in the body are not sensitive to insulin, meaning they do not respond to insulin (1). A longer disease duration of diabetes often leads to a variety of complications, such as retinopathy (2), cardiovascular disease, stroke (3, 4), and diabetic foot (5). It is estimated that about half of T2DM patients do not know they have diabetes (44.7%) (6). Therefore, screening for T2DM is essential to prevent or delay complications, avoid premature death, and improve quality of life.

Manual review of a large amount of clinical data is time-consuming and laborious, and missed diagnosis will be inevitable (6, 7). Thus, leveraging machine learning for T2DM screening has emerged as a notable approach in auxiliary diagnostics, enhancing both the accuracy and efficiency of diagnoses. Currently, machine learning models such as the random forest (RF) (8–10), support vector machine (SVM) (8, 11), logistic regression (LR) (11–13), and eXtreme gradient boosting (XGBoost) (9, 14) have been developed for constructing accurate system of T2DM prediction. Some studies have also employed machine learning techniques to identify indicators associated with T2DM, such as the white blood cell (WBC) (15), urinary and dietary metal exposure (16) and serum calcium (17). These works demonstrate the effectiveness of machine learning in predicting T2DM and identifying relevant indicator information.

For the construction of T2DM diagnostic models, the existing problems are as follows: (I) The effective extraction of T2DM diagnostic indicators through machine learning often relies on their interpretability (10, 12, 18–23). However, some of the current work lacks evaluation of important indicators, and some rely on third-party tools such as Shapley Additive exPlanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME) (8, 9, 11), which may bring potential deviation in clinical understanding (24). (II) The clinical indicators and datasets are critical to whether a model can be used in practice. At present, the frequently used diabetes dataset public like PIMA Indian dataset contains only 8 clinical indicators (25), and unconventional indicators using in some works are often difficult to obtain in community hospitals. Therefore, it is valuable to use physical examination indicators for T2DM prediction. (III) The problem of missing values in EHRs is unavoidable during data analysis. Currently, methods based on data imputation often require exhaustive searching (26). How to handle these missing values reasonably and efficiently is a matter that needs consideration.

To this end, we introduced three weighted diversity density (WDD)-based algorithms with a focus on intrinsic interpretability, which two of the algorithms could 'tolerate' missing value by adding penalty terms. By applying these algorithms to physical examination data for T2DM, we identified several clinical indicators related to T2DM diagnosis, including age-related markers like glomerular filtration rate (GFR) and triglycerides (TG). Additionally, by analyzing the model's internal parameters, we can gain a better understanding of the clinical indicators the model relies on for predictions, without the need for third-party interpretability tools.

2 Materials and methods

2.1 Dataset summary

All electronic health record (EHR) data came from the Affiliated Hospital of Southwest Medical University. A total of 16,004 EHRs and 43 usable physical examination indicators were screened out, of which half explicitly contained information about a confirmed T2DM diagnosis (Figures 1, 2; Table 1). In order to capture characteristics of early-stage T2DM, the EHRs of T2DM patients were limited to their first record in the hospital system. The physical examination indicators could be divided into three categories: routine urine indicators (9 indicators), blood cell analysis indicators (24 indicators), and biochemical indicators (10 indicators) (Figures 1, 2), the name and the abbreviation of the indicators were shown in Supplementary Table S1.

For these datasets divided according to the physical examination items, to facilitate their description here, we chose some standardized abbreviations: Whole physical examination indicators dataset (PEI dataset), Blood cell analysis dataset (BCA dataset), Urinalysis dataset (Uri dataset), Biochemical dataset (BioChem dataset).

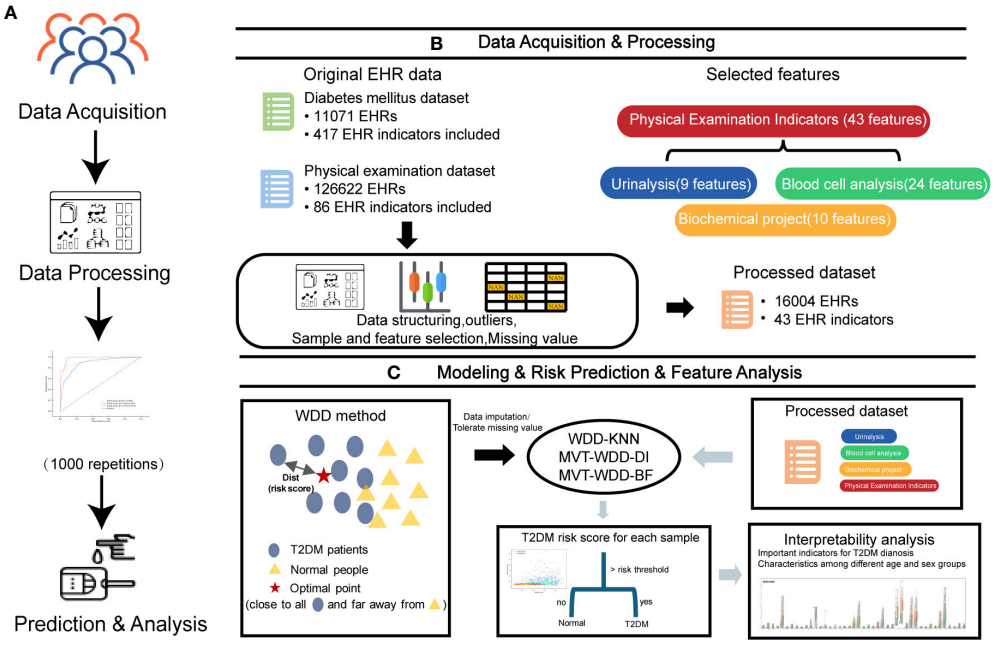

FIGURE 1
Overview of the study design. **(A)** The workflow of this work. **(B)** The first two steps in A, 11071 T2DM electronic health records (EHRs) and 126622 physical examination EHRs were collected. After preprocessing, 16004 EHRs were selected to build models for T2DM prediction. **(C)** The last two steps in A and the basic principle of the weighted diversity density method.

2.2 Data preprocessing

On the collected data, three steps were performed before modelling:

(1) First, we retained only the physical examination indicators for exploring the association of these indicators with T2DM diagnosis. In total, 181 features, of which 52 are physical examination features, remained afterwards.

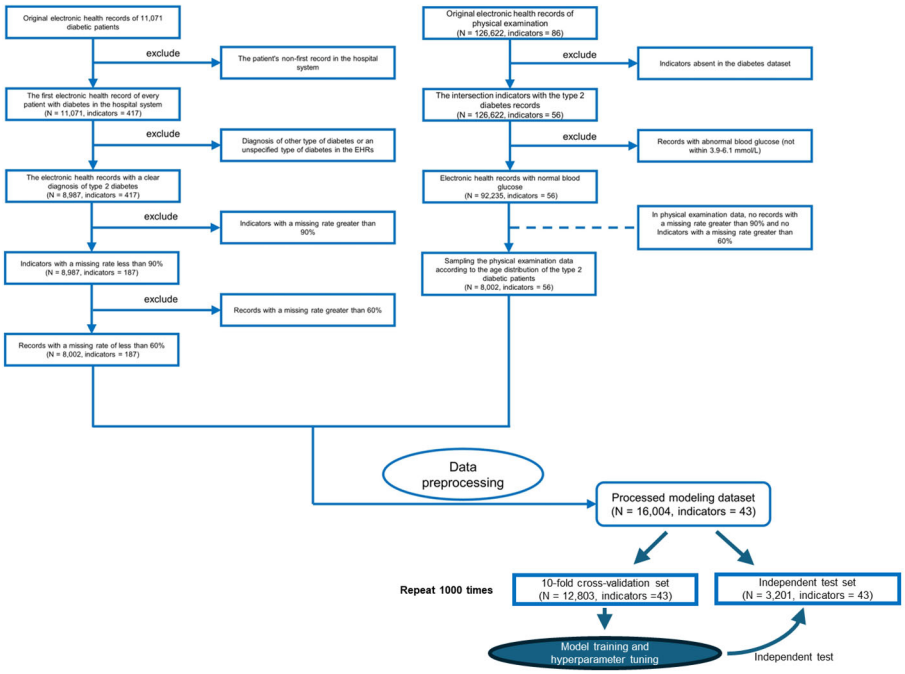

FIGURE 2
Flowchart of inclusion and exclusion criteria for the study populations of patients with type 2 diabetes mellitus (T2DM) and the physical examination population. We only use the first electronic health records for each patient in the hospital system.

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TABLE 1 Characteristics of the study population.

	Normal people	T2DM patients
TC, mmol/L	4.96 (0.932)	4.63 (1.393)
AST, U/L	24.58 (12.877)	25.20 (37.516)
GFR, mL/min	94.01 (14.660)	87.98 (29.298)
Crea, umol/L	68.48 (20.157)	86.93 (80.094)
HDL-C, mmol/L	1.40 (0.368)	1.14 (0.369)
TG, mmol/L	1.61 (1.313)	2.28 (2.377)
LDL-C, mmol/L	3.09 (0.900)	2.71 (1.014)
ALT, U/L	24.78 (19.111)	26.82 (32.369)
GGT, U/L	30.62 (40.086)	49.49 (110.088)
AST/ALT	1.19 (0.547)	1.18 (0.969)
MUCUS,/uL	12.88 (18.193)	2.75 (12.213)
BACT,/uL	21.38 (366.085)	1998.54 (7639.814)
EC,/uL	6.81 (25.506)	5.28 (14.011)
BLD	0.31 (0.628)	0.27 (0.603)
U-SG	1.02 (0.006)	1.02 (0.008)
U-pH	5.88 (0.729)	5.73 (0.719)
Crystal,/uL	6.09 (37.158)	23.45 (178.737)
RBC-Urine,/uL	7.29 (165.853)	20.96 (267.325)
WBC-Urine,/uL	14.43 (140.372)	61.44 (640.552)
NEU, 10E9/L	3.64 (1.290)	5.50 (3.591)
NEU-R, %	59.31 (8.511)	68.59 (11.639)
PCT, %	0.22 (0.051)	0.24 (0.086)
PDW, %	16.15 (1.010)	15.48 (2.733)
PLT, 10E9/L	210.83 (56.276)	206.96 (80.247)
MPV, fL	10.74 (1.412)	11.44 (1.400)
HGB, g/L	142.27 (15.014)	126.97 (21.740)
EOS, 10E9/L	0.16 (0.161)	0.13 (0.172)
EOS-R, %	2.62 (2.317)	1.99 (2.336)
BASO, 10E9/L	0.03 (0.018)	0.02 (0.020)
BASO-R, %	0.53 (0.283)	0.24 (0.258)
LYM, 10E9/L	1.88 (0.617)	1.57 (0.665)
LYM-R, %	31.65 (7.991)	23.10 (10.179)
HCT	0.44 (0.041)	0.39 (0.063)
RDW-SD, fL	43.18 (2.994)	42.91 (4.282)
RDW-CV, %	13.15 (0.975)	13.34 (1.305)
RBC, 10E12/L	4.66 (0.489)	4.33 (0.732)
MCHC, g/L	325.53 (8.441)	328.30 (14.113)
MCH, pg	30.62 (2.417)	29.40 (2.533)
MCV, fL	94.00 (6.445)	89.55 (6.784)
MONO, 10E9/L	0.35 (0.122)	0.45 (0.257)
MONO-R, %	5.88 (1.491)	6.12 (2.300)
P-LCR	31.37 (9.845)	36.20 (10.018)
WBC, 10E9/L	6.08 (2.075)	7.68 (3.860)

Data are mean (standard deviation).

(2) The features were normalized by $X'_{ij} = \frac{(X_{ij}-\mu_j)}{\sigma_j}$, where μ_j and σ_j are the average and standard deviation of the i th record, respectively. To avoid the influence from outliers, a featurewise box-plot analysis was performed to remove the features located outside of $[Q1 - 1.5IQR, Q3 + 1.5IQR]$ when calculating μ_j and σ_j. These outliers were replaced by null values. Any feature with a standard deviation of 0 (that is, the feature value is the same in all samples) was deleted, leaving 43 dimensions of physical examination features.

(3) When using the WDD-KNN algorithm for modelling, we used the K-nearest neighbour (KNN) imputer to impute the missing values of the data (n_neighbours = 15) and then normalized the processed data again in step (2).

The missing rate of each feature is shown in Supplementary Table S3. When using the MVT-WDD-DI and MVT-WDD-BF algorithms for modelling, we kept the missing value of each dimension feature of positive and negative samples consistent to eliminate bias. (Details in the Supplementary Note 4: Biased distribution misleading model using features).

2.3 Preliminary of weighted diversity density algorithm

The WDD algorithm, initially proposed by Maron for multi-instance learning problems (27), utilizes radial basis distance metrics to measure classification probabilities. We developed three new algorithms based on WDD in this work. Its non-linear nature and transparent framework make it particularly suitable for the medical field, where high interpretability in models is essential. Building upon the WDD framework, we have made enhancements to adapt it for medical classification problems, ensuring it can effectively handle missing values. Additionally, another reason for selecting the WDD method is its capability to provide a risk score for each sample, similar to the diagnostic approach of a clinical physician. This is achieved through its internal distance function, rather than merely outputting a categorical label. By decomposing the distance function at the feature level, we are further able to extract the feature-based criteria on which the model relies. This significantly enhances the transparency of the model. Unlike traditional models that offer limited insight into their decision-making process, WDD allows for a deeper understanding of how and why certain diagnostic conclusions are reached. This alignment with clinical practices not only aids in the interpretability of the

model but also fosters greater trust and reliability in its application in medical settings. The ability to dissect the model's reasoning at a feature level offers invaluable insights into the diagnostic criteria, bridging the gap between machine learning outputs and clinical decision-making.

The major principle of the WDD algorithm (Figure 1C) is to find an optimal point $x = \{x_1, x_2, \ldots, x_f\}$ in the data space that maximizes the probability density that positive samples ($b_i^+ = \{b_{i1}^+, b_{i2}^+, \ldots, b_{if}^+\}$) are near this point and minimizes the probability density that negative samples ($b_i^- = \{b_{i1}^-, b_{i2}^-, \ldots, b_{if}^-\}$) are near it, where i is the index of the sample, f is the number of features. The modified WDD algorithm can be represented as:

$$\arg\max_x \left(\prod_i \Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b_i^+}) \prod_i \Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b_i^-}) \right) \quad (1)$$

t is the target point, $\Pr(x = t \mid b_i^+)$ is the probability density that positive samples are near this point, and $\Pr(x = t \mid b_i^-)$ is the probability density of negative samples. The implicit functions could be given as:

$$\Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b_i^+}) = \exp(-\mathrm{Dist}(b_i^+, \boldsymbol{x})) \quad (2)$$

$$\Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b_i^-}) = 1 - \exp(-\mathrm{Dist}(b_i^-, x)) \quad (3)$$

where distance function (Dist) for both positive and negative samples is defined as the sum of weighted squares:

$$\mathrm{Dist}(\boldsymbol{b_i}, \boldsymbol{x}) = \sum_k \mathrm{Dist}_k \quad (4)$$

$$\mathrm{Dist}_k = s_k (b_{ik} - x_k)^2 \quad (5)$$

where k is the index of the feature.

The formulas yield a function to measure an optimal point based on both positive and negative samples, and the position of the point can be optimized during a deep learning process.

In this work, based on the idea of Maron's work, we modified the distance function to achieve our predictive goals. One of the algorithms first imputes the data with missing values by k-nearest neighbour (KNN) and then uses WDD for prediction. The other two algorithms, named MVT-WDD-DI and MVT-WDD-BF, do not need to impute data but use penalty mechanisms for missing value tolerance.

2.4 Our proposed modified WDD algorithm

As mentioned above, we modified the WDD algorithm proposed in Maron's work to improve the algorithms' ability to handle data containing missing values. The modifications are introduced in the following subsections:

2.4.1 WDD-KNN

The WDD-KNN algorithm uses data imputation by k-nearest neighbor (KNN) as input and then uses the modified WDD algorithm for modelling. Since all the missing values are imputed by KNN, we only modified Equations (2) and (3) by adding a hyperparameter γ to make the calculation more flexible:

$$\Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b_i^+}) = \exp(-\gamma \mathrm{Dist}(\boldsymbol{b_i^+}, \boldsymbol{x})) \quad (6)$$

$$\Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b_i^-}) = 1 - \exp(-\gamma \mathrm{Dist}(\boldsymbol{b_i^-}, \boldsymbol{x})) \quad (7)$$

Using WDD-KNN, we can classify a dataset containing missing values, but it still needs a step for missing value filling. This step limits the process of prediction. When given a new sample that contains a missing value, we need a dataset for imputing the missing value more than the trained model parameters. Therefore, we developed two missing value tolerant (MVT) algorithms for our predictive goals.

2.4.2 MVT-WDD-DI

We developed MVT-WDD-DI by adding penalty term for Equations (6) and (7) using division (DI) to handle missing values and finally obtain Equations (8) and (9):

$$\Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b_i^+}) = \exp\left(-\gamma\left(\frac{\mathrm{Dist}(\boldsymbol{b_i^+}, \boldsymbol{x})}{(f - f_{miss})^{\delta}}\right)\right) \quad (8)$$

$$\Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b_i^-}) = 1 - \exp\left(-\gamma\left(\frac{\mathrm{Dist}(\boldsymbol{b_i^-}, \boldsymbol{x})}{(f - f_{miss})^{\delta}}\right)\right) \quad (9)$$

where f is the number of features and f_{miss} is the number of missing values. Since the modification will influence the calculation of Equations (6) and (7), we added a rule to Equation (5): *if* b_{ik} *is missing*, $b_{ik} - x_k = 0$. We also added a hyperparameter δ for adjusting the value of the penalty term. The concept behind this modification is to diminish the influence of samples containing missing values. Specifically, when a sample has numerous missing values, indicating lower data quality, we increase the penalty term to reduce its distance metric value. This approach, during the optimization process, results in the target point relying less on these data segments. The penalty term can reduce the diversity density according to the number of missing features and will not influence a sample containing all the features.

2.4.3 MVT-WDD-BF

In addition to using division to penalize missing values, we also tried to design another method by ignoring the missing feature (BF) of a sample. To make the idea work, we modified Equations (2) through (5) of the original WDD algorithm. First, Equations (4) and (5) were modified to

$$\mathrm{Dist}'(\boldsymbol{b_i}, \boldsymbol{x}, \gamma, \lambda) = \sum_k \mathrm{Dist}_k'^{\lambda} \quad (10)$$

$$\mathrm{Dist}_k' = \exp(-\gamma s_k |b_{ik} - x_k|) \quad (11)$$

In Equation (11), *if* b_{ik} *is missing*, $\exp(-\gamma s_k |b_{ik} - x_k|) = 0$. This modification allows the algorithm to 'ignore' a missing feature when calculating. However, a reduced number of features will increase the diversity density based on the analysis of monotonicity. We modified Equations (2) and (3) to solve this problem:

$$\Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b_i^+}) = 1 - \exp(-\Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b_i^+})) \quad (12)$$

$$\Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b}_i^-) = \exp(-\Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b}_i^-)) \quad (13)$$

In Equations (12) and (13), we changed the monotonicity by removing the minuend Equations '1' in the production term and added Euler's number as the base for scaling an excessively large negative number to the range (0, 1) after a practical test.

2.5 Model setup

Since the goal of WDD is to find a point to maximize the diversity density, we used a deep learning framework for implementation. We used the Adam optimizer to solve the optimal problem, and the loss function of the three algorithms is shown in Equation (14):

$$loss = -\log\left(\prod_i \Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b}_i^+) \prod_i \Pr(\boldsymbol{x} = \boldsymbol{t} \mid \boldsymbol{b}_i^-)\right) \quad (14)$$

2.6 Model inference

After training, we obtained the optimal position x_{target} from the dataset, which optimized Equation (1). Thus, all the samples could be classified by calculating the maximum diversity density from its instances:

$$DD_i = \exp(-\mathrm{Dist}(\boldsymbol{b}_i, \boldsymbol{x})) \quad (15)$$

Using Equation (15) calculated diversity density, a sample could be assigned a label by setting a threshold. In this work, we used the method of analysing the ROC curve from the training set. First, we calculated all the diversity density values of the samples in the training dataset. Then, we calculated the false positive rate (FPR) and true positive rate (TPR), also called recall, under several different cut-off points and selected the best cut-off as the threshold when TPR-FPR reached its maximum The details are given in Equations (16) - (18):

$$\text{threshold} = \arg\max_{cutoff}(TPR - FPR) \quad (16)$$

$$TPR = \frac{TP}{(TP + FN)} \quad (17)$$

$$FPR = \frac{FP}{(TN + FP)} \quad (18)$$

Similar to many other works, we employed the area under the receiver operating characteristic curve (AUC), accuracy (ACC), precision, recall, and F1 score as the metrics, calculated as Equations (19) - (22):

$$ACC = \frac{TP + TN}{(TP + TN + FP + FN)} \quad (19)$$

$$Precision = \frac{TP}{(TP + FP)} \quad (20)$$

$$Recall = \frac{TP}{(TP + FN)} \quad (21)$$

$$F1\ score = 2 * \frac{Precision * Recall}{Precision + Recall} \quad (22)$$

where TP, TN, FP and FN represent the number of true positives, true negatives, false positives and false negatives, respectively.

Additional details about the method, such as parameter tuning and training process, are provided in Supplemental information.

2.7 Basic workflow

In this study, we optimized the WDD model using gradient descent to identify an optimal point that is close to the distribution center of data from T2DM patients and far from the distribution center of data from normal individuals (Figure 1C). The *Dist* function is engineered to directly reflect the T2DM risk score, enabling the model to predict an input sample as T2DM if its risk score exceeds the risk threshold which is learned by the model. Through the analysis of learnable parameters within the *Dist* function, we have identified key features. Utilizing this characteristic, we have been able to uncover significant features across different age and gender groups, enhancing our understanding of T2DM risk factors.

3 Result

In the results section, we first introduce the performance scores of the model, confirming the consistency of its performance by repeating the modeling process 1000 times. More importantly, our discussion centers on the model's transparency and interpretability, aimed at extracting effective clinical information internally. This includes the identification of key diagnostic indicators and the interpretation of the associations between model parameters and prediction result. These sections together demonstrate the model's transparency and potential clinical utility, contributing useful perspectives for T2DM prediction and diagnosis.

3.1 Performance of the prediction model

To the above four datasets, we applied three weighted diversity density (WDD)-based algorithms to construct diagnostic prediction models. WDD-KNN refers to an algorithm using k-nearest neighbor (KNN) for imputing missing values. The two MVT-WDD algorithms denote missing value tolerant (MVT) algorithms with penalty terms, where 'DI' and 'BF' represent two different methods of penalization. A total of 12 models were obtained. The models were evaluated by 10-fold cross-validation and independent test with 1000 repetitions (Figure 2, cross-validation set: independent test set = 8:2, the independent test

dataset was consistent for each repetition, details in Supplementary Note 1). The results are shown in Table 2, the best AUC achieved 0.9185 (± 0.0035) on the whole PEI dataset, which proves the accuracy of the model.

From the Table 2, we could see that the three algorithms had their own advantages on different sub-datasets. However, it was notable that the WDD-KNN algorithm had a KNN imputation step that the other 2 missing value adaptation algorithms did not have. Generally, imputation is limited by the template dataset. Large template datasets are often owned by a few large institutions and are difficult to share for reasons such as ethical review. To their advantage, the 2 missing value adaptation algorithms can skip this step when preprocessing dataset, and the built model does not need a template dataset for prediction, which will be beneficial in practical situations.

After ensuring the reliability of our modeling results through model scores, we delved deeper into the model's internal attributes and parameters in the following sections. This deeper analysis allowed us to extract valuable information pertinent to T2DM prediction, further validating the utility and interpretability of our algorithms.

3.2 Model scores provide auxiliary information other than blood glucose

The first aspect of our model's transparency is reflected in how the distance function illustrates the model and feature contributions to predict T2DM. In physical examinations, clinicians often use blood glucose, sometimes with urine glucose as a reference, to initially assess whether a person may have T2DM. For WDD, every sample was given a risk score (Dist for each algorithm, see Method details) by the models and classified according to a risk threshold. We compared the risk stratification through blood glucose and the risk scores (Dist) from our models (Figures 3A–C).

With the PEI dataset (Figures 3A–F), we saw that in the models WDD-KNN, MVT-WDD-DI, and MVT-WDD-BF gave scores of confirmed T2DM patients that clustered in the ranges of 0.5-0.75, 0.4-0.82, and 0.4-3, respectively, while the physical examination population was clustered in the score ranges of 0.3-0.53, 0.1-0.5, and 0-1, respectively. All three models performed well in distinguishing the two populations, with WDD-KNN working best. However, it was difficult to completely distinguish the two groups if they were separated only by the level of blood glucose (Figures 3A–C), and

TABLE 2 Performance of algorithms on each dataset: Mean (Standard) of 1000 repetitions.

10-fold cross-validation					
PEI dataset					
	AUC	ACC	Precision	Recall	F1 score
WDD-KNN	0.9185 (0.0034)	0.8439 (0.0042)	0.8761 (0.0049)	0.8014 (0.0073)	0.8368 (0.0047)
MVT-WDD-DI	0.9130 (0.0088)	0.8404 (0.0103)	0.8726 (0.0106)	0.7973 (0.0130)	0.8329 (0.0111)
MVT-WDD-BF	0.8882 (0.0096)	0.8138 (0.0093)	0.8291 (0.0096)	0.7910 (0.0135)	0.8091 (0.0103)
BCA dataset					
	AUC	ACC	Precision	Recall	F1 score
WDD-KNN	0.8770 (0.0018)	0.7992 (0.0021)	0.8386 (0.0039)	0.7418 (0.0058)	0.7868 (0.0028)
MVT-WDD-DI	0.8530 (0.0045)	0.7763 (0.0044)	0.8097 (0.0062)	0.7233 (0.0093)	0.7635 (0.0054)
MVT-WDD-BF	0.8910 (0.0094)	0.8156 (0.0089)	0.8379 (0.0081)	0.7829 (0.0152)	0.8087 (0.0109)
Uri dataset					
	AUC	ACC	Precision	Recall	F1 score
WDD-KNN	0.8442 (0.0069)	0.7768 (0.0096)	0.7621 (0.0133)	0.8133 (0.0240)	0.7837 (0.0109)
MVT-WDD-DI	0.8985 (0.0074)	0.8580 (0.0096)	0.8463 (0.0109)	0.8763 (0.0126)	0.8604 (0.0101)
MVT-WDD-BF	0.6414 (0.0175)	0.6321 (0.0129)	0.6993 (0.0203)	0.4795 (0.0355)	0.5580 (0.0265)
BioChem dataset					
	AUC	ACC	Precision	Recall	F1 score
WDD-KNN	0.7360 (0.0016)	0.6766 (0.0021)	0.6900 (0.0040)	0.6432 (0.0092)	0.6651 (0.0039)
MVT-WDD-DI	0.7395 (0.0128)	0.6801 (0.0089)	0.7075 (0.0084)	0.6137 (0.0237)	0.6540 (0.0185)
MVT-WDD-BF	0.6127 (0.0212)	0.5987 (0.0136)	0.6172 (0.0258)	0.4924 (0.0430)	0.5389 (0.0376)

(Continued)

TABLE 2 Continued

10-fold cross-validation					
Independent test					
PEI dataset					
	AUC	ACC	Precision	Recall	F1 score
WDD-KNN	0.9276 (0.0089)	0.8554 (0.0112)	0.8888 (0.0142)	0.8128 (0.0198)	0.8489 (0.0125)
MVT-WDD-DI	0.9194 (0.0254)	0.8475 (0.0310)	0.8826 (0.0299)	0.8014 (0.0411)	0.8398 (0.0340)
MVT-WDD-BF	0.9071 (0.0214)	0.8296 (0.0235)	0.8429 (0.0280)	0.8110 (0.0298)	0.8263 (0.0243)
BCA dataset					
	AUC	ACC	Precision	Recall	F1 score
WDD-KNN	0.8870 (0.0057)	0.8106 (0.0072)	0.8469 (0.0098)	0.7551 (0.0200)	0.7982 (0.0099)
MVT-WDD-DI	0.8625 (0.0151)	0.7851 (0.0152)	0.8198 (0.0192)	0.7273 (0.0294)	0.7704 (0.0184)
MVT-WDD-BF	0.8988 (0.0326)	0.8226 (0.0301)	0.8467 (0.0309)	0.7850 (0.0482)	0.8140 (0.0362)
Uri dataset					
	AUC	ACC	Precision	Recall	F1 score
WDD-KNN	0.8224 (0.0207)	0.7569 (0.0252)	0.7621 (0.0426)	0.7406 (0.0893)	0.7463 (0.0359)
MVT-WDD-DI	0.8893 (0.0230)	0.8499 (0.0291)	0.8355 (0.0348)	0.8635 (0.0356)	0.8488 (0.0303)
MVT-WDD-BF	0.6304 (0.0581)	0.6306 (0.0396)	0.6863 (0.0649)	0.4670 (0.1243)	0.5433 (0.0891)
BioChem dataset					
	AUC	ACC	Precision	Recall	F1 score
WDD-KNN	0.7482 (0.0045)	0.6885 (0.0065)	0.6975 (0.0141)	0.6588 (0.0256)	0.6771 (0.0098)
MVT-WDD-DI	0.7464 (0.0456)	0.6862 (0.0300)	0.7098 (0.0255)	0.6186 (0.0841)	0.6573 (0.0684)
MVT-WDD-BF	0.6290 (0.0653)	0.6104 (0.0442)	0.6245 (0.0738)	0.5192 (0.1228)	0.5594 (0.1050)

many people with T2DM still had the same blood glucose levels as normal people. Also, we analysed the risk scores on the three sub-datasets in Supplementary Note 6.

To provide more information on the importance of the EHR features to every patient, we also calculated the $Dist_k$ score (see Method details) for each feature between the patients and normal people (Figures 3G–I; Supplementary Figure S3). As we can see, the selected important features mostly had different scores by each model. For example, in the model built on the PEI dataset using the MVT-WDD-DI algorithm, the $Dist_k$ scores of selected important features (Figures 3H, 4) such as Bact, BLD, Baso, Baso-R, and MCV were much higher than those of other features. T2DM patients and normal people could be well distinguished by the $Dist_k$ score of these important features. The result indicates that our model assigns higher significance to features with more pronounced differences, identifying them as important and thus selecting them as effective indicators for T2DM screening.

The results show that our model effectively differentiated T2DM patients from healthy individuals in the PEI dataset, as shown in the scatter density heat map. Visualized model scores underscored performance differences, revealing potential for early T2DM detection. Notably, normal blood glucose levels don't rule out T2DM, highlighting our model's diagnostic value. Additionally, by analyzing the model's distance function, we gained a deeper understanding of the mechanism behind the model's selection of important features, enhancing our comprehension of the model.

3.3 The important indicators for T2DM diagnosis selected from different models

After understanding the scoring mechanism of the model and the mechanism for selecting important features, in this section and Supplementary Notes 3 and 7, we identified crucial diagnostic indicators for T2DM and analyzed the significance of the selected indicators for T2DM combining clinical knowledge.

The feature's significance is determined by its weight within the models, identifying the indicators most associated with T2DM. Important features were defined as those ranking in the top 25% by weight across the 12 models. We visually represented this distribution of relative feature weights with a histogram and the specific details of these crucial features are detailed in Figure 4. We employed the Mann-Whitney U test to evaluate the level of feature differences between the T2DM and normal groups, finding that the selected important features exhibited significant differences (P value< 0.0001) (Supplementary Table S6). In addition, we

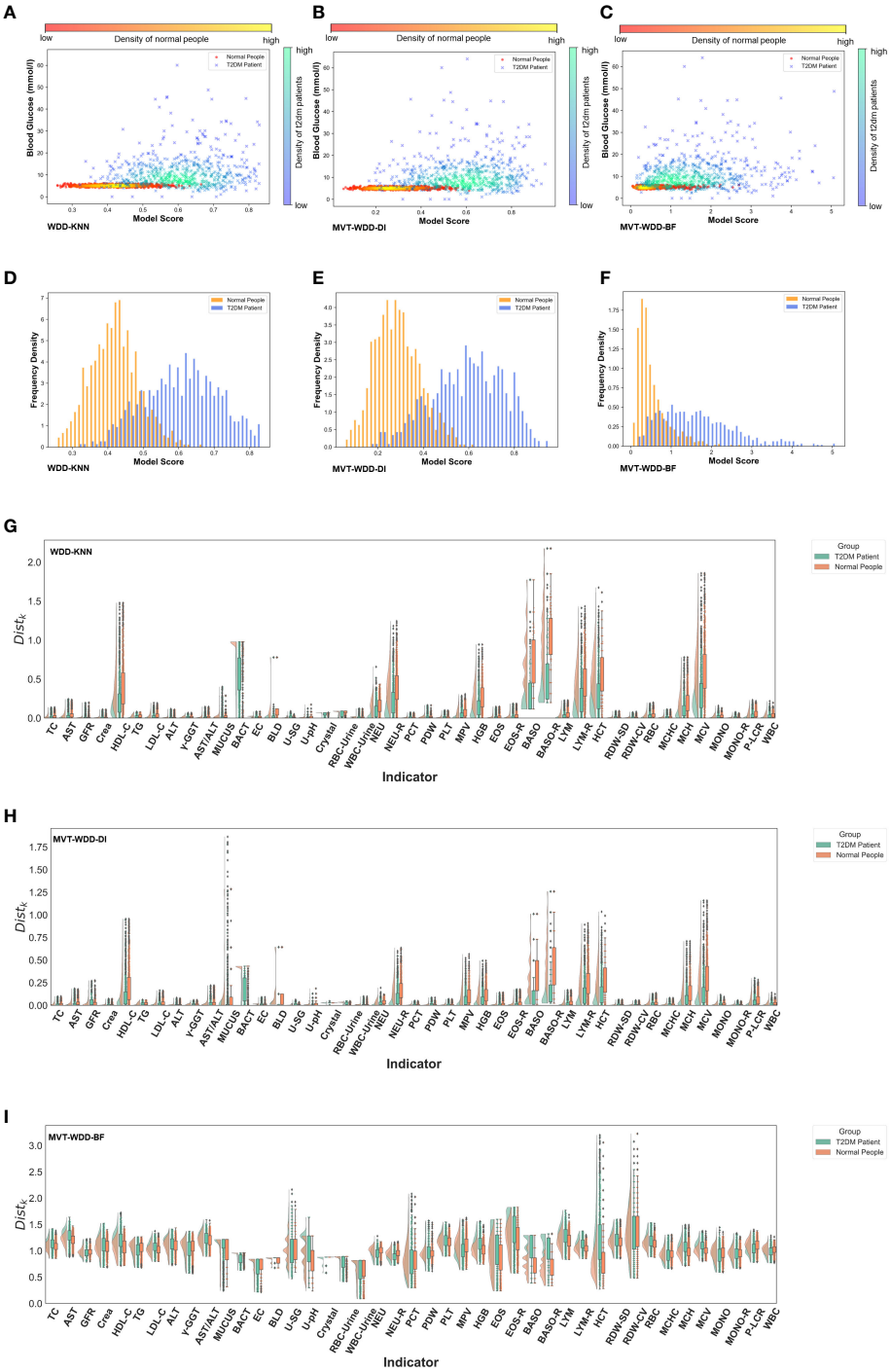

FIGURE 3
Model interpretability reflected by model scores. **(A-C)** Scatter-density heat maps of model score versus blood glucose of 3 models trained by whole PEI dataset. **(D-F)** Histograms of model score distribution of 3 models using whole PEI dataset. **(G-I)** The raincloud plots of distance scores ($Dist_k$) of the three models using the whole PEI dataset.

compared the important features selected by using the internal weights of WDD with least absolute shrinkage and selection operator (LASSO) regression and SHAP framework. The important features showed certain consistency (Supplementary Note 9, Supplementary Information Figures S14, S15).

When the three algorithms were applied each dataset, the selected important features intersected. For example, on the PEI dataset, the indicators judged as important features by all three models were BASO, BASO-R, and HCT, and the features given high weights by two of the three models were HDL-C, MUCUS, BACT, BLD, LYM-R, MCH, and MCV. In this dataset, the AUCs of all three models were higher than 0.88, so these indicators were selected as having great significance for T2DM prediction (Figure 4). On the BCA dataset, the important features selected

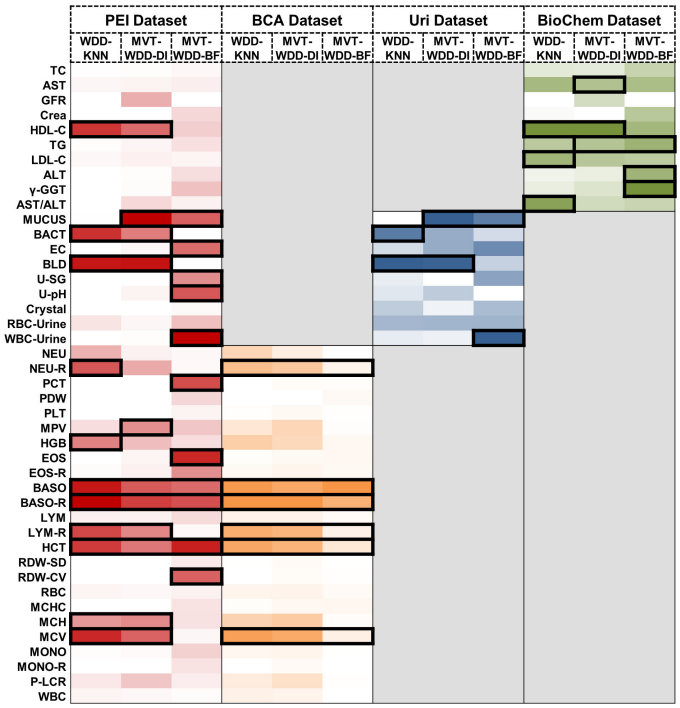

FIGURE 4
Important feature weights from different algorithms and datasets. Heat map based on the normalized feature weight values. The summation of a column (an algorithm) is 1. Darker colors represent larger weight values. The top 25% features in every column are framed by black rectangle.

by the three algorithms are the same, which further proves the potential diagnostic value of these indicators. Moreover, we analysed the same and different important features extracted by the three algorithms, details are shown in Supplementary Note 7.

We conducted a literature review to integrate our clinical expertise with published research findings and investigate the clinical correlations between these important features and T2DM. Our analysis revealed that most of these important features are shown to have direct or indirect associations with T2DM. For example, urinary tract infections are known to be correlated with diabetes (28) and some indicators associated with urinary tract infections, such as haematuria and bacteria in urine, have been selected as important biomarkers. The details are collated in the Supplementary Note 3.

3.4 Multi-model analysis reveals characteristics among different age and sex groups

Leveraging our model's transparency and feature extraction capabilities, we conducted group modeling for populations with varying demographic characteristics to unearth the diagnostic value of indicators across different groups. To mitigate the potential model bias introduced by data imbalance, we ensured basic balance in the sample volume of each age and sex category for both T2DM patients and normal individuals, as illustrated in Supplementary Figure S5 and Supplementary Table S2.

In most cases, age and sex will be correlated with T2DM incidence, which indicates that T2DM in different age and sex groups might have different characteristics. To further explore the importance of each feature for T2DM prediction in different age and sex groups, we tried three additional ways to divide the PEI Dataset: i. by age; ii. by sex; and iii. by age and sex. The number and proportion of people in different age and sex groups are shown in Supplementary Figure S6 and Supplementary Table S2. After the division of the datasets, 26 sub-datasets (8 ages + 2 sexes + 8 ages × 2 sexes) were generated, and 78 additional models (26 datasets × 3 models) were built. The performance of each model is shown in Figures 5A, B. The WDD-KNN and MVT-WDD-DI algorithms performed well on each group of datasets, with AUC values mostly above 0.9, while the performance of MVT-WDD-BF was not as good. Therefore, in the subsequent analysis, only the weights of the first two algorithms were taken into consideration.

The results showed that the importance of the clinical indicators varied in different age and sex groups (Figure 5C; Supplementary Figure S6). We not only integrated the results of these models using the WDD-KNN and MVT-WDD-DI algorithms but also analysed the distribution of their measured values (Supplementary Figures S7-13) to explain the various importance of these indicators for T2DM diagnosis in the different groups.

The significance of glomerular filtration rate (GFR) in T2DM diagnosis diminishes with age, showing greater importance in the 5-49 age group (Figures 5C, 6B). Elevated GFR in T2DM patients aged 5-49 distinguishes them from normal groups, particularly in the 5-39 (Figure 6). This aligns with studies linking diabetes and GFR,

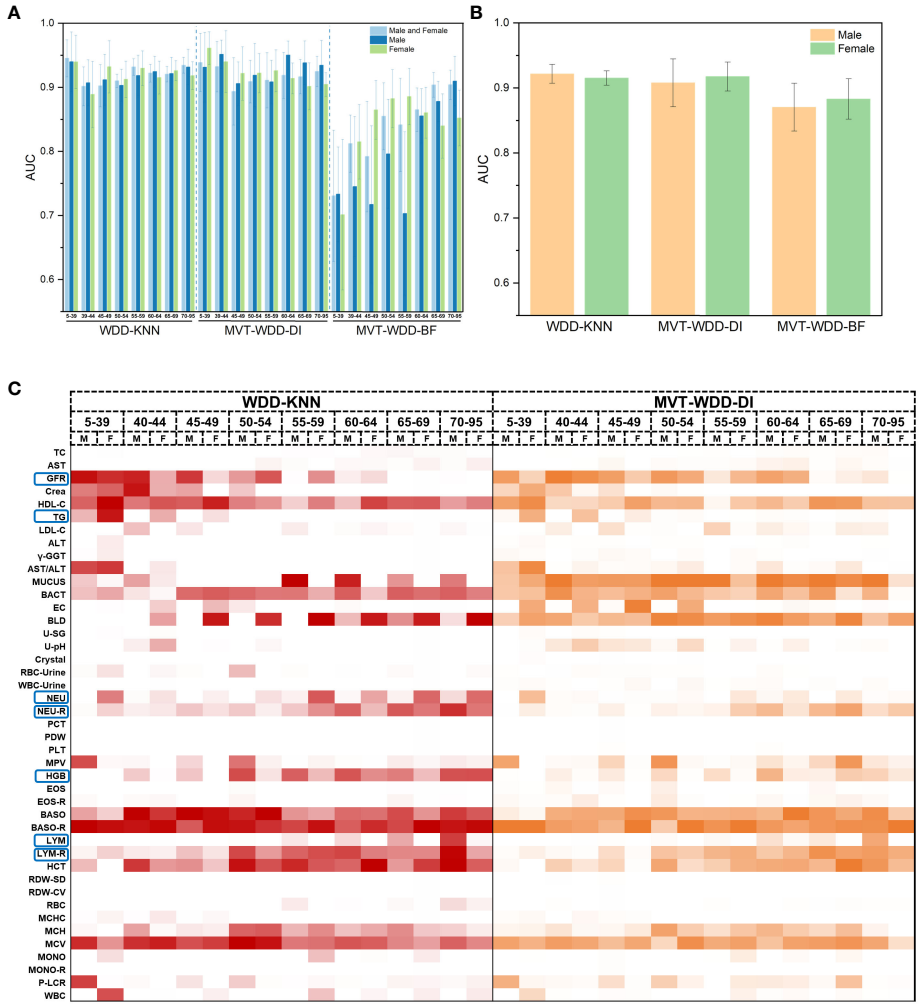

FIGURE 5
Model performance of 10-fold cross validation and feature importance in different age and sex groups. **(A)** The AUC values of the three algorithms when modeling male, female and both sexes of different ages. Error bars were generated by 10-fold cross validation (error bar represents standard deviation). **(B)** The AUC values of the three algorithms when modeling male and female of all ages. **(C)** Heat map of normalized feature weight values extracted from the model for male and female of different ages, 'M' represents male, 'F' represents female.

where early diabetic kidney disease (DKD) phases show increased GFR due to various changes in ultrastructural, vascular, and tubular factors (29). As renal health declines, GFR decreases (29, 30). Our findings suggest that GFR's diagnostic value for T2DM varies across ages, particularly useful for early screening in younger populations, extending beyond its role in DKD.

Triglycerides (TG) showed greater significance in the 5-39 age group compared to others (Figure 5C; Supplementary Figure S6), with notable differences in TG distribution between T2DM patients and normal individuals in this age range (Supplementary Figure S7). This variation is attributed to age-related dietary and metabolic differences and a genetic link identified by Saxena, R. et al. (31) High TG levels in T2DM patients are associated with increased cardiovascular risks (32) and metabolic changes (33). Our model emphasizes TG's importance in T2DM, especially in younger age groups, aligning with current research trends.

Haemoglobin (HGB) was more important in the 55- to 95-year-old group (Supplementary Figures S5C, S6A). In T2DM patients, as age increased, their lower HGB compared to that in normal people became more pronounced (Supplementary Figure S12). Based on our knowledge and experience, anaemia is diagnosed by HGB decline, so the association between anaemia and T2DM might be the use of metformin. There are reports supporting that long-term metformin use in T2DM patients can cause anaemia (34, 35), and our EHR included patients who used metformin since metformin has been a commonly prescribed drug for T2DM patients for decades. Similarly, in diabetic patients with chronic kidney disease (CKD), some factors cause iron-deficiency anaemia, such as low intestinal absorption and gastrointestinal bleeding (36). In addition, erythropoietin deficiency and hyporesponsiveness can lead to anaemia in diabetic patients with CKD (36–38). Nephrotic syndrome, characterized by oedema, hypoalbuminaemia, dyslipidaemia, and increased transferrin catabolism, contributes to anaemia due to iron and erythropoietin deficiency (36, 39, 40). Long-term administration of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists in diabetic

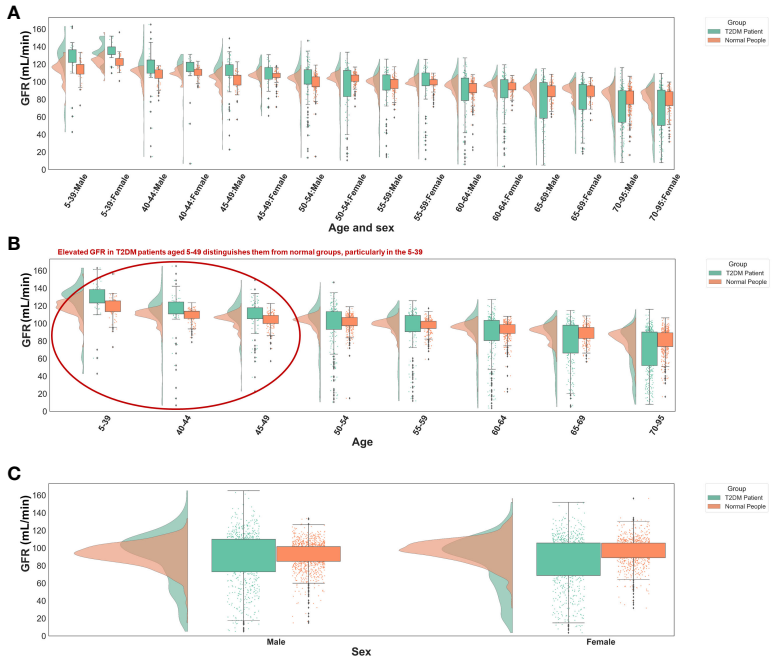

FIGURE 6
Distribution of GFR values in different groups. **(A)** Different age and sex groups. **(B)** Different age groups. **(C)** Different sex groups. All the GFR values were from origin EHRs.

patients also leads to a reversible decrease in HGB through a direct blockade of the proerythropoietic effects of angiotensin II on red cell precursors, degradation of physiological inhibitors of haematopoiesis, and suppression of IGF-I (36, 41). Thus, based on many studies and reports, taking HGB as an important feature will be a useful indicator for older patients with longer duration of diabetes, so HGB was selected after modelling the EHR data. In other words, HGB decline might be a marker of T2DM or T2DM-correlated disease, but it might be interfered with by some confounding factors, so its use for early diagnosis might be limited. This limitation is caused by the lack of medication information in our EHR data. Despite our meticulous selection of the patient's first record within the hospital system, we cannot guarantee that they have not undergone therapeutic interventions at other institutions. To address this shortcoming, cohort studies with long-term follow-up are needed.

The Neutrophils (NEU), neutrophil rate (NEU-R), lymphocyte rate (LYM), and lymphocyte rate (LYM-R) have also been observed to correlate with age or sex, as discussed in Supplementary Note 8.

The result of this section demonstrates that through group modeling and the model's feature extraction capability, we identified several age and sex-related biomarkers for T2DM prediction. Integrating insights from the results, it's evident that our model can glean valuable auxiliary diagnostic information from internal parameters like feature weights and distance functions. This effectively showcases the algorithm's transparency throughout the modeling process, highlighting its capacity to provide interpretable insights crucial for clinical application.

4 Discussion

Here, we developed WDD framework-based models for the prediction of T2DM using physical examination features in EHRs. Using the model parameters, the importance of the features can be measured by the distance between the sample and optimal point. Based on our investigation, the top 25% of indicators were found to be directly or indirectly related to T2DM, offering potential value as diagnostic markers for T2DM.

In our analysis, a variety of white blood cells—neutrophils, basophils, eosinophils, and lymphocytes—emerged as significant features. This aligns with existing literature, which indicates that T2DM patients experiencing concurrent infections may exhibit inflammation, leading to an altered white blood cell count (42, 43). While current research posits that the count or ratio levels of these white cells alone do not suffice as diabetes risk factors, a multifaceted approach is often necessary. For instance, the neutrophil-lymphocyte ratio is recognized as an independent predictor of T2DM (44). The inclusion of these white blood cells as important indicators by our model is consistent with current research insights, further affirming the potential of combining these white blood cell levels for aiding T2DM diagnosis. Moreover, this demonstrates our model's proficiency in capturing the complex interrelationships among indicators, highlighting its diagnostic relevance.

Indicators related to red blood cells and platelets, such as mean platelet volume, plateletcrit, hematocrit, coefficient of variation of red cell distribution width, mean corpuscular volume, and mean corpuscular haemoglobin, were also identified as significant by our

model. In T2DM patients experiencing insulin resistance and metabolic syndrome, the adverse metabolic conditions—including hyperglycemia, hypertension, dyslipidemia, inflammation, and impaired fibrinolysis—elevate the risk of atherosclerosis and lead to microvascular complications like diabetic retinopathy, nephropathy, and neuropathy (45, 46). Additionally, atherosclerosis, which may result from increased platelet adhesion and hypercoagulability in T2DM patients, is a key pathological mechanism behind macrovascular complications (46). These vascular complications can cause abnormalities in red blood cells and platelets. Therefore, the aforementioned indicators are linked to the common microvascular and macrovascular complications in diabetics, suggesting their potential as diagnostic markers for T2DM.

Urinalysis-related indicators, such as haematuria, leukocytes in urine, mucinous filaments, bacteria in urine, epithelial cells in urine, urine pH, and specific gravity, have been selected as significant markers by our model. These indicators are primarily associated with conditions prevalent among individuals with diabetes, such as urinary tract infections (28), which are notably common and can lead to haematuria or abnormal quantities of cells and bacteria in the urine. Moreover, the inflammation caused by these infections may result in an abnormal number of white blood cells, further validating the model's ability to discern potential relationships between indicators. The combination of increased net acid excretion and reduced use of ammonia buffers in individuals with diabetes leads to lower urine pH (47, 48). A lower urine pH heightens the risk of nephrolithiasis, including uric acid stones (47, 49). Diabetic nephropathy may manifest through abnormal urine specific gravity, where a lower-than-normal urinary specific gravity, along with increased polyuria, signals diabetes insipidus (50). These findings underscore the interconnectivity of urinary markers with diabetes-related infections and complications, emphasizing their potential diagnostic relevance.

While individual physical examination indicators often cannot serve as standalone diagnostic criteria for T2DM, our model successfully integrates multiple indicators to construct a diagnostic model for T2DM. Leveraging the model's high interpretability, we can determine the importance of each indicator in the diagnosis, enhancing its capability to aid in the auxiliary diagnosis of T2DM. This approach not only harnesses the collective diagnostic potential of various indicators but also provides valuable insights into their diagnostic significance, offering a refined perspective on T2DM diagnosis.

Besides, based on our clinical knowledge, the diagnosis of T2DM often correlates with demographic factors. Therefore, we segmented the data by age and gender, utilizing the feature weights provided by our model. Through this process, combined with a literature search, we identified several biomarkers related to age or sex, such as glomerular filtration rate, triglycerides, and haemoglobin. This further validates our model's efficacy in extracting medically valuable information and illustrates that different indicators may require attention when diagnosing diabetes in patients of varying ages and sexes. This approach not only enriches the diagnostic model with nuanced clinical insights but also underscores the importance of personalized medicine in the management and treatment of T2DM.

The results show that our algorithm boasts a high degree of internal interpretability, enabling the extraction of key indicators for T2DM diagnosis without the need for third-party tools. Furthermore, by analyzing the model's parameters (Figure 3), we can comprehend the mechanism behind the selection of important indicators, thereby providing reliable auxiliary diagnostic information. Additionally, our model possesses a distinct advantage as mentioned in the Methods section: benefiting from the transparency of WDD, its internal distance function is easily modifiable. Instead of imputing missing values, our approach involves 'tolerating' them by incorporating penalty terms into two of the algorithms. This strategy diminishes the necessity for exhaustive searches for high-quality template data during the imputation process, proving WDD to be a highly transparent and interpretable auxiliary diagnostic algorithm.

This work suggests that machine learning could extend beyond predictive accuracy to include interpretative insights, which might be useful in clinical settings. Such insights have the potential to aid clinicians in understanding the basis of diagnostic suggestions given by the model. This could lead to a more cooperative relationship between machine learning and healthcare professionals. However, the integration of these technologies in clinical practice requires careful consideration and ongoing evaluation.

5 Conclusion

Overall, we developed three WDD-based interpretability algorithms and built T2DM diagnostic models, identifying several relevant diagnostic indicators with potential utility in assisting T2DM diagnosis. However, it is crucial to acknowledge that the mechanisms of interaction among these indicators, as well as their causal connections with T2DM, cannot be directly deduced from the current model information. In our future work, leveraging the transparency of WDD, we plan to incorporate knowledge of causal probabilities to enhance our model further, uncover the complex relationships between indicators and T2DM.

Data availability statement

The code used for modelling in this work is available at: https://github.com/Lvxiang713/WDD_T2DMprediction. Rearchers should contact the corresponding authors for approval to obtain and use the source data. The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by This study protocol was approved by the ethics committee of the Affiliated Hospital of Southwest Medical University, China (KY2022266) and the Chinese Clinical Trial Registry (ChiCTR2200064435). The studies were conducted in accordance with the local legislation

and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

XL: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. JL: Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation. HW: Writing – review & editing, Investigation, Data curation. HG: Writing – review & editing, Visualization, Formal analysis. XB: Writing – original draft, Investigation, Formal analysis, Data curation. PY: Writing – original draft, Data curation. ZJ: Writing – review & editing, Data curation. YZ: Writing – original draft, Investigation, Formal analysis. RJ: Writing – review & editing, Writing – original draft, Validation, Methodology, Funding acquisition, Data curation, Conceptualization. QC: Writing – original draft, Supervision, Funding acquisition, Data curation, Conceptualization. ML: Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Conflict of interest

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

Publisher's note

Supplementary material

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A novel questionnaire for evaluating digital tool use (DTUQ-D) among individuals with type 2 diabetes: exploring the digital landscape

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Introduction: Effective healthcare currently incorporates a patient-centric system and accessible technology for patient self-management. This study aimed to develop and validate a novel questionnaire titled the Digital Tool Use Questionnaire for Diabetes (DTUQ-D) - a screening tool identifying the type, number, and frequency of digital tools used by Type 2 Diabetes Mellitus (T2DM) patients with within HMOs, online, and via applications.

Methods: The questionnaire was administered to two ethnic groups and both genders. A mixed-methods approach was used. In the qualitative phase, the questionnaire was developed through phone surveys of 29 T2DM patients, two endocrinologists and two technology experts. In the quantitative phase, involving 367 participants, convergent validity, construct validity, and reliability were examined.

Results: Findings indicated that the DTUQ-D is valid and reliable, successfully identifying digital tools utilized by T2DM patients, notwithstanding variations in factor structures between ethnic groups. This questionnaire provides a foundation for future research, offering a standardized approach to evaluating digital tool usage.

Discussion: The study enhances understanding of the role of digital tools in healthcare, especially for T2DM self-management. It also can be easily adapted to assess digital tool use for other illnesses by adjusting instructions and the wording of certain items

KEYWORDS

digital tools, questionnaire, type 2 diabetes, eHealth, DTUQ-D

Introduction

Today's healthcare system faces such challenges as remote patient residence and costly long-term treatment of chronic diseases tied to increased life expectancy (1). These obstacles may hinder effective disease management due to challenges in accessing suitable care. Currently, healthcare improvement opportunities include a patient-centric system (i.e., Human-Centered Design), accessible technology for a broader population, and smart tools identifying patient needs (2).

Electronic health (eHealth), a term coined in the 21st century to describe electronic information and communication technology in the health sector (3), offers an efficient and updated solution to healthcare challenges. It holds the potential to improve healthcare on local, regional, and national levels by making it more accessible (4). eHealth was found to be related to health literacy (knowledge of how to obtain and use health-related information to inform

health-related decisions), as higher health literacy was linked to elevated eHealth literacy (5). This suggests that individuals with strong eHealth literacy possess the skills to navigate and utilize online health information effectively (6).

For individuals with Type 2 Diabetes Mellitus (T2DM), various digital tools have been proven effective for self-management of the illness (7, 8). In light of the multitude of tools from different sources (HMO, apps, online) on the one hand, and the value of understanding precisely which digital uses actually promote healthy management of *T2DM*, on the other hand, there is a need to investigate what digital tools people with diabetes prefer to use.

To address this issue, we aimed to develop and validate a novel questionnaire – the Digital Tool Use Questionnaire for Diabetes (DTUQ-D) – a screening instrument that explores the usage of digital tools provided to T2DM patients to enhance their successful self-management. Considering the differences between the two major ethnic groups in Israel, including variations in the use of digital tools and the prevalence of T2DM, the study was conducted among Israeli Jewish patients (the majority group) and Israeli Arab patients (the minority group), including both genders. It is our hope that the data collected through this instrument will serve as a valuable resource for planning interventions aimed at optimizing the use of digital technology while mitigating potential challenges.

T2DM self-management, eHealth literacy, and digital tool use

T2DM is a global epidemic, with the number of patients constantly rising (approximately 422 million) (9). In Israel, according to the International Diabetes Federation the age-standardized diabetes rate, for those aged 20–79 (9.7%) is higher than the average in European countries (6.3%) (10). It is one of the major diseases that can result in premature death and medical complications (9), thus putting a heavy, often financial, burden on both the healthcare system and T2DM patients and their families. Successful self-management of the illness, such as continuous glucose monitoring, can reduce these burdens (11).

Beneficial coping with chronic diseases, such as T2DM, has been associated with eHealth, which can enhance health protection, prevent hospitalizations and premature mortality, and reduce financial costs (12). Encompassing advanced information technologies (e.g., medical information sites, digital tools) for health improvement (13), eHealth aims to increase healthcare efficiency, improve the quality of care, empower patients and their families, and foster better relationships and communication between patients and healthcare professionals (14). Consequently, eHealth presents a substantial opportunity for proactive health management. eHealth literacy, defined as the ability to seek, comprehend, and assess health information from digital sources, can foster positive attitudes to eHealth services (15), augmenting self-management for T2DM patients.

In recent years, the landscape of digital services designed for individuals with T2DM has experienced rapid development, marked by the proliferation of smartphone uses, advancements in wireless communication quality, and the emergence of numerous applications dedicated to health and fostering a healthy lifestyle. While many of these applications function as health "consultants," an increasing number are designed to establish health goals, modify health indicators, and guide patients in their daily routines (16). Several digital tools have been found to do so successfully (17). They play a pivotal role in T2DM self-management, offering a range of benefits. Notable examples of digital tools relevant to T2DM patients include websites (e.g., diabetes associations websites) and social media (e.g., Facebook forums), providing information, and mobile apps such as nutrition apps (18), physical activity apps (19), glucose monitoring apps (20), insulin titration apps (18), digital home glucose meters (glucometers) (21), bluetooth-enabled blood glucose meters (22) and T2DM treatment AI-based algorithms (23). Integrating these tools into T2DM care holds transformative potential for managing and preventing this chronic condition (24). A recent study (25) found that registration for the use of HMO-provided digital tools, such as online medical consulting services, was associated with adherence to a medication regimen and positive treatment outcomes. These tools seem to offer real-time insights into blood glucose dynamics, trends, and indications for hypoglycemia and hyperglycemia, enhancing the safety and effectiveness of T2DM care (24). Additional advantages of digital tools are their convenience in overcoming logistical challenges, reaching populations that may avoid seeking treatment, and their relatively low cost (26).

Despite the advancements in digital tools for T2DM self-management, there remains a dearth of information regarding available applications and how often they are used. This lacuna underscores the need for more efficient and accurate assessment tools (27). To thoroughly explore the utilization of digital tools among individuals with T2DM within such a diverse landscape, it is crucial to construct and implement an evaluation instrument, notably a questionnaire. It is essential to have a standardized, reliable, and validated questionnaire to assess the type, number and frequency of such digital tools used for self-management of the illness.

Digital tool use questionnaires for T2DM patients

To date, to the best of our knowledge, only two questionnaires are available for evaluating the use of digital tools among individuals with diabetes. The first is the Instrument for Assessing Mobile Technology Acceptability in Diabetes Self-Management (28), which was developed to gauge patients' attitudes to and intentions to use mobile technology for diabetes self-management. This questionnaire was developed through comprehensive interviews of both patients and physicians. However, its focus is on assessing attitudes rather than the actual usage of digital tools for diabetes management. While the reported reliability of 0.7 suggests moderate response consistency, it also implies some variability. Moreover, the instrument's development could benefit from further consideration of cultural nuances, potentially enhancing its effectiveness in diverse populations with varying cultural perspectives on technology.

The second instrument, The Diabetes Self-Management and Technology Questionnaire [DSMT-Q; (29)], is designed to assess self-management among patients with T2DM utilizing web-based and mHealth tools (i.e., mobile health, namely, health practices aided by mobile devices). The questionnaire has high reliability, with Factor 1, "Understanding individual health and making informed decisions," comprising seven items and a Cronbach's alpha level of 0.90. Factor 2, "Confidence to reach and sustain goals," includes six items with a

Cronbach's alpha level of 0.88. To ensure the suitability of the DSMT-Q for T2DM patients, a preliminary study was carried out involving in-depth interviews with patients and evaluation by diabetes experts. Despite its strengths, it is essential to acknowledge that the effectiveness of this questionnaire could be enhanced by a more substantial representation of ethnic minorities in the validation sample. This would broaden the generalizability of findings to diverse populations. Moreover, considering the dynamic nature of digital tools for T2DM, regular updates to the questionnaire items and structure would ensure its continued relevance in the ever-evolving medical landscape. Finally, this questionnaire does not address the utilization of specific digital tools or the frequency of their use.

In sum, in the last decade, as far as we know, only two inventories have been developed to assess the utilization of digital tools among T2DM patients, and existing questionnaires have limitations in their scope of assessing digital tool use. To address these limitations, it is crucial to add up-to-date and well-validated tools that align with the latest digital innovations (e.g., apps for monitoring/tracking glucose, apps on a smart watch or mobile phone). Such tools should capture additional degrees and complexities of T2DM patients' perspectives and digital tool use, while accounting for gender differences and ethnic diversity.

Ethnic diversity

Despite the advantages of using digital tools, there is a digital divide that is characterized by differences in technological usage and accessibility to Internet infrastructure among different populations. Ethnic diversity has recently become a significant focus of T2DM research, indicating higher percentages of the illness among minority groups [e.g., (9, 30)].

In Israel, the rate of Arab T2DM patients is double that of Jewish patients (12% of Arabs and 6.2% of Jews). While the Israeli Jewish majority group is basically westernized, the Israeli Arab minority group [comprising 21% of the population; (31)] is more collectivist and is undergoing a transition from traditionalism to modernity (such as urbanization and changes in family patterns, lifestyle, and dietary habits, including increased consumption of foods rich in simple carbohydrates), such that most Arabs are considered bicultural (32, 33). Indeed, Israeli Arabs are a unique minority with affinities both to modern Israeli society and to the Arab traditional world (34). At the same time, Israeli Arabs are found to have lesser T2DM self-management and a poorer health and clinical profile than the Jewish population (35). A review of the literature highlights the high prevalence of T2DM among Arab populations in Israel, as well as the need for improved care and counseling for these populations (36).

Though considered a developed country in technological advancement and despite its strong economy, Israel is characterized by income inequality, financial gaps, and a lack of social unity between ethnic groups, leading to social and digital gaps. The digital gap between Jews and Arabs is a crucial element of Israeli society, originating from their different cultural backgrounds and aggravated by the lower socio-demographic status of Arabs (30, 32). This digital divide takes the form of differences in Internet infrastructure accessibility between these groups (37, 38). These disparities between Israeli Arabs and Jews can adversely affect T2DM self-management and exacerbate the consequences of the disease.

The present study

For individuals with chronic conditions like T2DM, the use of eHealth tools shows promise for enhancing self-management and improving health outcomes (39). However, more research is needed to understand how these patients use digital tools, whether they use recommended tools and approaches, and how technology impacts health behaviors and health status. Limited initiatives have been undertaken to create questionnaires with which to evaluate digital tool use among patients with T2DM. In light of the lacuna of research instruments for evaluating such usage, there is a compelling need to develop a valid, reliable questionnaire that is up-to-date and culturally sensitive, incorporating technological innovations.

The current study aimed to address this gap by using a mixed-methods approach to develop (qualitative) and validate (quantitative) a novel tool, DTUQ-D. This questionnaire was specifically designed as a screening tool to evaluate the utilization (type, number, and frequency) of digital tools among diverse populations. Therefore it was posited that DTUQ-D would be associated with a similar content measure, eHealth Literacy Scale [eHEALS; (40)], supporting its validity. To this aim, the study included two phases. The first phase was qualitative with the aim of generating questionnaire items. Our research question was: what digital tools are utilized by and available to T2DM patients for self-management of their illness?

The second phase of the study was quantitative with the research question of whether the DTUQ-D is valid among the two major ethnic groups in Israel, Jewish and Arab T2DM patients, including both genders. We hypothesized that the DTUQ-D would demonstrate a positive association with the eHealth Literacy Scale among T2DM patients of both ethnic groups and genders. This instrument measures understanding and proficiency in utilizing digital medical care. Given evidence underscoring a higher incidence of T2DM among Israeli Arabs (30), we also hypothesized that Jewish T2DM patients would demonstrate higher digital tool use than their Arab counterparts. Lastly, gender differences in the research variables were examined.

Methods

The study used a mixed-methods sequential exploratory (qualitative-quantitative) design (41). In the qualitative exploratory phase, data was collected on T2DM digital tools for DTUQ-D development. The subsequent quantitative phase involved validity, reliability, and factor analysis tests.

Phase 1: qualitative exploratory

The first phase of the study explored the digital tools utilized by and available to T2DM patients for self-management of their illness, with the aim of generating questionnaire items. We used an inductive method of gathering information (42) about digital tools available for T2DM patients' self-management.

Participants and information sources

To obtain information on relevant digital tools, we conducted a telephone survey of patients with T2DM. Inclusion criteria were diagnosis of T2DM and treatment in one of the main HMOs in Israel.

Using cluster sampling, a diabetes HMO clinic in a large city in northern Israel was selected. For 2 months, patients coming for their regular checkup were offered the opportunity to participate. Of those, 29 T2DM patients (20 Jews and 9 Arabs), of whom 18 were men (14 Jews) and 11 were women (6 Jews), chose to take part in the study. Their mean age was 60.7 ($SD = 8.17$), with Jewish participants ($M = 61.9$, $SD = 8.19$) older on average than Arab ones ($M = 58.1$, $SD = 7.90$). Twenty-five participants (18 Jews) were married, two Arabs were widowed, and one Jewish participant each was divorced and single. We also interviewed two endocrinologists in an HMO clinic treating T2DM patients and two experts in eHealth, one a researcher in the field of T2DM and the other an employee in the digital services of the T2DM clinic. In addition, we explored a list of available digital tools for diabetes treatment with the aid of a diabetes HMO nurse. Finally, the resources provided to T2DM patients on the HMO website and on other public websites, including apps, were researched.

Instruments

Demographic questionnaire

The research team constructed two demographic questionnaires. The questionnaire for the T2DM patients included questions about age, gender, ethnicity, level of education, and year of diagnosis. It was constructed in Hebrew and translated to Arabic using back translation. In the initial phase, two native Arabic speakers, fluent in Hebrew, performed the translation. Subsequently, two educational counselors holding master's degrees, who are native speakers of Arabic and speak Hebrew fluently, translated the questionnaire back from Arabic to Hebrew. The questionnaire items for the endocrinologists and technology experts inquired about age, gender, and years of expertise.

A semi-structured interview guide

The research team developed interview guides in Hebrew to inquire about digital tools used and available for T2DM patients' self-management of the illness. To verify the suitability of the questions, the interview guide for patients with T2DM was first tested with two individuals who met the inclusion criteria, and changes were made accordingly. The guide was then translated into Arabic using the above-mentioned back translation method. Sample questions were: "Which HMO digital tools do you use to manage T2DM?" (patients); "What digital services are available at the HMO for diabetes treatment?" (endocrinologists); "What digital tools are available for diabetes treatment?" (eHealth experts). Follow-up questions inquired about each digital tool's characteristics, purpose, and frequency of use.

Procedure

Following the approval of ethics from the college IRB (masked), T2DM patients who arrived at the diabetes HMO clinics were invited to participate in the study by the clinic nurse, and interested volunteers left their contact information. All study participants (including physicians and eHealth experts) signed an informed consent slip and filled out the demographic questionnaire. Phone interviews were conducted by two female research assistants (Jewish and Arab), graduate students in educational counseling, who each interviewed their respective participant group. Interviews lasted about 15 min and were recorded verbatim.

Data analysis

A manifest content analysis was applied to create a registry of digital tools available to and used by T2DM patients (43, 44). The content was analyzed using stages of decontextualization (e.g., identifying units of meaning), recontextualization (e.g., labeling similar units with a code), categorization (e.g., grouping similar codes into a category), and compilation (e.g., integrating the categories into themes and a coherent understanding of the topic). Interview data, the HMO website, and other public websites and apps were searched for types of digital tools provided and their purpose. These were tallied and grouped into codes, categories, and themes by type of tool and provider (HMO, non-HMO). A list of types of digital tools available from HMOs and non-HMOs was created and served as a basis for creating the DTUQ-D items.

Construction of the DTUQ-D

The identified types of digital tools available for patients' self-management of T2DM were listed as questionnaire items (please see Appendix). Instructions were: "In the last 6 months, how often have you used the following tools for your diabetes management?" Possible responses were on a 4-point Likert scale ranging from 0 (*never*) to 3 (*regularly*). Five items were listed under HMO resources (e.g., a phone appointment with the physician), and five items were listed under non-HMO resources (e.g., websites providing relevant information for diabetes patients). In addition, to verify that no relevant tools had been overlooked, three additional open-ended items were added. Two read: "An additional tool that you are familiar with or use that was not mentioned" and provided space to add this information. The third item was included to verify that the six-month time frame did not exclude tools used annually; it read: "In the past year, have you used an additional tool (that was mentioned or not mentioned so far) to manage your diabetes? If so, what tool?" Thus, the questionnaire included 13 items overall.

To check for wording, accurateness, and clarity, the questionnaire was reviewed by an endocrinologist treating T2DM patients and was administered to two T2DM patients. Minor changes were made accordingly.

The questionnaire was then translated from Hebrew to Arabic by two experts proficient in both languages, with thorough attention to cultural sensitivity, ensuring the relevance and appropriateness of its content in the specific cultural context. Subsequently, it underwent a back translation from Arabic to Hebrew, facilitated by two educational counselors fluent in both languages. A few disagreements were discussed and resolved by the researchers, along with another research assistant proficient in Arabic and Hebrew. For international use, the questionnaire was also translated to English through a similar process, involving two native-speaking individuals fluent in both English and Hebrew.

Phase 2: quantitative

The aim of this part of the study was to validate the newly developed Digital Tool Use Questionnaire for Diabetes (DTUQ-D). We assessed the reliability and validity of the questionnaire in both Hebrew and Arabic to establish its utility as a measurement tool for T2DM patients.

Participants

The sample was gathered via a survey company that ensures representation across all societal sections. Table 1 displays

demographic characteristics of participants. There were 367 participants in total, 259 of whom were Jewish (70.6%) and 108 of whom were Arab (29.4%). Arab participants were Muslim ($n = 75$, 69.4%), Christian ($n = 27$, 25.0%), Muslim Bedouin ($n = 4$, 3.7%), and Druze ($n = 2$, 1.9%). About half the participants were male (around 55%), with a somewhat greater percentage of males among Arabs (about 64%) than Jews (about 51%). On average, participants were close to the age of 60, with Jews older (about 59) than their Arab counterparts (about 53). Jewish participants had higher levels of education than Arab participants. Diagnosis of the disease occurred up to 43 years ago, with an average of about 12 years, and with no ethnic difference.

Instruments

Demographic questionnaire

The inventory was constructed for the purpose of the current research. It included such demographic details as ethnicity, weight and height (BMI), access to mobile phone/Internet, and gender.

Digital tool use questionnaire for diabetes (DTUQ-D)

This questionnaire was constructed for the current study to examine the type, number, and frequency of digital tool use (for details, see Phase 1 above). Means were calculated for the purpose of the current study.

eHealth literacy scale (eHEALS)

The eHEALS (40) includes eight items dealing with awareness of health resources and the search for, utilization, and appraisal of health resources. Sample item: "I know how to find helpful health resources online." Possible responses fall along a five-point Likert scale, ranging from 0 (*highly disagree*) to 4 (*highly agree*). The Hebrew version was found to be valid and reliable and is commonly used [e.g., (45)]. The questionnaire was translated to Arabic for the present study. It was first translated from Hebrew to Arabic by two experts proficient in both languages and then back translated from Arabic to Hebrew by two educational counselors fluent in the two languages. In the current study, principal components factor analysis yielded one factor explaining 76.72% of the variance (Eigenvalue = 6.14). Internal consistency for the whole sample was $\alpha = 0.96$ (Jews: $\alpha = 0.95$, Arabs: $\alpha = 0.96$).

Procedure

The study followed the eHealth Code of Ethics (46). Upon obtaining approval from the college's Ethics Committee (masked), the questionnaire was distributed by a survey company with an attached link. The survey company guaranteed a representative sample of Israeli society by adhering to key demographic criteria. Financial incentives were provided for participation, and demographic quotas were set before data collection began, ensuring a balanced and representative sample. Participants were informed of the voluntary nature of the study and their ability to terminate involvement at any point. We assured participants of the confidentiality of their responses, clarifying that the results would be used solely for research purposes. Patient data were anonymized in the collected questionnaires. Participants signed an informed consent form. Questionnaire completion time was approximately 10 min.

Data analysis

Data were analyzed using SPSS ver. 29. Descriptive statistics were employed for the demographic and background variables of the participants, with ethnic comparisons calculated by *t*-tests, Chi-squared tests, and *Z* ratios for the significance of the difference between independent proportions. Internal consistencies for eHEALS were calculated using Cronbach's α. The DTUQ-D items were presented with frequencies and percentages, and ethnicity-based comparisons were performed using Chi-squared tests. To assess construct validity of the DTUQ-D, a multi-group confirmatory factor analysis (MGCFA) was conducted, utilizing AMOS software ver. 29. Fit measures, including CFI, NNFI, and RMSEA, were used to compare the unconstrained model, structural covariances model, and the measurement residuals model. Due to low fit, an exploratory principal axis factoring (EFA) with the criterion of Eigenvalue greater than 1 was calculated for the DTUQ-D by ethnicity. The total score

TABLE 1 Demographic characteristics of participants ($N = 367$).

		Total	Arab	Jewish	
Gender *n* (%)	Male	202 (55.0)	69 (63.9)	133 (51.4)	$Z = 2.20$ ($p = 0.028$)
	Female	165 (45.0)	39 (36.1)	126 (48.6)	
Age *M* (*SD*) range		57.52 (10.26) 28–84	52.85 (10.44) 28–79	59.46 (9.55) 34–84	$t(365)^{(1)} = 5.88$ ($p < 0.001$)
Level of education *n* (%)	Less than high school	19 (5.2)	12 (11.1)	7 (2.7)	$\chi^2(4) = 17.15$ ($p = 0.002$)
	High school	68 (18.5)	26 (24.1)	42 (16.2)	
	Non-academic higher education	94 (25.6)	19 (17.6)	75 (29.0)	
	Bachelor's degree	88 (24.0)	24 (22.2)	64 (24.7)	
	Master's or Ph.D.	98 (26.7)	27 (25.0)	71 (27.4)	
Duration of T2DM *M* (*SD*) range		12.21 (9.62) 1–43	11.13 (8.04) 1–31	12.66 (10.19) 1–43	$t(251.53)^{(1)} = 1.545.88$ ($p = 0.126$)

[(1)] *t* for unequal variances.

was calculated using item means and compared across ethnic groups and genders with an analysis of variance. Pearson and Spearman correlations were calculated between DTUQ-D and eHEALS, as well as between DTUQ-D and the demographic variables.

Sample size was first calculated for a CFA, using Soper's (47) online calculator. Using a moderate effect size of 0.30, power level of 0.80, three latent variables, and the 20 items of eHEALS and DTUQ-D, with $\alpha = 0.05$, the minimum desired N is 323 participants. For a two-way ANOVA, with a moderate-low effect size of $f = 0.15$, $\alpha = 0.05$, and a power level of 0.80, the minimum desired N is 351 [G*Power 3: (48, 49)].

The additional three open-ended items (11–13) of the DTUQ-D were not included in the statistical analysis but rather were assessed by content analysis post-administration. The responses of participants were reviewed and clustered into codes, categories, and themes of the digital tools mentioned.

Results

The research aimed to assess the validity of the DTUQ-D to evaluate the type, number, and frequency of digital tools utilized by T2DM patients and to assess for variability among both genders and ethnic groups. The findings revealed that the digital tools used most often by Arab participants were the glucometer (about 63% used it often or regularly), websites with diabetes-related information (about 43%), the HMO website/app (to set an appointment, order medication, leave a message; about 31%), and diabetes management reminders (taking medication, making appointments, etc.; about 30%). The digital tools used most often by Jewish participants were the HMO website/app (to set an appointment, order medication, leave a message, etc.; about 80% used them often or regularly), the glucometer (about 69%), lifestyle apps (on a smart watch or mobile phone; about 41%), websites with diabetes-related information (about 38%), the HMO website/app (to get relevant information; about 35%), and diabetes management reminders (about 30%). That is, the extent of use of digital tools was generally higher among Jewish participants than among Arab participants. This trend applies to 6 of the 10 questionnaire items and is most notable regarding use of the HMO website and apps, as well as lifestyle apps (see Table 2).

Multi-group confirmatory factor analysis (MGCFA) was calculated for the 10 questionnaire items to evaluate the instrument's construct validity. Items were divided into two factors, according to the initial definition of the questionnaire, and two groups were assessed: Jewish and Arab participants. Results showed that the unconstrained model had a good fit (CFI = 0.966, NNFI = 0.944, RMSEA = 0.036). Higher order comparisons showed low fit values (structural covariances model: CFI = 0.746, NNFI = 0.695, RMSEA = 0.083; measurement residuals model: CFI = 0.637, NNFI = 0.645, RMSEA = 0.090). The model was next assessed for one total factor, including all 10 items. The unconstrained model had a reasonable fit (CFI = 0.898, NNFI = 0.936, RMSEA = 0.061). Higher order comparisons showed low fit values (structural covariances model: CFI = 0.706, NNFI = 0.652, RMSEA = 0.089; measurement residuals model: CFI = 0.609, NNFI = 0.622, RMSEA = 0.092). Thus, the initial definition of the two factors of the questionnaire and its total score did not demonstrate construct validity across the two ethnic groups.

Based on these findings, an exploratory factor analysis (EFA) of the 10 DTUQ-D items was conducted separately for each ethnicity. Given that the correlations between the items ranged up to $rs = 0.67$ and $rs = 0.40$ among the Arab and Jewish sub-samples, respectively ($p < 0.001$), a principal axis factoring with oblique rotation was used. The criterion of Eigenvalue greater than one yielded three factors for each ethnicity, as shown in Table 3.

The three factors entail distinct combinations of items for each ethnicity, with low to good internal consistencies. In the Arab sector, the first factor involves information and monitoring tools, the second factor entails the HMO website and app, and the third factor includes online meetings. In the Jewish sector, the first factor comprises non-HMO digital tools, while the second and third factors entail specific digital tools offered by the HMO. Due to these ethnic variations in factor definitions, the total score for digital tool use was defined separately for each ethnic group (Arab sector: $\alpha = 0.84$, Jewish sector: $\alpha = 0.69$) and utilized for ethnic comparisons.

Table 4 presents t-values for eHEALS and DTUQ-D by ethnicity. The findings demonstrate notable ethnic disparities, indicating higher levels of both eHEALS and DTUQ-D scores among Jewish participants than Arab ones.

Pearson and Spearman correlations were calculated to examine the associations between eHEALS and DTUQ-D, as well as between demographic variables and DTUQ-D, as presented in Table 5. Positive and significant correlations were found between eHEALS and DTUQ-D, indicating that higher eHEALS scores were associated with increased DTUQ-D scores and providing convergent validity to the newly developed questionnaire. Notably, demographic variables showed no significant associations with DTUQ-D. It is noteworthy that gender differences in DTUQ-D scores were not significant, males: $M = 1.08$, $SD = 0.64$, females: $M = 1.07$, $SD = 0.56$, $t(363.54) = 0.24$, $p = 0.810$; nor was the interaction between ethnicity and gender significant, $F(1, 363) = 1.57$, $p = 0.210$, $\eta^2 = 0.004$. Gender differences in eHEALS scores were also non-significant, males: $M = 2.51$, $SD = 1.10$, females: $M = 2.71$, $SD = 0.92$, t (364.77) = 1.84, $p = 0.066$; as was the interaction between ethnicity and gender, $F(1, 363) = 0.01$, $p = 0.941$, $\eta^2 = 0.001$.

Post-administration adjustment of DTUQ-D

Based on the analysis of the three open-ended questions, an additional item was added to the questionnaire in retrospect, "Other digital tools (such as Excel for monitoring, blood pressure monitor, digital scale)." This item, number 11, addresses digital tools that were not included in the original version but rather were mentioned by the participants in the validation sample. We recommend adding this item to the questionnaire.

Discussion

This study aimed to develop and assess the effectiveness of the DTUQ-D as a screening tool for identifying the type, number, and frequency of digital tools used by T2DM patients for self-management of the illness, both within HMOs, online, and through apps. This investigation holds significant importance given rapid technological

TABLE 2 Distribution of DTUQ-D items by ethnicity ($N = 367$).

	Arab			Jewish			$\chi^2(2)$
	Never *n*(%)	Seldom *n*(%)	Often[(1)] *n*(%)	Never *n*(%)	Seldom *n*(%)	Often[(1)] *n*(%)	
HMO digital tools							
(1) Glucometer (at a subsidized fee)	32 (29.6)	8 (7.4)	68 (63.0)	40 (15.4)	40 (15.4)	179 (69.1)	12.01 ($p = 0.002$)
(2) Online training workshop with a nurse/nutritionist (at a subsidized fee)	78 (72.2)	12 (11.1)	18 (16.7)	175 (67.6)	54 (20.8)	30 (11.6)	5.76 ($p = 0.056$)
(3) Phone meeting with the physician	62 (57.4)	16 (14.8)	30 (27.8)	113 (43.6)	70 (27.0)	76 (29.3)	7.95 ($p = 0.019$)
(4) HMO website/app (to set an appointment, order medication, leave a message for a physician, etc.)	61 (56.5)	13 (12.0)	34 (31.5)	25 (9.7)	26 (10.0)	208 (80.3)	99.17 ($p < 0.001$)
(5) HMO website/app (to access information on diabetes, proper nutrition, physical activity, etc.)	71 (65.7)	15 (13.9)	22 (20.4)	95 (36.7)	73 (28.2)	91 (35.1)	26.12 ($p < 0.001$)
Other digital tools							
(6) Websites with T2DM-related information	44 (40.7)	18 (16.7)	46 (42.6)	74 (28.6)	86 (33.2)	99 (38.2)	11.23 ($p = 0.004$)
(7) Apps for monitoring/tracking glucose	68 (63.0)	13 (12.0)	27 (25.0)	169 (65.3)	38 (14.7)	52 (20.1)	1.30 ($p = 0.522$)
(8) Apps on a smart watch or mobile phone to promote a healthy lifestyle (e.g., counting steps or calories, recipes)	78 (72.2)	14 (13.0)	16 (14.8)	106 (40.9)	46 (17.8)	107 (41.3)	31.93 ($p < 0.001$)
(9) T2DM management reminders (e.g., taking or injecting medication, making appointments with a physician)	59 (54.6)	17 (15.7)	32 (29.6)	137 (52.9)	43 (16.6)	79 (30.5)	0.10 ($p = 0.953$)
(10) Individual or group support for T2DM on social networks (e.g., WhatsApp, Facebook, forums)	79 (73.1)	14 (13.0)	15 (13.9)	159 (61.4)	51 (19.7)	49 (18.9)	4.68 ($p = 0.096$)

[(1)]The DTUQ-D has a four-point scale: 0 = never, 1 = seldom, 2 = often, and 3 = regularly. As responses at level 3 (regularly) were rare, levels 2 and 3 (often and regularly) are combined.

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TABLE 3 Factor loadings for the DTUQ-D by ethnicity ($N = 367$).

	Arab			Jewish		
Factor	1	2	3	1	2	3
HMO digital tools						
(1) Glucometer (at a subsidized fee)	0.58	−0.04	0.10	0.14	−0.08	−0.33
(2) Online training workshop with a nurse/ nutritionist (at a subsidized fee)	0.27	0.24	−0.32	−0.05	−0.60	0.02
(3) Phone meeting with the physician	0.22	0.18	−0.25	0.04	−0.47	−0.08
(4) HMO website/app (to set an appointment, order medication, leave a message for a physician, etc.)	−0.05	0.99	0.16	−0.03	−0.15	−0.77
(5) HMO website/app (to access information on diabetes, proper nutrition, physical activity, etc.)	0.02	0.70	−0.15	0.02	−0.57	−0.22
Other digital tools						
(6) Websites with T2DM-related information	0.84	0.02	0.02	0.49	−0.24	0.04
(7) Apps for monitoring/ tracking glucose	0.59	0.01	−0.29	0.54	0.10	−0.06
(8) Apps on a smart watch or mobile phone to promote a healthy lifestyle (e.g., counting steps or calories, recipes)	0.30	−0.01	−0.56	0.58	0.02	−0.04
(9) T2DM management reminders (e.g., taking or injecting medication, making appointments with a physician)	0.58	0.12	−0.16	0.57	0.09	−0.11
(10) Individual or group support for T2DM on social networks (e.g., WhatsApp, Facebook, forums)	−0.12	−0.01	−0.95	0.44	−0.17	0.20
Eigenvalue	3.01	2.30	2.70	1.63	1.42	1.09
% of variance	38.56	10.54	6.92	20.55	9.09	4.93
Internal consistency	$\alpha = 0.81$	$r = 0.67$ ($p < 0.001$)	$\alpha = 0.67$	$\alpha = 0.66$	$\alpha = 0.60$	$r = 0.37$ ($p < 0.001$)

advancements in recent years, which have led to substantial changes characterized by digital, efficient, and cost-effective management of T2DM [e.g., (2)]. In the first phase our research questions addressed the digital tools utilized by and available to T2DM patients for self-management of their illness. Based on interviews we generated the questionnaire items.

An additional objective was to assess the tool's validity among individuals with T2DM, including both Jewish and Arab populations in Israel and looking at both genders. The main research hypothesis regarding the validity and reliability of the constructed tool was corroborated. On the whole the results indicate the questionnaire can effectively identify digital tools used by T2DM patients of both genders, despite some differences in factor structures between the two ethnic groups.

The first hypothesis, suggesting a positive correlation between DTUQ-D and eHEALS scores, was supported, confirming the

TABLE 4 Means, *SD*, and ranges of eHEALS and DTUQ-D by ethnicity (*N* = 367).

	Total *M* (*SD*)	Arab *M* (*SD*)	Jewish *M* (*SD*)	
eHEALS (0–4)	2.60 (1.02)	2.27 (1.13)	2.74 (0.95)	$t(173.20)^{(1)} = 3.78$ ($p < 0.001$) ($d = 0.46$)
DTUQ-D (0–3)	1.07 (0.61)	0.85 (0.69)	1.17 (0.54)	$t(163.84)^{(1)} = 4.20$ ($p < 0.001$) ($d = 0.53$)

(1)*t* for unequal variances.

TABLE 5 Pearson and Spearman correlations for DTUQ-D with eHEALS and demographic variables (*N* = 367).

	eHEALS[(1)]	Age[(1)]	Duration of T2DM[(1)]	Level of education[(2)]
DTUQ-D				
Total	0.30***	0.03	−0.01	0.05
Arab	0.33***	0.01	−0.05	0.14
Jewish	0.22***	−0.06	−0.02	−0.04

(1)Pearson correlations; (2)Spearman correlations; ***$p < 0.001$.

convergent validity of the questionnaire. Moreover, a reasonable internal reliability was observed among Jewish T2DM patients and a good internal reliability among Arab T2DM patients. This finding holds dual significance. First, it indicates that the newly developed questionnaire assesses the digital tools used by T2DM patients and gauges the extent of their usage. Second, it is reasonable to assume that individuals possessing elevated eHealth literacy levels are more inclined to actively utilize websites and applications that offer self-management treatments for T2DM.

In addition, a factor analysis was conducted to assess the construct validity of the DTUQ-D. This analysis was conducted separately for Jewish and Arab participants, in line with the second hypothesis suggesting potential cultural differences in the identified factors of the DTUQ-D. The hypothesis, which suggested lower digital tool usage by Arabs, was subsequently confirmed.

The analysis for Arab participants yielded three distinct factors. The first included: (item 1) "glucometer" from the first scale of HMO Digital Tools, and three items from the second scale of Other Digital Tools, i.e., digital medical services not provided by the HMO, namely: (item 6) "websites with T2DM-related information," (item 7) "apps for monitoring/tracking glucose," and (item 9) "T2DM management reminders (e.g., taking or injecting medication, making appointments with a physician)." The second factor consisted of two items related to services provided by the HMO: (item 4) "HMO website/app (to set an appointment, order medication, leave a message for a physician, etc.)" and (item 5) "HMO website/app (to access information on diabetes, proper nutrition, physical activity, etc.)." Finally, the third factor included two items from the HMO Digital Tools subscale: (item 2) "online training workshop with a nurse/nutritionist" and (item 3) "phone meeting with the physician," as well as two items from the Other Digital Tools subscale: (item 8) "apps on a smart watch or mobile phone to promote a healthy lifestyle (e.g., counting steps or calories, recipes)," and (item 10) "individual or group support for T2DM on social networks (e.g., WhatsApp, Facebook, forums)."

The first factor found for Arabs encompasses digital tools that can be frequently used or easily accessed at home, including websites with T2DM-related information, apps for monitoring/tracking glucose, and T2DM self-management reminders. The focus on the glucometer in the first factor could indicate a specific interest or reliance on this tool for self-management, given its convenience for use at home. The second factor focuses specifically on services the HMO offers, such as setting appointments, ordering medication, and accessing relevant information through the HMO website/app. The third factor involves online interaction with professionals (nurse, nutritionist, and physician) and participation in T2DM online support on social networks and lifestyle apps. Notably, the services in this last factor were those used most infrequently by Arab participants.

Three factors were also identified for Jewish T2DM patients. The first factor included all five items in the Other Digital Tools subscale (items 6–10; see above for details of each item). This factor suggests that non-HMO tools are used similarly by Jewish participants and consist of tools that can be accessed at home. The second factor included several items from the HMO Digital Tools subscale – items 2, 3, and 5. This second factor primarily consists of information provided by online interaction with professionals and via the HMO website and are services that were moderately to infrequently used. Finally, the third factor included the rest of the items in the HMO Digital Tools scale (items 1 and 4), which are related to the most frequently used tools and services provided by the HMO.

In line with the second hypothesis, some variations can be identified between Jewish and Arab T2DM patients in their preferences and usage patterns of digital tools related to T2DM self-management. Based on the provided information, Jewish patients appear to have a more pronounced focus on HMO services. Nonetheless, there are differences in the frequency of use of these services, with the third factor tools the most frequently used (glucometer and HMO website to set appointments, etc.). Although overall, Arab T2DM patients use digital tools less than Jewish patients, they show a more diverse range of digital tool usage, including both HMO tools and lifestyle and self-management components that are not HMO-provided.

Cultural variations in perceptions of healthcare providers and trust in health systems suggest that Arab T2DM patients in Israel are likely to exhibit lower levels of trust in the medical system, potentially diminishing the adoption of digital services provided by the HMO. Indeed, research conducted in Israel within the Arab minority population revealed them to have significantly lower levels of trust in the healthcare system than Israeli Jews, which impacts adherence to public health recommendations (50).

Another possible explanation for the observed ethnic differences is limited access to web infrastructure and lower eHealth literacy in Arab society in Israel. The digital disparity between the Jewish majority and Arab minority is notably apparent in terms of Internet access and usage patterns (51). Furthermore, the distinctive characteristics of the Arab minority, including their socio-demographic status and the conservative nature of the culture, may contribute to the digital divide (30, 32). Understanding these distinctions can be valuable in tailoring T2DM self-management interventions to better suit the needs and preferences of each community. For example, HMOs can provide training in digital tool

usage for T2DM self-management geared to each population group. For groups with low eHealth literacy, such training can be initially face-to-face while practicing online interaction later. Further research and qualitative exploration could provide deeper insights into the specific reasons behind these observed differences, allowing for more targeted and culturally sensitive healthcare interventions.

Limitations

The current study is subject to a few limitations. Firstly, the sample comprised a total of 367 participants: 259 Jews and 108 Arabs. Although the sample size of the Jewish T2DM patients was adequate, the smaller number of Arab participants could produce less stable results, such that findings for the Arab sample should be considered preliminary. Secondly, given the specific characteristics of the ethnic groups studied in the current research, caution is advised in generalizing the study findings to a broader population, as there is a potential for Type I error, stemming from multiple comparisons. It is strongly recommended that future research replicate this study with a larger sample size and explore group differences by cultural background, gender, and age. This will help validate the findings and evaluate psychometric properties of the instrument. Thirdly, the study is based on a cross-sectional research design limiting the results' generalizability. In future research it is strongly recommended to further examine this issue using in-depth interviews or longitudinal studies. Thus, it will be possible to delve into the internet usage patterns of each group in relation to T2DM. Such an approach will aid in uncovering the factors influencing internet usage rates among various groups, including the Arab population in Israel. Finally, the questionnaire was primarily tailored for application within a specific cultural framework, thus restricting its generalizability to other cultural or linguistic contexts. It is strongly recommend to further examine its effectiveness in international settings.

Contributions

This study has theoretical, methodological, and practical implications. The results contribute to the theoretical understanding of digital tool use among Israeli Jewish and Arab individuals with T2DM. By identifying distinct factors and patterns, our study may enrich the theoretical framework in the field of health behavior and technology adoption. In addition, the research lays the groundwork for cross-cultural comparisons between different populations in the context of T2DM self-management. This comparative approach can deepen insights into the factors influencing digital tool use across diverse cultural settings.

In terms of methodological advancements, we developed an innovative questionnaire through a combination of qualitative and quantitative methods, proposing a foundation for a construction method that other researchers can adopt. In addition, the research introduces and assesses the DTUQ-D, providing a valuable screening tool for studying digital tool utilization in the context of T2DM self-management. This questionnaire could serve as a foundation for future research, offering a standardized and systematic approach to assess digital tool usage. Researchers can build upon the identified factors and explore additional dimensions, thereby enhancing understanding of the evolving role of digital tools in healthcare, particularly in the context of T2DM self-management. Furthermore, the questionnaire can be easily modified, by adjusting the instructions and some of the specific T2DM items, to assess digital tool use by patients with other illnesses.

The questionnaire can be scored and coded in several ways, depending upon the research question. It can provide researchers with information about the number, frequency, and types of digital tools used. For example, in a study examining the number of digital tools used, the *number* of items that received responses in the range of 1 to 3 (*seldom* to *regularly*) should be counted. When the research question examines the frequency of digital tool use, we recommend calculating a *total* score (based on the Likert scale values) that reflects accumulated tool use. It is also possible to calculate a *mean* score, rendering a frequency score across all items, as done in the current study. This latter approach takes into account individual differences in digital use that can be related, for instance, to the severity of the illness or the inclination to use digital tools. Lastly, to gauge the *type* of tools used, it is possible to calculate the sum of items within each factor.

From a practical point of view, the information gleaned from the DTUQ-D can assist in developing targeted interventions or guidelines to optimize the use of digital technologies while reducing potentially problematic usage patterns (52). Thus, our findings have practical implications for healthcare practitioners, policymakers, and digital health intervention developers. Comprehending the specific digital tools favored by Jewish and Arab populations can contribute to the development of such targeted interventions, enhancing the efficacy of T2DM self-management strategies. Moreover, by tailoring digital tools and interventions to the preferences and needs of specific cultural groups, it is possible to enhance engagement in and the effectiveness of the support provided by HMOs.

In sum, the contributions of the research lie in advancing theoretical understanding, providing a methodological tool, and offering practical insights that can inform healthcare practices and the development of culturally sensitive digital health interventions. This knowledge can facilitate more effective communication and collaboration between healthcare professionals and patients in managing T2DM.

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 humans were approved by the college's Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

OP: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. EH: Conceptualization, Funding acquisition, Investigation, Resources, Visualization, Writing – review & editing. MB-N: Conceptualization, Investigation, Resources, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Appendix

DTUQ-D					
Over the last 6 months, to what degree have you utilized the following tools for managing your diabetes?					
		0 Never	1 Seldom	2 Often	3 Regularly
HMO digital tools					
1	Glucometer (at a subsidized fee)				
2	Online training workshop with a nurse/nutritionist (at a subsidized fee)				
3	Phone meeting with the physician				
4	HMO website/app (to set an appointment, order medication, leave a message for a physician, etc.)				
5	HMO website/app (to access information on diabetes, proper nutrition, physical activity, etc.)				
Other digital tools					
6	Websites with T2DM-related information				
7	Apps for monitoring/tracking glucose				
8	Apps on a smart watch or mobile phone to promote a healthy lifestyle (e.g., counting steps or calories, recipes)				
9	T2DM management reminders (e.g., taking or injecting medication, making appointments with a physician)				
10	Individual or group support for T2DM on social networks (e.g., WhatsApp, Facebook, forums)				

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Comprehensive machine learning models for predicting therapeutic targets in type 2 diabetes utilizing molecular and biochemical features in rats

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Introduction: With the increasing prevalence of type 2 diabetes mellitus (T2DM), there is an urgent need to discover effective therapeutic targets for this complex condition. Coding and non-coding RNAs, with traditional biochemical parameters, have shown promise as viable targets for therapy. Machine learning (ML) techniques have emerged as powerful tools for predicting drug responses.

Method: In this study, we developed an ML-based model to identify the most influential features for drug response in the treatment of type 2 diabetes using three medicinal plant-based drugs (Rosavin, Caffeic acid, and Isorhamnetin), and a probiotics drug (Z-biotic), at different doses. A hundred rats were randomly assigned to ten groups, including a normal group, a streptozotocin-induced diabetic group, and eight treated groups. Serum samples were collected for

biochemical analysis, while liver tissues (L) and adipose tissues (A) underwent histopathological examination and molecular biomarker extraction using quantitative PCR. Utilizing five machine learning algorithms, we integrated 32 molecular features and 12 biochemical features to select the most predictive targets for each model and the combined model.

Results and discussion: Our results indicated that high doses of the selected drugs effectively mitigated liver inflammation, reduced insulin resistance, and improved lipid profiles and renal function biomarkers. The machine learning model identified 13 molecular features, 10 biochemical features, and 20 combined features with an accuracy of 80% and AUC (0.894, 0.93, and 0.896), respectively. This study presents an ML model that accurately identifies effective therapeutic targets implicated in the molecular pathways associated with T2DM pathogenesis.

KEYWORDS

type 2 diabetes, therapeutic targets, machine learning, drug response, rats

1 Introduction

Globally, the burden of diabetes mellitus (DM) is projected to rise to 1.3 billion people by 2050, making it one of the most widely spread diseases worldwide (1). Type 2 diabetes mellitus (T2DM) is the prevalent form of DM, it is hallmarked by hyperglycemia, insulin resistance, and ultimate decrease in β-cells insulin secretion (2). When it develops further worsening comorbidities emerge including micro- and macrovascular disease, leading to kidney dysfunction, diabetic retinopathy, blindness, heart disease, stroke, and lower limb amputations (3).

Diabetes mellitus is a highly heterogeneous entity (4). To enhance our comprehension of the underlying biological mechanisms and identify individuals at risk, it is crucial to investigate the genetic contributions to diabetes. Such knowledge can ultimately lead to the development of more precise and effective therapeutic approaches. As T2DM progresses, it often necessitates the simultaneous administration of multiple medications that target different pathophysiologic pathways (5). This combined treatment approach aims to regulate blood glucose levels and mitigate the progression of complications.

However, emerging evidence suggests that inflammatory pathways play a pivotal role as common mediators in the natural course of diabetes when influenced by risk factors (6). Interestingly, a previous study discovered that HFD-induced mice increased mitochondrial DNA (mtDNA) release into the cytosol of adipocytes, activating the cGAS-STING pathway and inflammatory response, resulting in chronic inflammation in adipose tissue and insulin resistance (7, 8). Moreover, autophagy plays a crucial role in T2DM pathogenesis as it protects cells from the damaging effects of oxidative stress and endoplasmic reticulum stress, which is essential for the survival and proper functioning of β-cell and insulin sensitivity, however, when the autophagic system in β-cells fails, it can exacerbate β-cell dysfunction, particularly in the presence of insulin resistance, potentially leading to hyperglycemia (9). A growing body of evidence suggests that enhanced autophagy, triggered by insulin resistance, may act as a safeguarding mechanism against the deterioration and increased apoptosis of pancreatic β-cells (10). This underscores the potential significance of autophagy modulation in the pursuit of therapeutic strategies aimed at preserving β-cell function in T2DM and ultimately managing hyperglycemia.

The growing availability of high-throughput technologies in large populations, such as genomics and transcriptomics with linked medical record data supports the development of new computational approaches for drug targeting using molecular biomarkers in addition to the traditional biomarkers. Noncoding RNAs (ncRNAs) including microRNAs (miRNAs) and long noncoding RNAs (LncRNAs), exhibit diverse functions in post-transcriptional gene regulation, epigenetic gene silencing, modulation of insulin secretion, and endoplasmic reticulum stress (11, 12). These ncRNAs have been intricately linked to the development of T2DM (13, 14) For instance, mir-375, a highly expressed miRNA in islet cells, plays a crucial role in insulin secretion and β-cell functioning. Dysregulation of mir-375 has been linked to impaired insulin secretion and β-cell dysfunction (15). On the other hand, lncRNAs have been implicated in the pathogenesis of insulin resistance and the maintenance of glucose homeostasis by regulating inflammatory and lipogenic processes (16, 17).

Despite the presence of chemical anti-diabetic agents, possible adverse effects and limited efficiency could occur. As a result, recent endeavors have explored other treatment options for the rising T2DM prevalence (18). Medicinal plants are of paramount importance in maintaining body health with no side effects compared with synthetic

drugs (19). Likewise, several clinical studies have been conducted to examine the impact of probiotics on improving glycemic index, lipid profile, glucose metabolism, and insulin sensitivity (20). These investigations were fuelled by the observation that the gut microbiota of diabetic patients tends to be altered (21). Such changes in the gut microbiota could lead to metabolic endotoxemia, which occurs through the release of lipopolysaccharides and could trigger inflammation and insulin resistance (22).

Several researches has confirmed that inflammation is closely linked to the pathogenesis of T2DM and its complications. Many anti-diabetic drugs are usually prescribed to diabetic patients, to decrease the progression of T2DM through modulation of inflammation. However, those anti-diabetic drugs are often not successful as a result of side effects; such as sulphonylureas & biguanides may cause acute severe hypoglycemia and lactic acidosis. Therefore, researchers are searching for efficient natural therapeutic targets with less or no side effects. Natural products' derived bioactive molecules have been proven to improve insulin resistance and associated complications through suppression of inflammatory signaling pathways (23). Moreover, the utilization of probiotics as dietary supplements gains popularity because gut microbiota dysbiosis significantly contributes to T2DM (24). Zbiotics as newly implemented enginerred probiotics as a new complementary therapeutic strategy that alleviate oxidative stress and beneficial effect on reducing blood glucose levels, HOMA-IR, and HbA1c.

This study investigates the potency of medicinal plant-based drugs and probiotics in modulating T2DM in streptozotocin-high-fat diet-induced induced rats. Isorhamnetin is a flavonoid found in sea buckthorn, medicinal plants, and ginkgo fruits (25). It possesses various pharmacological effects, including anti-inflammatory, anti-tumor, antioxidant, antibacterial, and antiviral properties (26, 27). It has been found to promote glucose uptake, maintain glucose homeostasis, and improve dyslipidemia in mice with T2DM (28). It can also reduce the expression of inflammatory cytokines and enhance the health of the gut microbiota in T2DM mice (29). *Rhodiola rosea L.* is abundant in flavonoids, glycosides, coumarins, and organic acid compounds (30). Rosavin, the R. rosea bioactive compound, possesses protective properties against inflammation, reduces blood glucose levels, exhibits antiviral and antitumor effects, and promotes blood circulation activation (31, 32). The caffeic acid extract derived from *Artemisia dracunculus L.* has been proven to enhance insulin receptor signaling. Semisynthetic compounds derived from caffeic acid induce DNA damage and apoptosis in tumor cells by activating autophagy (33). Furthermore, it plays a protective role in preventing renal damage (34, 35). ZBiotics is an engineered probiotic that involves the use of a genetically modified strain of *B. subtilis* by incorporating an acetaldehyde dehydrogenase gene. The modified strain converts acetaldehyde derived from ethanol into acetic acid,thereby reducing the potential harm caused by alcohol consumption (36). Animal toxicity studies have indicated ZBiotics' high level of safety (37). However,its potential as a therapeutic drug for diabetes has not been investigated yet.

In order to examine the clinical trials' data related to caffeic acid and related compounds in diabetic patients, we searched the largest clinical trial database at 'https://clinicaltrials.gov'. No search results were obtained with the keywords 'saffeic acid and diabetes mellitus'. Since propolis found in beehive is a major source of caffeic acid derivatives, therefore we searched with keywords 'propolis and diabetes mellitus' on the database. Three studies were found in which propolis was administered orally or applied topically to diabetic patients(ClinicalTrials.gov Identifier: NCT03416127 phase 2 in patients with type 2 DM for 12 weeks, NCT02794506 Phase: 4. in Type 2 DM, periodontitis, and NCT03649243 in diabetic foot ulcer). Similarly, no results found for rosavin in T2DM except one recent clinical trial in diabetic kidney disease (NCT06176599). More than 20 clinical trials were found correlating Rhodiola Rosea the origin of rosavin in many mental disorders, metabolic diseases, coronary diseases. Additionally, one clinical trial (NCT00961909) assessing the efficacy of Artemisia dracunculus plant rich in isorhamantin in T2DM. Moreover, no results found for Zbiotics in T2DM (Supplementary Table S1).

To minimize the consequences of diabetes and improve patient care, researchers have explored various fields, such as machine learning (ML) and artificial intelligence (AI), by applying ML techniques in the field of biology, researchers have significantly improved the precision of prediction models (38). Numerous studies have looked into using ML techniques to predict the occurrence of diabetes (39, 40).

Deberneh et al. created an ML model that can predict the occurrence of type 2 diabetes (T2D). The models categorize input data instances into three conditions: normal (non-diabetic), prediabetes, or diabetes. To construct their prediction model, they identified key features using a data-driven technique that includes an analysis of variance (ANOVA) test and recursive feature elimination methods. Also, they compared the performance of various machine learning models, such as LR, support vector machine (SVM), RF, and XGBoost algorithms (41). Wei S et al. built an ML model for diabetes detection. The study assessed two crucial data processing techniques: Principal Component Analysis (PCA) and Linear Discriminant Analysis (LDA) across various machine learning algorithms. The highest accuracy achieved among the five algorithms tested (Neural Network, Support Vector Machine, Decision Tree, LR, and Naïve Bayes) was 77.86% using 10-fold cross-validation (42).

Elsherbini AM et al. employed machine learning techniques to identify significant genes associated with diabetes and assess their potential as biomarkers for early detection. The analysis highlighted the *HLA-DQB1* gene as a promising biomarker to detect diabetes through ML algorithms with decent accuracy (43). Xu et al. introduced a computational model utilizing stochastic gradient boosting. They incorporated six features, encompassing molecular structures, structural similarities, ATC code similarities, protein–protein interaction, chemical-chemical interaction, and disease pathways (44). Moreover, Costello et al. and Jang et al. performed extensive comparative analyses of machine learning methods for drug response prediction in cancer cell lines, recommending using elastic net or ridge regression with input features from all genomic profiling platforms (45, 46).

In this study, we aimed to utilize standard statistical methods and machine learning techniques to leverage the gene expression patterns and their epigenetic regulators in the livers and adipose tissues, along with conventional biochemical parameters to identify predictive

features that could be used to assess the response to medicinal plant-based drugs and probiotics in an animal model of T2DM.

2 Materials and methods

2.1 Chemicals

Rosavin was obtained from Aktin Chemicals, Inc (Cat.No. APC-380, China), While isorhamnetin 3-O-acylglucosides, Z-Biotics, Caffeic acid, and sodium citrate buffer were purchased from Sigma Chemical Co, St. Louis, Mo, USA.

2.2 Experimental design

A hundred male Wistar rats (150–170 g) were purchased from the Holding Company for Biological Products and Vaccines based in Giza, Egypt. Rats were randomized into 10 groups (N=10 per group) and kept one week for acclimation with free access to normal rat chow and water under well-controlled condition (20 ± 2°C), 12 h light/dark cycle. The animal procedures followed the guidelines outlined in the National Institutes of Health guide for the care and use of Laboratory Animals (8th edition, 2011). Ethical approval for the experiments was obtained from the Institutional Animal Ethics Committee of Ain Shams University, Faculty of Medicine NO. FWA000017585. The Diabetic rat model was induced by feeding rats with a high-fat diet (HFD) that consists of 58% fat, 17% carbohydrate, and 25% protein and libitum for a total of 12 weeks. After the initial 4 weeks, the rats were administered two low-dose intraperitoneal (i.p.) injections of streptozotocin (STZ; 30 mg/kg) dissolved in citrate buffer (pH 4.5), with a one-week interval between injections. The Normal control rats were administered citrate buffer only. After one week following the last STZ injection, blood samples were collected from the tail vein, and blood glucose levels were measured using a glucometer (Accu-check, Roche Diagnostics, Risch-Rotkreuz, Switzerland). The onset of diabetes was confirmed when the non-fasting blood glucose levels were equal to or higher than 200 mg/dl. Throughout the study, the rats were allowed to continue consuming their respective diets until its completion. Then, T2DM-induced rats were randomly divided into 9 groups, 10 rats each, including; (I) the T2DM control group (N=10): that received intraperitoneal STZ, fed HFD, and 0.9% saline orally, (II) Rosavin-10, and 30 groups: the T2DM induced rats received 10 mg/kg-30 mg/kg of rosavin, respectively dissolved in 0.9% saline for 4 weeks, (III) Z-Biotic 0.5, and Z-Biotic 1 groups: T2DM induced rats received 0.5 mg/kg- 1 mg/kg Z-Biotic, respectively dissolved in DMSO for 3 weeks. (IV) Isorhamnetin-10, and Isorhamnetin-40 groups: the T2DM induced rats received 10 mg/kg-40 mg/kg Isorhamnetin dissolved in DMSO for 3 weeks, (V) Caffeic acid groups: the T2DM induced rats received 10 mg/kg-50 mg/kg caffeic acid, respectively dissolved in cold water. Rats received the medicinal plant-based drugs and the probiotics orally by gastric gavage. (VI) The Normal group (N=10): rats received sodium citrate buffer 1 ml/kg intraperitoneally, the same amount injected in the weight-matched rat in the other groups. At the end of the experiment, blood samples were obtained from the retro-orbital veins of the animals under ether anesthesia. Subsequently, the animals were euthanized through cervical dislocation. Both the right and left gastrocnemius muscles, along with adipose tissue, were collected from all the animal groups. One gastrocnemius muscle and a portion of adipose tissue from each animal were frozen at -80°C for biochemical analysis. The other gastrocnemius muscle and a portion of adipose tissue were fixed in 10% formalin for histopathological evaluation (Figure 1).

2.3 Biochemical analysis

Prior to euthanization, blood samples were obtained from the optical vein of the rats and then subjected to centrifugation at 2000g for 10 minutes at 4°C. The resulting serum was collected for further analysis. Commercial ELISA kits from RayBiotech, USA, were utilized to measure the levels of cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), alanine transaminase (ALT), aspartate transaminase (AST), total cholesterol (TC), serum creatinine, Blood Urea Nitrogen (BUN), fasting blood glucose, postprandial blood glucose, and fasting blood insulin following the manufacturer's instructions. The calculation of the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was performed using the equation: fasting insulin (µU/L) multiplied by fasting glucose (nmol/L)/22.5. Urine samples were collected for one day using individual metabolic cages, which took place on the day before the completion of the treatment. The level of albumin in the urine was evaluated using commercially available colorimetric kits from RayBiotech, USA, following the instructions provided by the supplier.

2.4 Histopathological analysis

Liver and adipose tissue specimens underwent dissection and fixation in neutral buffered formalin for 72 hours. Subsequently, the samples underwent a series of processing steps involving ethyl alcohol, Xylene clearance, and embedding in paraplast tissue-embedding media. Employing a rotatory microtome, tissue sections with a thickness of 5µm were acquired and affixed onto glass slides. The staining procedure utilized Hematoxylin and Eosin (H and E), following standard protocols outlined by Culling, C.F.A. 2013. Skilled histologists, operating in a blinded fashion, scrutinized these tissue sections.

2.5 Morphometric analysis

For the analysis of white fat cells and the determination of average cell diameter, a minimum of 6 non-overlapping fields were randomly selected and scanned. Following the approach outlined by Batts and Ludwig (47), individual biopsy specimens were assessed for the grade of inflammation, rated on a scale from 0 to 4 [0: no activity; 1: minimal; 2: mild; 3: moderate; and 4: severe]. All data were acquired through the Leica Application module linked to Leica Microsystems GmbH (Germany).

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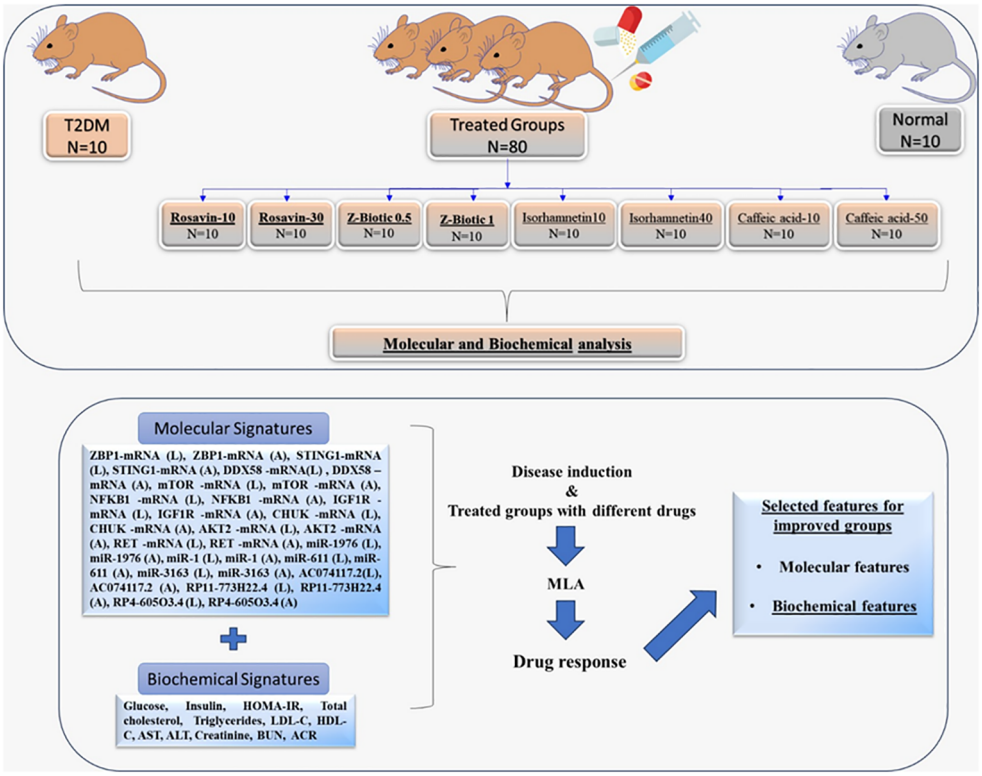

FIGURE 1
Workflow describing the animal groups subjected to molecular and biochemical analysis for ML-model building identify signatures associated with drug response.T2DM, Type 2 Diabetes Mellitus; (L) extracted from the Liver tissues; (A) extracted from the Adipose tissues; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; BUN, Blood Urea Nitrogen; ACR, urine albumin to creatinine ratio; MLA, Machine learning Algorithm.

2.6 Bioinformatics analysis

- In this study, we conducted a comprehensive analysis of genes that are differentially expressed relevant to diabetes. To identify these genes, we performed a search in the Gene Expression Omnibus (GEO) database http://www.ncbi.nlm.nih.gov/geo, accessed on Jan 2024. In this study, we conducted a comprehensive analysis of genes that are differentially expressed relevant to diabetes. To identify these genes, we performed a search in the Gene Expression Omnibus (GEO) database http://www.ncbi.nlm.nih.gov/geo, accessed on Jan 2024. We utilized keywords related to diabetes mellitus type 2 such as 'type 2 diabetes,' 'diabetic nephropathy,' 'tissue,' 'pancreas'. After obtaining a pool of potential datasets, we proceeded to screen them based on specific inclusion criteria. The first criterion was related to the tissue type, where we focused on tissues relevant to T2DM. The second inclusion criterion was the availability of normal tissues used as controls in the dataset. The inclusion of normal tissues ensures a suitable baseline for comparative analysis with tissues from T2DM patients. Furthermore, we also considered the sample size in the dataset. To ensure statistical robustness and reduce potential bias, we set a minimum threshold of ten or more samples in each dataset.

Specifically, we selected two datasets, GSE20966 and GSE142025, and used the "GEO2R/Limma R" package to screen for highly significant differentially expressed genes (DEGs). We considered genes with a p-value less than 0.05 and a log twofold change (LogFC) value of ≥ 1 or ≤ -1, using the Benjamini and Hochberg method for false discovery rate adjustment. In order to identify the biological pathways of DE-mRNAs, a thorough enrichment analysis was conducted using Enrichr (http://amp.pharm.mssm.edu/Enrichr, Jan 2022) with the Kyoto Encyclopedia of Genes and Genomes (KEGG) selected as the analysis tool. The analysis revealed The DE-mRNAs were related to Pancreatic secretion, ECM-receptor interaction, HNF3B pathway,RANKL regulation of apoptosis and immune response (Supplementary Figure S2). then filtered based on their association with, specific pathways that are of interest in diabetes research, such as insulin resistance, autophagy, cGAS/STING, and NOD-like receptor pathways(Supplementary Figure S2). To identify genes associated with these pathways, we utilized the GeneCards database https://www.genecards.org/, accessed on Jan 2024. Accordingly, we selected nine genes: Z-DNA Binding Protein 1 (*ZBP1*), Stimulator

Of Interferon Response CGAMP Interactor 1 (*STING1*), RIG-I, Retinoic Acid-Inducible Gene 1 Protein (*DDX58*), mammalian target of rapamycin (*mTOR*), Nuclear Factor Kappa B Subunit 1 (*NFKB1*), insulin-like growth factor-1 (*IGF-1*), Component Of Inhibitor Of Nuclear Factor Kappa B Kinase Complex (*CHUK*), RAC-beta serine/threonine-protein kinase (*AKT2*), and Ret Proto-Oncogene (*RET*). To explore the interactions between the differentially expressed genes, we utilized the String database https://string-db.org/, accessed on Jan 2024 to construct a protein-protein interaction (PPI) network. Furthermore, to identify miRNAs that target the selected DEGs, we used the mirwalk database http://mirwalk.umm.uni-heidelberg.de/, accessed on Jan 2024. Finally, to predict the interaction of miRNAs-LncRNAs, we used RNA22 https://cm.jefferson.edu/rna22/, accessed on Jan 2024, mirwalk database http://mirwalk.umm.uni-heidelberg.de/, accessed on Jan 2024 and DIANA Tools https://diana.e-ce.uth.gr/lncbasev3/interactions, accessed on Jan 2024. Thus, the following LncRNAs (AC074117.2, RP11–773H22.4, and RP4–605O3.4) and miRNAs (miR-1976, miR-1, miR-611, and miR-3163) were chosen (Supplementary Table S2, S3, Supplementary Figures S3-S8).

2.7 Total RNA extraction and quantitative real-time PCR

Total RNA was isolated from the Liver (L) and Adipose tissue (A) samples using the miRNeasy kit (Qiagen, USA; Cat no. 74104). Next, the RNA quality, integrity, and concentration were measured using the DeNovix DS-11 microvolume spectrophotometer (Wilmington, USA) and stored at -80°C. The obtained RNA samples were reverse transcribed into cDNA by the two-step RT-PCR using the miScript II RT kit (Qiagen, USA; Cat no. 218161). Then the qRT-PCR was performed using Applied Biosystems Tm 7500 system (Foster City, California, United States). Regarding the expression of mRNAs, QuantiTect SYBR Green PCR Kit (Qiagen, Helman Germany; Cat no. 204143) was used. The relative expression of the miRNAs was obtained using the miScript SYBR Green PCR Kit (Qiagen, Helman Germany; Cat no. 218073). The relative expression of the lncRNAs was performed using RT^2 SYBR Green ROX qPCR Master mix (Qiagen, Helman Germany; Cat no: 330500). Glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) and U6 were regarded as internal controls for the mRNAs, LncRNAs, and miRNAs, respectively. The Livak method RQ = $2^{-\Delta\Delta Ct}$ method was adopted to analyze the relative expression. For each sample, 2 replicates were set. Ct values of more than 35 were deemed negative. Melting curve analysis validated the amplicons' specificities for SYBR Green-based PCR amplification. In this study, proper standardization procedures were used to detect any experimental error produced at any stage of the RNA extraction and processing according to MIQE recommendations. The PCR procedure was as follows: an initial activation phase at 95°C for 15 minutes was followed by 40 cycles of PCR at 94°C for 15 s, 55°C for 30 seconds, and 72°C for 30 s.

2.8 Statistical analysis

The Statistical analysis was performed with SPSS 26. Software. Data are presented as mean ± SD and significant differences were compared using a 1-way analysis of variance followed by *post hoc* Tukey's test. The Shapiro-Wilk test confirmed that the data in this study followed a normal distribution. Categorical data were expressed as percentages and compared using the chi-square test.

3 Machine learning model

3.1 Data

One of the main objectives of this study is to create a predictive model using machine learning algorithms to thoroughly identify a promising set of features that strongly indicate the drug's response to T2DM. The dataset in this study is a mouse model data with 100 samples distributed among normal, treated, and diseased groups (Table 1) with molecular features expressed in adipose tissues (A) and liver tissues (L) besides the biochemical features (Table 2). To determine treatment response, two key features were focused on: inflammation grade and fat cell diameter. Samples exhibiting a fat cell diameter exceeding 70 and an inflammation grade of 3 or higher were categorized as "not improved" (binary 0), while those falling below these thresholds were labeled as "improved" (binary 1). The analysis showed the relative ratio is 1:2.44 for the improved and not improved samples as shown in Figure 2.

The dataset was divided into 70 samples for training and 30 samples for testing. Also, Multi-classifiers approaches were implemented using 5 classifiers including K-Nearest Neighbors (KNN), Light Gradient Boosting Machine (LGBM), Random Forest (RF), Logistic Regression (LR), and Ada Boost Classifier.

3.2 Dataset preprocessing

In the development of machine learning models, data preprocessing stands as a critical step. Herein, thorough measures were taken to ensure the data's quality by addressing several factors and they were null feature removal, noise reduction, and outlier elimination. Additionally, the column index was reset to accurately assign each column its respective index. Moreover, the creation of a 'status' column in binary format (1,0) was undertaken to reflect treatment response whether it was improved or not improved (49).

3.3 Feature selection

The feature selection technique was utilized, this method effectively reduces the complexity and size of the data, enhancing the learning process. Additionally, by selecting only the relevant features, the model becomes faster and more precise, thereby enhancing its predictive capabilities through noise reduction.

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TABLE 1 The number of samples per normal, disease model, and treatment groups.

Condition	Number of samples
Normal (Healthy)	10
T2DM	10
Rosavin-10	10
Rosavin-30	10
Z-Biotic 0.5	10
Z-Biotic 1	10
Isorhamnetin-10	10
Isorhamnetin-40	10
caffeic acid-10	10
caffeic acid-50	10

3.3.1 Selecting top features with recursive feature elimination cross validation

An initial trial was carried out to determine the selected machine learning features for predicting T2DM drug response. The Recursive Feature Elimination Cross-Validation (RFECV) technique was employed for this purpose. RFECV functions by iteratively eliminating features and evaluating prediction accuracy. The most optimal reduced set of features, which either matches or surpasses the original accuracy of the complete feature set, is then identified as the optimal set of predictive features. Various combinations of features yield different accuracy levels (50). Furthermore, relevant model hyperparameters for the RF model (e.g., maximum tree depth, minimum samples split, and estimators) were fine-tuned to achieve the best-performing model. Optimization involves experimenting with different parameter sets to determine the most effective configuration for our dataset. The top selected features for molecular, biochemical, and both combined were reported.

TABLE 2 Molecular and biochemical features used in ML models.

Molecular (32 features)	Biochemical (12 features)
1. ZBP1-mRNA (L)	1. Glucose
2. ZBP1-mRNA (A)	2. Insulin
3. STING1-mRNA (L)	3. HOMA-IR
4. STING1-mRNA (A)	4. Total cholesterol
5. DDX58 -mRNA (L)	5. Triglycerides
6. DDX58 -mRNA (A)	6. LDL-C
7. mTOR -mRNA (L)	7. HDL-C
8. mTOR -mRNA (A)	8. AST
9. NFKB1 -mRNA (L)	9. ALT
10. NFKB1 -mRNA (A)	10. Creatinine
11. IGF1R -mRNA (L)	11. BUN
12. IGF1R -mRNA (A)	12. ACR
13. CHUK -mRNA (L)	
14. CHUK -mRNA (A)	
15. AKT2 -mRNA (L)	
16. AKT2 -mRNA (A)	
17. RET -mRNA (L)	
18. RET -mRNA (A)	
19. miR-1976 (L)	
20. miR-1976 (A)	
21. miR-1 (L)	
22. miR-1 (A)	
23. miR-611 (L)	
24. miR-611 (A)	
25. miR-3163 (L)	
26. miR-3163 (A)	
27. AC074117.2 (L)	
28. AC074117.2 (A)	
29. RP11–773H22.4 (L)	
30. RP11–773H22.4 (A)	
31. RP4–605O3.4 (L)	
32. RP4–605O3.4 (A)	

(A), means expressed in the adipose tissues; (L), means expressed in liver tissues.

3.4 Cross validation

In k-fold cross-validation, the training set is partitioned into k distinct and equally-sized subsets. The classifier is trained on each subset using the union of all other subsets. Consequently, the average error rate across all subsets provides an estimate of the classifier's error rate. Each data point is included in the test set precisely once and appears in the training set k-1 times. Increasing k helps reduce the variance of the resulting estimate. We utilized the k-fold cross-validation method, employing k=3 in our analysis (51).Of note, we utilized Stratified K-Fold cross-validation with a number of folds set to 3 to validate the performance of our machine learning model. This technique was chosen to ensure that each fold preserves the proportion of samples for each class, thereby mitigating potential biases and enhancing the reliability of our results. During the validation process, we partitioned the dataset into three subsets, with each subset containing a representative distribution of the target variable classes. We then iteratively trained the model on two-thirds of the data (training set) and evaluated its performance on the remaining one-third (validation set), ensuring that the model was tested on unseen data in each fold. By adopting Stratified K-Fold cross-validation, we aimed to demonstrate the independence and rigor of our model validation, thereby enhancing the reproducibility and accuracy of our results.

3.5 Models predictions

A multi-class approach using five machine learning algorithms (KNN, RF, LGBM, LR, and Ada Boost) was employed on three separate models as follows: one using only Molecular features, one using only Biochemical features, and one combining both feature groups as shown in Table 3. The top selected features obtained from RFECV were used in each model. This comprehensive strategy aimed to identify a potential set of highly predictive features for drug response. Also, the top-performing classifier applied on the training set for each feature group was selected and then applied to the testing set to evaluate their performance on an unseen dataset.

3.6 Machine learning evaluation

The three model's performance were assessed using the test dataset. The evaluation was based on key performance metrics, such as the area under the curve (AUC). To further analyze the model's

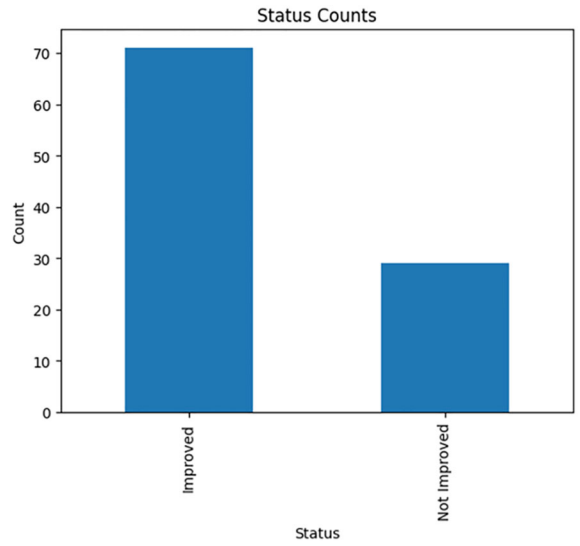

FIGURE 2
Show the number of improved (48) and not improved (29) samples.

efficacy, a 2 × 2 confusion matrix was constructed using the test dataset, allowing for the calculation of true positive, false positive, true negative, and false negative values.

3.7 Visual analysis for molecular and biochemical features

a graphical implementation has been used to analyze the relationship between each molecular and biochemical features of treated samples against the T2DM group as well, as to the normal group to capture insights for drug response.

3.8 Python packages

This study's data were processed using Python 3.7 as the programming language. We used many Python-based packages and modules as well to ease the processing pipeline. The 'pandas' package (version 1.3.5) and 'NumPy' (version 1.20.3) are utilized for data manipulation and analysis. 'Seaborn' (version 0.13. 2) enhances data visualization capabilities. 'Matplotlib.pyplot' (version 3.5.0) is another data visualization package, offering a versatile toolkit for creating static, interactive, and animated plots. The scikit-learn (version 1.0.2) is extensively used for machine learning tasks. 'statistics' provides functions for mathematical statistics.

TABLE 3 The three predictive models were applied to the five classifiers.

Model	Data Type
1	Molecular
2	Biochemical
3	Molecular + Biochemical

4 Results

4.1 Effect on diabetic parameters, serum biochemicals, and liver inflammation

Table 4 presents the observed changes in different parameters in the T2DM group compared to the normal group, along with the effects of medicinal plant-based drugs and probiotics drug administration. In the T2DM group, there was a significant increase in serum glucose, insulin, and HOMAIR levels. However, these elevated levels were modulated after the administration of our selected drugs, particularly at higher doses, suggesting that the drugs have the potential to suppress hyperinsulinemia and improve insulin resistance. Furthermore, renal function biomarkers including serum creatinine, BUN, and albumin-to-creatinine ratio (ACR) showed a significant increase in the T2DM group. On the other hand, the administration of different doses of drugs led to a modulation of these biomarkers. The lipid profile analysis revealed a significant increase in total cholesterol, triglycerides, and LDL levels, along with reduced HDL levels in the T2DM rat group. While the treated groups exhibited improvements in the lipid profile levels. Moreover, hepatic damage biomarkers such as AST and ALT were elevated in the T2DM group but decreased in the treated groups. Similarly, liver inflammation grades exhibited an increase in the T2DM group but decreased in the treated groups, particularly at higher doses. The fat cells' diameter increased significantly in the T2DM group as well as the treated groups except for the Rosavin-30 treated group which showed decreasing in the fat cells' diameter.

4.2 Histopathological results

The normal group demonstrated a normal architecture. The hepatic lobule is composed of hepatocytes (h) that are arranged into branching cords with sinusoids (S) in between. Hepatocytes appeared as polygonal cells with granular eosinophilic cytoplasm and round nuclei. Central vein (CV) is located at the center of the lobule whereas the T2DM group showed an altered architecture with marked hepatocellular microvesicular steatosis (Arrow) all over hepatic lobule accompanied, widespread of necrotic cells (Arrowhead), inflammatory cells infiltrate (asterisks) and pyknotic cells (Curved arrow). The Rosavin-10 treated group showed altered architecture with mild hepatocellular microvesicular steatosis (Arrow), in addition to the presence of pyknotic cells (Curved arrow), necrotic cells (Arrowhead), and inflammatory cells (asterisks) whereas the Rosavin-30 treated group showed a normal histological feature of the hepatic lobule with wide sinusoids (S). The Z-Biotic 0.5 treated group showed an altered architecture of the liver with moderate hepatocellular microvesicular steatosis (Arrow), and the presence of inflammatory cell infiltrates (asterisks) whereas the Z-Biotic 1 treated group showed an altered architecture of the liver with mild hepatocellular microvesicular steatosis (Arrow) with minimum mononuclear inflammatory cells infiltrates. The Isorhamnetin-10 treated group demonstrated necrotic changes (Arrowhead) in the hepatocytes, several hepatocytes showed pale

TABLE 4 Serum biochemical parameters, liver inflammation in the normal, T2DM, and treated rats.

	Normal	T2DM	Rosavin-10	Rosavin-30	Z-Biotic 0.5	Z-biotic 1	Isorhamnetin-10	Isorhamnetin-40	caffeic acid-10	caffeic acid-50	P-value	F
Glucose(mmol/L)	5.8 ± .36	29.07 ± 2.4^{a}	12.51 ± 0.76^{ab}	6.87 ± .467^{b}	11.754.8 ± 12.91^{ab}	5.63 ± .38^{b}	12.73 ± 4.54^{ab}	7.08 ± 0.54^{b}	15 ± .9^{ab}	7.63 ± 1^{ab}	1.62E-73	519.032
Insulin(μU/ml)	4.64 ± 0.91	16.29 ± 1.14^{a}	13.78 ± 0.92^{ab}	5.76 ± 0.97^{b}	12.96 ± 0.87^{ab}	4.72 ± 0.8^{b}	14.18 ± 0.92^{ab}	5.36 ± 0.97^{b}	14.06 ± 0.94^{ab}	5.87 ± 0.99^{b}	2.76E-60	258.422
HOMAIR	1.2 ± 0.24	21.06 ± 2.18^{a}	7.69 ± 0.85^{ab}	1.77 ± 0.36^{b}	6.79 ± 0.75^{ab}	1.19 ± 0.24^{b}	8.02 ± 0.57^{ab}	1.68 ± 0.28^{b}	9.4 ± 1.03^{ab}	2 ± 0.41^{b}	3.64E-72	483.638
Total cholesterol (mmol/L)	1.86 ± 0.14	10.44 ± 1.25^{a}	6.07 ± 0.59^{ab}	3.08 ± 0.58^{ab}	5.67 ± 0.55^{ab}	2.2 ± 0.42^{b}	9.1 ± 0.89^{ab}	2.16 ± 0.41^{b}	7.89 ± 0.77^{ab}	3.7 ± 0.7^{ab}	1.12E-55	201.870
Triglycerides(mmol/L)	1.73 ± 0.22	17.11 ± 0.95^{a}	8.49 ± 0.64^{ab}	4.03 ± 0.34^{ab}	9.34 ± 0.71^{ab}	4.43 ± 0.37^{ab}	7.72 ± 0.58^{ab}	1.55 ± 0.13^{b}	5.94 ± 0.45^{ab}	2.82 ± 0.24^{ab}	7.47E-82	800.876
LDLC(mmol/L)	0.51 ± 0.04	6.83 ± 1.03^{a}	3.19 ± 0.46^{ab}	1.38 ± 0.33^{ab}	2.66 ± 0.38^{ab}	1.15 ± 0.28^{b}	4.46 ± 0.64^{ab}	1.93 ± 0.46^{ab}	5.28 ± 0.76^{ab}	2.15 ± 0.52^{ab}	8.54E-48	131.283
HDLC(mmol/L)	1.68 ± 0.24	0.73 ± 0.18^{a}	0.91 ± 0.06^{a}	1.38 ± 0.23^{ab}	1.14 ± 0.07^{ab}	1.72 ± 0.28^{b}	0.8 ± 0.05^{a}	1.21 ± 0.2^{ab}	1 ± 0.06^{ab}	1.52 ± 0.25^{b}	1.2943E-26	37.205
AST(IU/L)	19.3 ± 3.13	152 ± 11.32^{a}	83.5 ± 8.24^{ab}	30.4 ± 3.24^{ab}	68.5 ± 8.24^{ab}	25.6 ± 3.06^{b}	96.3 ± 4.97^{ab}	40.2 ± 4.43^{ab}	98.5 ± 8.24^{ab}	42.4 ± 3.24^{ab}	8.18E-70	427.572
ALT(IU/L)	11.5 ± 2.17	152.4 ± 19.77^{a}	79.5 ± 6.1^{ab}	18.1 ± 3.54^{b}	56.8 ± 4.29^{ab}	12.9 ± 2.69^{b}	72.2 ± 5.49^{b}	16.5 ± 3.17^{b}	95.4 ± 7.37^{ab}	21.7 ± 4.19^{b}	2.88E-67	374.018
Creatinine((mmol/L))	5924 ± 44.2	345.7 ± 39.79^{a}	186.5 ± 12.38^{ab}	68.79 ± 5.31^{b}	150.3 ± 9.73^{ab}	55.7 ± 4.42^{b}	237.8 ± 17.6^{ab}	96.83 ± 7.07^{ab}	231.62 ± 15.03^{ab}	8.88 ± 0.07^{ab}	3.63E-68	392.145
BUN(mmol/L)	57.09 ± 2.04	169.65 ± 17.99^{a}	91.3 ± 7.89^{ab}	61.09 ± 2.46^{b}	73.63 ± 6.3^{ab}	49.27 ± 1.988^{b}	127.83 ± 10.99^{ab}	85.53 ± 3.4^{ab}	113.22 ± 9.79^{ab}	75.75 ± 0.19 ^{ab}	7.76E-56	203.614
Urine ACR(mg/mmol)	1.9 ± 0.12	9.7 ± 1.04^{ab}	5.8 ± .4^{ab}	2.33 ± 0.33^{ab}	4.69 ± 0.33^{ab}	1.91 ± 0.27^{b}	8.14 ± 0.63^{ab}	3.25 ± 0.47^{ab}	7.21 ± 0.49^{a}	2.88 ± 0.41^{ab}	3.6853E-65	334.688
Fat cells diameter	36.3 ± 3.5	82.2 ± 3.61^{a}	71.3 ± 2.95^{ab}	40.6 ± 2.41^{b}	68.6 ± 2.95^{ab}	46.7 ± 4.45 ^{ab}	68.9 ± 2.42 ^{ab}	45.2 ± 4.29 ^{ab}	68.5 ± 3.6 ^{ab}	42.89 ± 3.07 ^{ab}	3.6426E-58	230.744
Liver inflammation											9.82E-25	
0	10(100%)	0	0	0	0	3(30%)	0	0	0	4(40%)		
1	0	0	0	8(80%)	0	7(70%)	0	4(40%)	0	6(60%)		
2	0	0	6(60%)	2(20%)	6(60%)	0	2(20%)	6(60%)	7(70%)	0		
3	0	5(50%)	4(40%)	0	4(40%)	0	8(80%)	0	3(30%)	0		
4	0	5(50%)	0	0	0	0	0	0	0	0		

Data represented as mean ± SD or N(%), the statistical significance between groups was calculated using the ANOVA-Tukey post hoc test for numerical data and the Chi-square test for the categorical data where 'a' represents statistical significance when compared to the normal group, and 'b' represents statistical significance when compared to the T2DM group.

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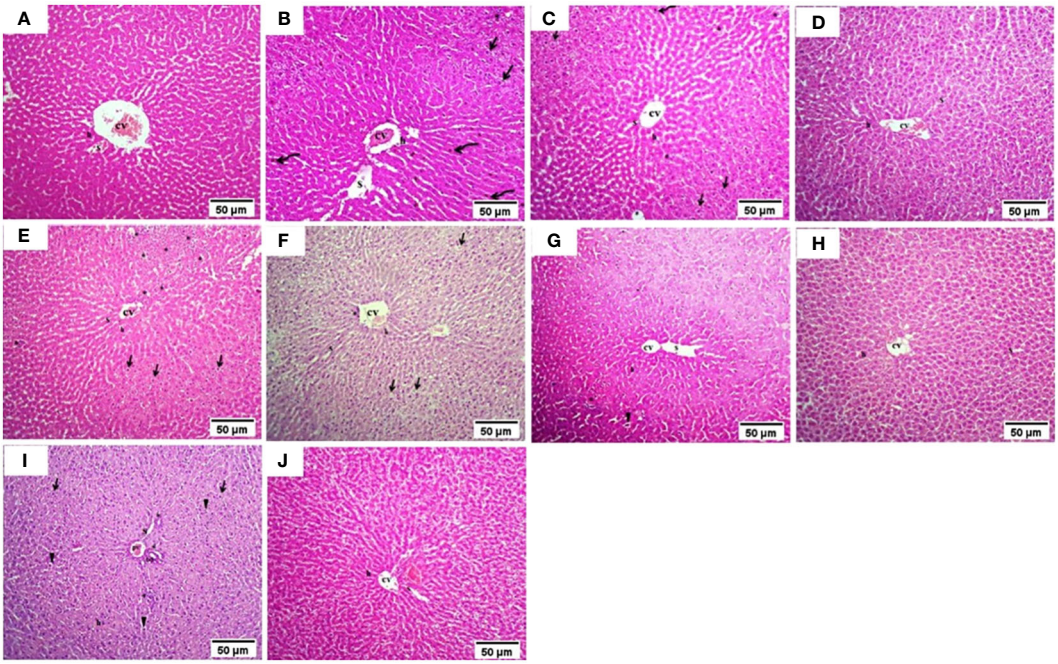

FIGURE 3
Histopathology examination of liver tissue in experimental animals. **(A)** the Normal group, **(B)** the T2DM group, **(C)** Rosavin-10 group, **(D)** Rosavin-30, **(E)** Z-Biotic 0.5, **(F)** Z-Biotic 1, **(G)** Isorhamnetin-10, **(H)** Isorhamnetin-40, **(I)** Caffeic acid-10, **(J)** Caffeic acid-50. Microvesicular steatosis (Arrow), Inflammatory cells infiltrate (asterisks), Necrotic cells (Arrowhead), Pyknotic hepatocytes (Curved arrow), Sinusoids (S), Central vein (CV), Portal vein (PV), Bile duct (BD). Hepatocytes (h) (10X magnifications).

cytoplasm with vacuolated nuclei. Inflammatory cells (asterisks) are scattered in the hepatic lobule whereas the Isorhamnetin-40 treated group demonstrated a slightly normal histological feature. The Caffeic acid-10 treated group showed an altered architecture with hepatocellular microvesicular steatosis (Arrow), scattered necrotic cells (Arrowhead), and inflammatory cell infiltrates (asterisks) whereas the Caffeic acid-50 treated group demonstrated a slightly normal histological feature (Figure 3). Analysis of adipose tissue revealed a significant increase in fat cell diameter in T2DM animals. However, treatment of the diabetic animals with rosavin, Z-biotic, isorhamnetin, or Caffeic acid exhibited notable decreases in epididymal adipocyte cell size compared to the normal group. Interestingly, the most pronounced ameliorative effect was observed in the high-dose-treated groups (Figure 4).

4.3 Effect on molecular targets mRNAs-miRNAs-LncRNAs

The results presented in Table 5 demonstrate significant changes in various biomarkers among the different experimental groups expressed in liver tissues (L) and adipose tissues (A). In comparison to the normal group, the T2DM group exhibited markedly elevated levels of *ZBP1*, *STING1*, *DDX58*, *mTOR*, *NFKB1*, *IGF1R*, *CHUK*, *RET*, hsa-miR-1976, hsa-miR-611, and lnc-RP11–773H22.4 ($p < 0.05$) while *AKT2*, hsa-miR-1, hsa-miR-3163, lnc-AC074117.2, and lnc-RP4–605O3.4 were decreased. However, after drug administration, particularly at higher doses, this disturbance was significantly modulated.

4.5 ML Analysis

4.5.1 Feature selection using RFECV-based Random Forest for T2DM drug response prediction

The feature selection procedure employing RFECV yielded 13 features out of 32 for the molecular model, 10 out of 12 for the biochemical model, and 20 out of 44 for the combined model. These selections, as shown in Table 6, were made while maintaining the same prediction accuracy level as shown in Figure 5. Molecular accuracy achieved 80% while the biochemical and both of them combined achieved 85%.

4.5.2 Model prediction results

Initial results applied on the training set showed the top-performing classifiers for each feature group. Table 7 summarizes the accuracy of the adopted classifiers for each feature group. Notably, the KNN was the top classifier for the molecular model and the combined model while LGBM Classifier performed the best for the biochemical model.

Then, the selected classifiers were applied to the testing set for the T2DM drug response prediction and to evaluate their predictive performance on unseen data. Using this strategy, we ensured that only the most effective classifiers were applied for prediction for

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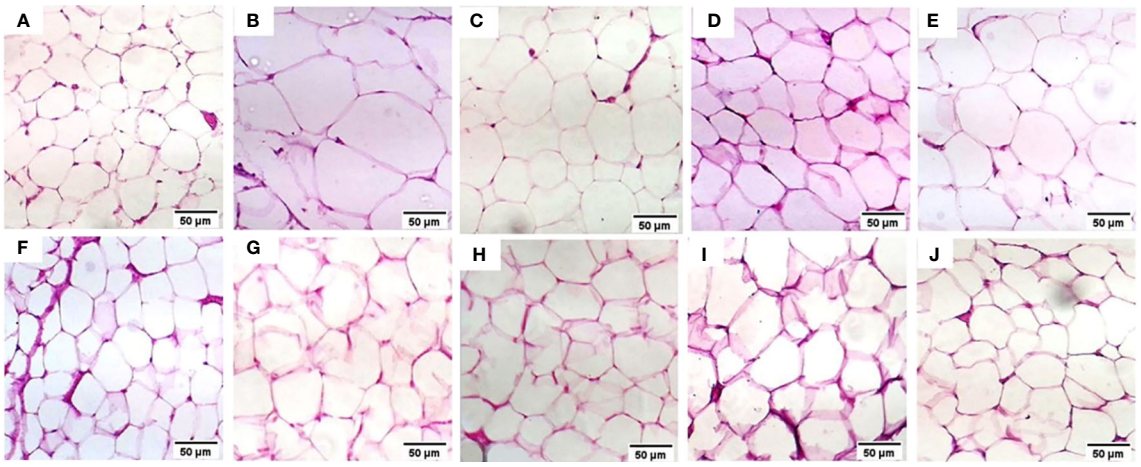

FIGURE 4
Histopathology examination of adipose tissue in the experimental animals. **(A)** the Normal group, **(B)** the T2DM group, **(C)** the Rosavin-10 group, **(D)** Rosavin-30, **(E)** Z-Biotic 0.5, **(F)** Z-Biotic 1, **(G)** Isorhamnetin-10, **(H)** Isorhamnetin-40, **(I)** Caffeic acid-10, **(J)** Caffeic acid-50. (40X magnifications).

each feature group, thereby enhancing the reliability and robustness of our predictive models. Table 8 summarizes the evaluation metric for the testing set. Notably, all classifiers in the three models achieved the same prediction power (0.8).

4.5.3 Performance evaluation of machine learning models for drug response prediction

The confusion matrix presented in Figure 6 displays the correctness of the prediction of whether the sample is improved (1), or not improved (0) on the test set, for the molecular, biochemical, and combined model. Roc curve displays how accurate the prediction models are (Figure 7).

4.5.4 Visual analysis results for molecular and biochemical features

The implemented graphical approach displayed the differences in feature values by showing measures such as mean values and standard deviations between the different treated groups (drugs), against the normal and the T2DM groups (Supplementary Figures S6, S7).

5 Discussion

Diabetes mellitus is a metabolic disorder that impacts various organs and is primarily characterized by a deficiency in insulin production or response. This deficiency leads to impaired glucose tolerance and high blood glucose levels, accompanied by disruptions in the metabolism of fats, carbohydrates, and proteins (52).

Various factors, including modified dietary patterns, metabolic stress, and genetic predisposition, have the potential to activate the innate immune system. This activation leads to insulin resistance, T2DM, and related complications like dyslipidemia, diabetic nephropathy, retinopathy, and atherosclerosis. Among the drugs tested in our study, rosavin has garnered attention due to its antioxidant and anti-inflammatory properties, which help mitigate oxidative stress and chronic inflammation often observed in diabetes (53). Rosavin has been shown to lower total cholesterol, TGs, and LDL levels while increasing HDL, thereby exerting lipid-lowering effects. Insulin resistance precedes the abnormal elevation of blood glucose levels, which is the primary clinical indicator of T2DM. In the prediabetic stage, the body responds to insulin resistance by increasing insulin production to meet the normal insulin requirements. This leads to a state of chronic hyperinsulinemia and, as a result of sustained high blood sugar levels, the failure of pancreatic beta cells. Eventually, this progression leads to the development of T2DM. Prolonged and exaggerated metabolic stress can lead to detrimental inflammatory reactions, resulting in insulin resistance and inflammatory diseases. This chronic inflammatory state eventually gives rise to long-term complications associated with diabetes, including microvascular complications such as diabetic liver disease, diabetic nephropathy, neuropathy, and macrovascular complications like cardiovascular and cerebrovascular diseases. The cGAS-STING pathway plays a crucial role in diabetic complications and has been increasingly reported in diabetic nephropathy and diabetic angiopathy, which is linked to mitochondrial dysfunction caused by lipotoxicity. Evidence suggests that the cGAS-STING pathway is over-activated in diabetes and its complications. This heightened activation of cGAS-STING may serve as a protective mechanism, considering that diabetic patients are more susceptible to infections. Notably, knocking out STING has been shown to reduce insulin resistance induced by a high-fat diet in peripheral tissues and improve overall glucose intolerance. However, it is important to note that STING deficiency also impairs the ability of beta cells to secrete insulin in response to glucose stimulation. Autophagy is crucial in T2DM, serving to sustain cellular energy levels during fasting while eliminating damaged components like organelles, lipids, and misfolded proteins. Moreover, it contributes to pancreatic beta cell function and insulin resistance. Recent findings highlight the role of autophagy in T2DM pathophysiology, particularly in maintaining

TABLE 5 The differential expression of mRNAs-miRNAs-LncRNAs in liver tissues (L) and adipose tissues (A) among different animal groups, including a normal group, T2DM group, and various treatment groups with Rosavin, Z-Biotic, Isorhamnetin, and caffeic acid.

	Normal	T2DM	Rosavin-10	Rosavin-30	Z-Biotic 0.5	Z-Biotic 1	Isorhamnetin-10	Isorhamnetin-40	caffeic acid-10	caffeic acid-50	P-value	F
ZBP1 (L)	1.84 ± 0.31	170.13 ± 10.61^{a}	92.33 ± 3.96^{ab}	25.2 ± 3.42 ^{ab}	71.03 ± 3.04 ^{ab}	14.82 ± 2.01 ^{ab}	46.17 ± 1.98 ^{ab}	10.08 ± 1.37 ^{ab}	61.56 ± 2.64 ^{ab}	14 ± 1.9 ^{ab}	8.39E-95	1563.68
ZBP1 (A)	1.43 ± 0.2	20.97 ± 1.98^{a}	4.71 ± 0.64^{ab}	1.39 ± 0.24^{b}	9.42 ± 1.28^{ab}	2.64 ± 0.45^{b}	4.06 ± 0.55^{ab}	1.20 ± 0.21^{b}	7.07 ± 0.96^{ab}	2.09 ± 0.36^{b}	5.5293E-72	479.054
STING1(L)	1.44 ± 0.2	7.7 ± 0.82^{a}	2.04 ± 0.16^{ab}	0.34 ± 0.03^{ab}	4.09 ± 0.33^{ab}	0.64 ± 0.06^{ab}	1.76 ± 0.14^{b}	0.29 ± 0.03^{ab}	3.07 ± 0.24^{ab}	0.5 ± 0.05^{ab}	2.74E-75	569.3
STING1(A)	1 ± 0.05	14.64 ± 1.72^{a}	5.59 ± 0.54^{ab}	1.96 ± 0.11^{b}	8.38 ± 0.8^{ab}	2.55 ± 0.14^{ab}	3.29 ± 0.31^{ab}	1.16 ± 0.06^{b}	9.5 ± 0.91^{ab}	3.34 ± 0.18^{ab}	1.4297E-68	400.573
DDX58 (L)	1.03 ± 0.09	50.49 ± 5.48^{a}	13.29 ± 2.16^{ab}	0.95 ± 0.17^{b}	19.94 ± 3.25^{ab}	1.23 ± 0.23^{b}	7.82 ± 1.27^{ab}	0.56 ± 0.1^{b}	22.6 ± 3.68^{ab}	1.61 ± 0.3^{b}	2.52E-69	416.732
DDX58 (A)	1.17 ± 0.22	120.16 ± 11.65^{a}	55.77 ± 6.87^{ab}	3.6 ± 0.6^{b}	83.65 ± 10.3^{ab}	4.67 ± 0.78^{b}	32.8 ± 4.04^{ab}	2.12 ± 0.35^{b}	94.81 ± 11.68^{ab}	6.11 ± 1.02^{b}	3.9696E-71	458.061
mTOR (L)	1.68 ± 0.28	82.8 ± 6.05^{a}	29.72 ± 4.22^{ab}	5.21 ± 0.55^{b}	14.86 ± 2.11^{ab}	2.41 ± 0.25^{b}	35.67 ± 5.06^{ab}	6.78 ± 0.71^{b}	24.77 ± 3.52^{ab}	4 ± 0.42^{b}	1.84E-77	637.509
mTOR (A)	0.95 ± 0.09	4.46 ± 0.65^{a}	1.21 ± 0.14^{b}	0.1 ± 0.02^{ab}	2.42 ± 0.28^{ab}	0.2 ± 0.03^{ab}	1.04 ± 0.12^{b}	0.09 ± 0.01^{ab}	1.81 ± 0.21^{ab}	0.16 ± 0.03^{ab}	2.3057E-64	320.894
NFKB1 (L)	1.05 ± 0.12	50.92 ± 5.5^{a}	22.3 ± 2.38^{ab}	8.44 ± 1.75^{ab}	12.63 ± 1.93^{ab}	2.83 ± 1.93^{b}	8.45 ± 0.52^{ab}	0.65 ± 0.07^{b}	17.5 ± 1.59^{ab}	2.27 ± 0.21^{b}	8.36E-73	500.059
NFKB1 (A)	1.04 ± 0.1	41.56 ± 6.33^{a}	13.7 ± 1.71^{ab}	4.96 ± 1.03^{ab}	9.03 ± 0.84^{ab}	2.91 ± 0.27^{b}	23.78 ± 2.54^{ab}	2.92 ± 0.61^{b}	10.96 ± 1.37^{ab}	1.03 ± 0.12^{b}	1.8857E-63	305.761
IGF1R (L)	1.2 ± 0.21	62.26 ± 5.46^{a}	35.68 ± 3.81^{ab}	11.72 ± 1.66^{ab}	11.73 ± 3.82^{ab}	5.2 ± 0.84^{ab}	12.54 ± 1.46^{ab}	2.79 ± 0.45^{b}	3.83 ± 0.24^{b}	0.38 ± 0.04^{b}	4.61E-76	592.74
IGF1R (A)	1.05 ± 0.08	75.72 ± 8.2^{a}	20.27 ± 2.7^{ab}	1.79 ± 0.29^{b}	30.4 ± 4.05^{ab}	2.32 ± 0.38^{b}	11.92 ± 1.59^{ab}	1.05 ± 0.17^{b}	34.45 ± 4.59^{ab}	3.03 ± 0.5^{b}	1.565E-72	492.988
CHUK (L)	1.17 ± 0.17	38.05 ± 4.99^{ab}	14.36 ± 1.72^{ab}	3.25 ± 0.68^{b}	8.62 ± 1.02^{ab}	2.62 ± 0.31^{b}	2.63 ± 0.25^{b}	0.48 ± 0.06^{b}	4.21 ± 0.51^{ab}	0.21 ± 0.02^{b}	1.04E-70	448.166
CHUK (A)	0.99 ± 0.07	82.2 ± 9.38^{a}	27.23 ± 1.72^{ab}	6.18 ± 0.74^{b}	10.11 ± 1.29^{ab}	4.65 ± 1.11^{b}	54.56 ± 6.55^{ab}	9.62 ± 1.15^{ab}	23.03 ± 4.8^{ab}	0.75 ± 0.08^{b}	1.6302E-70	443.572
AKT2(L)	1.04 ± 0.11	0.08 ± 0.01	4.37 ± 0.64^{b}	15.16 ± 3.44^{ab}	3.25 ± 0.42	7.37 ± 1.18^{a}	3.59 ± 0.41	9.5 ± 1.52^{ab}	15.77 ± 2.97^{ab}	67.11 ± 7.45^{ab}	2.16E-72	489.394
AKT2(A)	1.57 ± 0.36	0.21 ± 0.02	11.49 ± 1.78^{ab}	40.75 ± 2.99^{ab}	10.9 ± 1.67^{ab}	19.98 ± 2.13^{ab}	4.54 ± 0.43	48.82 ± 5.86^{ab}	23.89 ± 2.41^{ab}	147.88 ± 10.15^{ab}	1.2722E-89	1197.044

(Continued)

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TABLE 5 Continued

	Normal	T2DM	Rosavin-10	Rosavin-30	Z-Biotic 0.5	Z-Biotic 1	Isorhamnetin-10	Isorhamnetin-40	caffeic acid-10	caffeic acid-50	P-value	F
RET (L)	1 ± 0.09	59.31 ± 3.97 [a]	38.72 ± 1.82 [ab]	8.9 ± 1.18 [ab]	15.39 ± 2.41 [ab]	3.08 ± 0.48[b]	28.07 ± 2.24 [ab]	6.87 ± 1.08 [ab]	3.98 ± 0.62 [ab]	0.8 ± 0.12 [b]	6.81E-89	1152.837
RET (A)	1.07 ± 0.1	71.19 ± 5.46[a]	52.71 ± 2.87[ab]	11.62 ± 1.13[ab]	12.82 ± 2.01[ab]	2.56 ± 0.4[b]	36.81 ± 2.66[ab]	5.73 ± 0.9[ab]	3.32 ± 0.52[b]	0.24 ± 0.04[b]	7.5164E-90	1211.250
hsa-miR-1976(L)	1.21 ± 0.16	106.28 ± 10.14[a]	62.55 ± 7.11[ab]	12.81 ± 2.01[ab]	40.58 ± 3.25[ab]	9.08 ± 0.99[ab]	8.24 ± 1.03[ab]	3.95 ± 0.37[b]	88.12 ± 7.18[ab]	20.51 ± 1.97[ab]	2.27E-77	634.5
hsa-miR-1976(A)	0.88 ± 0.08	13.85 ± 2.06[a]	2.77 ± 0.31[ab]	0.7 ± 0.14[b]	1.34 ± 0.15[b]	0.3 ± 0.06[b]	5.52 ± 1.15[ab]	1.13 ± 0.12[b]	5.72 ± 0.63[ab]	1.57 ± 0.19[b]	8.2892E-62	280.236
hsa-miR-1(L)	1.06 ± 0.11	0.06 ± 0.01	2.94 ± 0.43[b]	10.19 ± 2.31[ab]	2.19 ± 0.28	4.95 ± 0.79[ab]	2.42 ± 0.27	6.39 ± 1.02[ab]	10.6 ± 1.99[ab]	45.13 ± 5.01[ab]	2.55E-72	487.556
hsa-miR-1(A)	1.61 ± 0.38	0.16 ± 0.02	7.73 ± 1.2[ab]	27.4 ± 2.01[ab]	7.33 ± 1.13[ab]	13.44 ± 1.43[ab]	3.05 ± 0.29	32.83 ± 3.94[ab]	16.07 ± 1.62[ab]	99.45 ± 6.82[ab]	1.5192E-89	1192.289
hsa-miR-611(L)	1.14 ± 0.16	47.56 ± 6.23[a]	32.34 ± 3.71[ab]	11.58 ± 1.53[ab]	20 ± 3.13[ab]	4 ± 0.63[b]	36.5 ± 2.91[ab]	8.94 ± 1.4[ab]	5.17 ± 0.81[ab]	1.03 ± 0.16[b]	1.66E-66	359.336
hsa-miR-611(A)	0.92 ± 0.13	98.7 ± 8.79[a]	68.52 ± 3.73[ab]	15.11 ± 1.47[ab]	16.67 ± 2.61[ab]	3.33 ± 0.52[b]	47.85 ± 3.46[ab]	7.45 ± 1.17[ab]	4.31 ± 0.67[b]	0.32 ± 0.05[b]	2.346E-86	1011.174
hsa-miR-3163(L)	1.39 ± 0.22	0.15 ± 0.02	10.13 ± 1.16[ab]	75.2 ± 6.89[ab]	2.86 ± 0.33	9.15 ± 1.59[ab]	6.13 ± 0.7[b]	55.57 ± 8.21[ab]	1.91 ± 0.4	12.44 ± 1.44[ab]	8.24E-75	555.277
hsa-miR-3163(A)	1.23 ± 0.19	0.09 ± 0.01	0.68 ± 0.07	2.21 ± 0.49	7.26 ± 0.94[b]	18.58 ± 2.36[ab]	12.04 ± 1.38[ab]	139.5 ± 13.89[ab]	3.37 ± 0.7	49.84 ± 5.22[ab]	2.127E-82	823.840
lnc-AC074117.2(L)	1.63 ± 0.36	0.18 ± 0.03	0.93 ± 0.12	4.08 ± 0.76[b]	11.6 ± 1.6[ab]	47.35 ± 3.8[ab]	1.9 ± 0.22	9.82 ± 1.56[ab]	8.09 ± 0.86[ab]	29.36 ± 2.78[ab]	3.28E-82	815.841
lnc-AC074117.2(A)	1.44 ± 0.27	0.14 ± 0.03	1.89 ± 0.3	6.28 ± 1[ab]	30.6 ± 1.87[ab]	99.56 ± 5.14[ab]	2.47 ± 0.23	26.8 ± 3.22[ab]	4.43 ± 0.6[b]	15.81 ± 1.86[ab]	6.056E-100	2037.489
lnc-RP11–773H22.4(L)	1.01 ± 0.09	49.84 ± 4[a]	18.12 ± 2.5[ab]	3.34 ± 0.65[b]	20.34 ± 3.31[ab]	3.67 ± 0.61[b]	13.56 ± 2.21[ab]	1.25 ± 0.23[b]	7.98 ± 1.3[ab]	0.57 ± 0.1[b]	3.57E-75	565.887
lnc-RP11–773H22.4(A)	1.26 ± 0.15	91.85 ± 6.94[a]	40.81 ± 2.5[ab]	11.13 ± 0.88[ab]	35.22 ± 4.23[ab]	1.01 ± 0.19[b]	61.41 ± 0.63[ab]	2.26 ± 0.38[b]	59.67 ± 7.35[ab]	5.1 ± 0.85[b]	4.5705E-73	506.957
lnc-RP4–605O3.4(L)	0.99 ± 0.1	0.09 ± 0.01	2.18 ± 0.32[b]	7.58 ± 1.72[ab]	1.63 ± 0.21	3.68 ± 0.59[a]	1.8 ± 0.2	4.75 ± 0.76[ab]	7.88 ± 1.48[ab]	33.56 ± 3.73[ab]	2.94E-72	485.973
lnc-RP4–605O3.4(A)	1.5 ± 0.34	0.23 ± 0.02	5.75 ± 0.89[ab]	20.37 ± 1.5[ab]	5.45 ± 0.84[ab]	9.99 ± 1.06[ab]	2.27 ± 0.21	24.41 ± 2.93[ab]	11.95 ± 1.21[ab]	73.94 ± 5.07[ab]	1.7806E-89	1188.052

Data represented as mean ± SD, the statistical significance between groups was calculated using ANOVA-Tukey post hoc test where 'a' represents statistical significance when compared to the normal group, and 'b' represents statistical significance when compared to the T2DM group.

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TABLE 6 Show the top selected features by RFECV for each model.

Model	Included Features
	Feature
Molecular Included: 13 Excluded: 19 Total: 32	ZBP1-mRNA (A) STING1-mRNA (L) DDX58 -mRNA (L) mTOR -mRNA (L) NFKB1 -mRNA (A) CHUK -mRNA (A) RET -mRNA (L) RET -mRNA (A) miR-1976 (A) miR-611 (L) miR-611 (A) RP11–773H22.4 (L) RP11–773H22.4 (A)
Biochemical Included: 10 Excluded: 2 Total: 12	Glucose Insulin HOMA-IR Total cholesterol Triglycerides AST ALT Creatinine BUN ACR
Combined Included: 20 Excluded: 24 Total: 44	STING1-mRNA (L) mTOR -mRNA (L) NFKB1 -mRNA (A) CHUK -mRNA (A) RET -mRNA (L) RET -mRNA (A) miR-1976 (A) miR-611 (L) miR-611 (A) RP11–773H22.4 (L) RP11–773H22.4 (A) Insulin Total cholesterol Triglycerides Glucose AST ALT Creatinine BUN ACR

pancreatic beta cell function. Furthermore, increased autophagy serves as a protective mechanism against oxidative stress in insulin-targeted tissues like the liver, adipose tissue, and skeletal muscle. NOD1 and NOD2 are implicated in the development of diabetes, likely through their interaction with the gut microbiota. Antibiotic-induced changes in the gut microbiota are crucial for enhancing insulin sensitivity. Nucleotide-binding oligomerization domain (NOD)-like receptors, such as NOD1 and NOD2, both recruit receptor-interacting protein kinase 2 (RIPK2), but they exert opposite effects on blood glucose regulation. While NOD1 links signals from bacterial cell walls to metabolic inflammation and insulin resistance, NOD2 can foster immune tolerance, improve insulin sensitivity, and enhance blood glucose control in obesity. Similarly, NLR family pyrin domain-containing (NLRP) inflammasomes can elicit different metabolic outcomes. NLRP1 may protect against obesity and metabolic inflammation, possibly due to its preference for regulating IL-18, whereas NLRP3 tends to promote IL-1β-mediated metabolic inflammation and insulin resistance. Additionally, Rosavin may protect against diabetic complications such as neuropathy and nephropathy by reducing nerve damage, kidney injury, and hepatic damage as indicated by decreased levels of creatinine, BUN, ALT, and AST (30). Specifically, rosavin has demonstrated protective anti-inflammatory effects in various models, including bleomycin-induced pulmonary fibrosis. Rosavin exerts its effects by downregulating the expression of pro-inflammatory molecules such as NF-κB, p65, TGF-β1, and α-SMA while upregulating the expression of nuclear erythroid 2-related factor 2 (*Nrf2*), a transcription factor involved in antioxidant defense (54) Our findings supported the hypoglycemic (lower serum glucose, insulin, and HOMA-IR) and hypolipidemic (lower serum TG, TC, LDL, and higher HDL levels) effects of rosavin treatment (55). Mao. reported that Rhodiola rosea L. root extracts improved oral glucose tolerance, decreased serum TG, and LDL levels, and increased HDL levels in KKAy mice, a T2D model (56). Liu et al. proved that rosavin has been shown to attenuate LPS-induced activation of the TLR-4/NF-κB signaling pathway in RAW264.7 cells and inhibit the release of inflammatory factors in A549 cells. In a dose-dependent manner, rosavin ameliorated histopathological alterations, reduced the levels of inflammatory factors, and inhibited the TLR-4/NF-κB/MAPK signaling pathway and apoptosis activation. It also significantly reduced the number of inflammatory cells in bronchoalveolar lavage fluid and the expression of NF-κB p65 protein in the lung tissue of a mouse model. Moreover, it reduced the expression of hydroxyproline and malondialdehyde while enhancing the activities of superoxide dismutase and glutathione peroxidase in lung tissue (57).

Zbiotics, a newly engineered probiotic, has not been fully investigated for its impact on the pathogenesis of DM. Therefore, we conducted a study to assess its effectiveness on biochemical and molecular markers associated with DM. Both low and high doses of zbiotics demonstrated hypoglycemic and hypolipidemic effects, along with hepatoprotective and renoprotective effects evidenced by reductions in AST, ALT, creatinine, and BUN levels, particularly noticeable with the high dose. Histopathological analysis revealed mild hepatocellular microvesicular steatosis with minimal inflammatory cell infiltration. Our findings indicate that zbiotics with engineered acetaldehyde dehydrogenase can eloquently explain the results of the present study regarding how ZBiotics® reversed the toll of diabetes on the studied histopathological, biochemical and molecular levels. The concept was based on two major mechanisms that could elicit inflammation that leads over time to diabetic settings and evolves diabetic complications; firstly, the oxidative-stress-induced inflammation, and secondly the disturbance in diabetic gut microbiota and barriers that could lead to the activation of subsequently inflammation.

Isorhamnetin has emerged as a promising therapeutic agent for T2DM by improving gut health and insulin resistance (29). Previous studies have demonstrated its efficacy in lowering fasting blood glucose levels, improving renal function, and ameliorating dyslipidemia in T2DM rats by upregulating autophagy in renal tissues (26). In animal models, Isorhamnetin supplementation has been found to reduce reactive oxygen species levels, inhibit

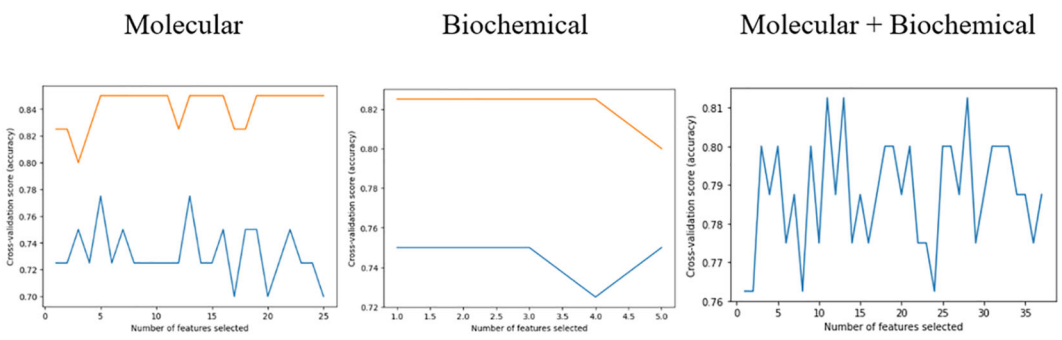

FIGURE 5
Number and accuracy scores for each feature set and both of them combined.

atherosclerotic plaque formation, and mitigate myocardial hypertrophy and fibrosis ((58) (Mechanistically, Isorhamnetin acts through various pathways, including inhibition of the PI3K/AKT signaling pathway, activation of the AMPK/mTOR pathways, and modulation of insulin secretion via phosphorylation of insulin receptor substrate-2 (*IRS-2*), phosphatidylinositol 3-kinase (*PI3K*), Akt, and activated pancreatic and duodenal homeobox-1 (*PDX-1*) (59, 60). Moreover, Yang et al. proved that isorhamnetin exhibited hepatoprotective effects by reducing liver fibrosis through inhibition of HSC activation and ECM formation, and by downregulating the TGF-β1/Smad3 and TGF-β1/p38 MAPK pathways (61). In our previous study, we demonstrated that Isorhamnetin acted as an effective therapy for DM by modulating the insulin resistance signaling pathway and autophagy-related RNA network (28). Building upon our previous findings, our current study expands on the beneficial effects of isorhamnetin. We observed that isorhamnetin improved insulin resistance parameters, reduced elevated glucose levels, and alleviated inflammation infiltration in liver sections. Furthermore, isorhamnetin treatment led to the recovery of elevated levels of ALT and AST, indicating its hepatoprotective effects against chronic injury. isorhamnetin efficiently improves altered lipid metabolism by decreasing TGs, LDL, and TC, while increasing HDL. These lipid-lowering effects contribute to the hepatoprotective role of isorhamnetin, which can be attributed to its anti-inflammatory properties. Additionally, Lu et al. demonstrate that Isorhamnetin affects the P38/PPAR-α pathway, which in turn regulates the expression of apoptosis and autophagy-related proteins (62). This finding is consistent with our study, where Isorhamnetin modulated autophagy-related genes such as *STING1, IGF-1*, and *AKT2*.

Caffeic acid demonstrates anti-diabetic effects through multiple mechanisms, including the enhancement of antioxidant enzymes, inhibition of NF-κB signaling pathways, and activation of the NrF2 transcription factor (63). In a study by Xu et al., it was shown that caffeic acid administration at doses of 25 and 35 mg/kg significantly reduced plasma glucose, TG, TC, and LDL levels, while notably increasing HDL, insulin, and antioxidant levels in streptozotocin-induced diabetic Wistar rats after five weeks of treatment (64). The findings from Xu's study align with our research, where we investigated the effects of caffeic acid treatment at doses of 10 and 50 mg/kg and we observed significant improvements in plasma glucose, lipid profiles, and insulin levels in diabetic rats treated with caffeic acid. Additionally, our results showed hepatoprotective and renoprotective effects of caffeic acid, along with a reduction in inflammatory cell infiltration in the liver and a decrease in epididymal adipocyte cell size, particularly with the higher dose. Furthermore, our previous research indicated that caffeic acid may activate the mitogen-activated protein kinases (MAPK) signaling pathway through the regulation of miR-636, leading to the induction of autophagy and attenuation of diabetic nephropathy (65). Consistent with this, our recent findings demonstrate that caffeic acid treatment significantly downregulates the expression of autophagy-related genes such as *IGF1R, NFKB1*, and *STING1* in adipose and liver tissues, further supporting its beneficial effects in diabetes management. Bhattacharya et al. investigated the effects of caffeic acid on glucose sensitivity, glucose-stimulated insulin secretion (GSIS), and gene expression in INS-1E cells under normoglycemic conditions (NC) and glucotoxic conditions (GC). They found that caffeic acid significantly increased the expression of Insulin-1 (*Ins-1*), *Ins-2*, pancreatic and duodenal homeobox 1 (*Pdx-1*), *Akt-1, Akt-2*, insulin receptor substrate-1 (*Irs1*), *Bcl2*, heat shock protein 90 and 70 (*Hsp90* and *Hsp70*) during NC. Additionally, caffeic acid downregulated acetyl coenzyme A carboxylase 1 (*ACC1*) without affecting Glucokinase (*Gck*) and Glucose transporter-2 (*Glut-2*) expressions in INS-1E cells. However, under GC conditions, caffeic acid did not change the expression of *GLUT-2, Gck, Ins2, Beta2, Pdx1, Akt2, Irs1, Bcl2, and Hsp90*. Instead, it upregulated *Ins1, Akt2*, and *Hsp70*, while downregulating *Beta2*, Caspase 3 (*Casp3*), and *Bax*. caffeic acid also significantly increased glucose sensitivity and GSIS in INS-1E cells and thereby caffeic acid may enhance the survival and function of β-cells during glucotoxic conditions by modulating the expression of these genes (66).

Many human and animal studies investigated prolonged drug exposure on both safety and efficacy outcomes. Lekomtseva et al. investigated the effects of Rhodiola rosea extract on prolonged or chronic fatigue symptoms, 100 subjects were administered 2 × 200 mg of the extract daily over 8 weeks of an open-label clinical trial. Results showed the greatest improvement after just 1 week of treatment, with continued reduction in fatigue symptoms throughout the study, reaching statistically significant improvement by week 8. Importantly, safety assessments

TABLE 7 The evaluation metric for the top-performing classifier on the training set.

Model (Molecular)	Accuracy	AUC	Recall	Precision	F1-Score
KNN	0.8714	0.9177	0.9387	0.8974	0.9137
Random Forest	0.8424	0.9051	0.9007	0.8833	0.8918
Ada Boost	0.8152	0.8370	0.8811	0.8648	0.8727
LGBM	0.8140	0.8739	0.8603	0.8867	0.8719
Logistic Regression	0.8001	0.8801	0.8419	0.8750	0.8580
Model (Biochemical)	Accuracy	AUC	Recall	Precision	F1-Score
LGBM	0.8714	0.9397	0.9203	0.9029	0.9108
Ada Boost	0.8575	0.8950	0.8603	0.9386	0.8969
Random Forest	0.8297	0.9075	0.8799	0.8819	0.8803
KNN	0.8285	0.9449	0.8419	0.9265	0.8707
Logistic Regression	0.8001	0.9047	0.8419	0.8760	0.8563
Model (Molecular+Biochemical)	Accuracy	AUC	Recall	Precision	F1-Score
KNN	0.8714	0.9000	0.9600	0.8848	0.9159
Random Forest	0.8571	0.9100	0.9200	0.8981	0.9029
Ada Boost	0.8571	0.8900	0.9200	0.8933	0.9014
LGBM	0.8286	0.9100	0.8800	0.8933	0.8812
Logistic Regression	0.7857	0.8500	0.8400	0.8700	0.8455

indicated favorable outcomes, with most adverse events being mild and unrelated to the study drug (67). Ochoa-Morales et al. conducted a 12-week double-blind, randomized placebo-controlled trial that assessed the efficacy of propolis compared to placebo in controlling glycemic levels in 36 patients with T2DM. Administered twice daily before breakfast and dinner, propolis (300 mg) significantly reduced fasting plasma glucose (FPG) and 2-hour post-load glucose (2-h PG) levels compared to placebo (48). In a 6-month masked, randomized clinical trial conducted by El-Sharkawy et al. individuals with chronic periodontitis (CP) and T2DM undergoing scaling and root planning (SRP) were given either a placebo or a daily regimen of 400 mg oral propolis. Results showed that the propolis group exhibited significant reductions in hemoglobin A1c (HbA1c) levels by 0.82% and 0.96% units at 3 and 6 months, respectively, along with decreases in fasting plasma glucose (FPG) and serum N€-(carboxymethyl) lysine (CML) levels. Additionally, both groups showed improvements in periodontal parameters after therapy, but the propolis group demonstrated significantly greater reductions in probing depth and gains in clinical attachment level compared to the control group (68). In a study investigating the effects of caffeic acid on diabetic cardiomyopathy, it was found that caffeic acid, along with ellagic acid, demonstrated protective effects in diabetic mice. Various parameters, including lipid profile, coagulability, oxidative stress, and inflammation, were assessed. After 12 weeks, the treated animals showed beneficial effects, including decreased triglyceride levels, increased plasma insulin levels, decreased plasma glucose levels, anti-coagulatory effects, antioxidative effects, and anti-inflammatory properties in the cardiac tissue (69). Moreover, Rodríguez-Rodríguez et al. investigated the metabolic effects of an extract from Opuntia ficus-indica (OFI) for 12 weeks, known for its high isorhamnetin glycoside content, in a mouse model of diet-

TABLE 8 The evaluation metric for the best classifiers on the testing set for each feature group.

Model (Molecular)	Accuracy	AUC	Recall	Precision	F1-Score
KNN Classifier	0.8	0.8942	0.8095	0.8947	0.85
Model (Biochemical)	Accuracy	AUC	Recall	Precision	F1-Score
LGBM	0.8	0.93	0.9048	0.8261	0.8633
Model (Molecular+Biochemical)	Accuracy	AUC	Recall	Precision	F1-Score
KNN Classifier	0.8	0.8968	0.8571	0.8571	0.8571

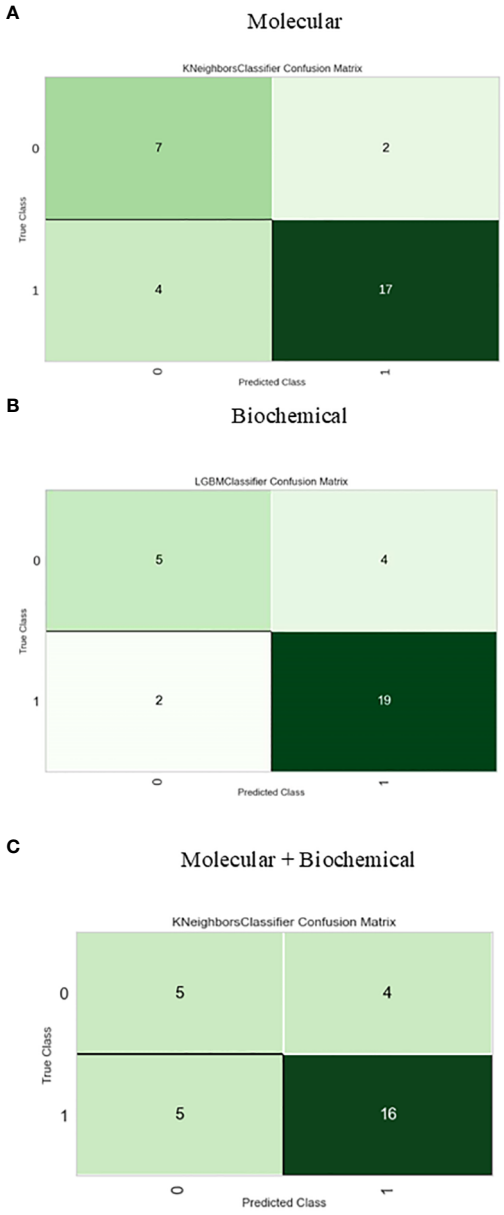

FIGURE 6
Confusion matrix for the best-performing classifiers for each feature group. **(A)** Molecular, **(B)** Biochemical, **(C)** Molecular+Biochemical.

induced obesity and isolated pancreatic islets. Mice fed a high-fat (HF) diet supplemented with OFI extract exhibited reduced body weight gain and lower levels of circulating total cholesterol, LDL cholesterol, and HDL cholesterol compared to those on the HF diet alone. Furthermore, HF-OFI diet-fed mice showed lower glucose and insulin concentrations but slightly higher insulin levels compared to control mice. These metabolic enhancements were associated with decreased adipocyte size, enhanced hepatic phosphorylation of IRS1 tyr-608 and S6 K thr-389, and reduced hepatic lipid content (70). Jamali-Raeufy et al. studied the effect of Isorhamnetin on diabetic male rats for 12 weeks. Isorhamnetin, administered intraperitoneally at a dose of 10 mg/kg body weight once daily, elicited significant effects on various parameters. Notably, Isorhamnetin treatment led to a marked reduction in pain severity and blood glucose levels, while also promoting a significant increase in body weight compared to the control group. Moreover, Isorhamnetin demonstrated inhibitory effects on astroglial activation, acetyl-cholinesterase activity, oxidative stress markers, apoptosis, and inflammatory markers within diabetic rats (58).

In this study, we incorporated molecular biomarkers (mRNAs-miRNAs-LncRNAs) expressed in livers and adipose tissues of animal models representing normal, T2DM, and treated groups alongside conventional biochemical parameters. Our objective was to utilize these predictive targets to select the most potent candidates for treating T2DM using medicinal plant-based drugs such as Rosavin, isorhamnetin, and Caffeic acid, as well as probiotics like Z-biotic. To achieve this goal, we developed a

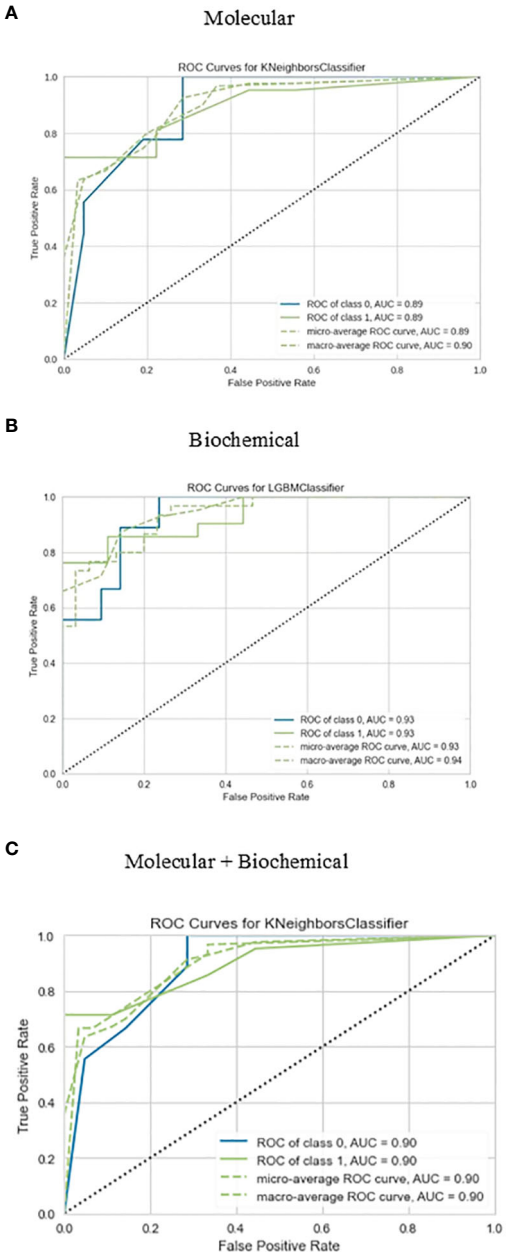

FIGURE 7
Roc curve for the best-performing classifiers for each feature group for the prediction of drug response. **(A)** Molecular, **(B)** Biochemical, **(C)** Molecular+Biochemical.

machine-learning model using 5 different algorithms (KNN, RF, LR, LGBM, and Ada Boost) to recognize the significant features associated with T2DM to achieve a reliable and effective improvement prediction.

As expected, the diabetic rat models exhibited the highest levels of serum insulin resistance index (HOMA-IR), insulin, fasting blood glucose, as well as biomarkers indicating renal function impairment, liver damage, and lipid profiles. Conversely, the normal group, as well as the groups treated with medicinal plants and probiotics, displayed the lowest levels of these markers, more obvious in the highest drug doses, with an opposite relationship observed for HDL (Table 4). As a heterogeneous condition, T2DM is typified by impaired insulin secretion (known as the beta cell secretory defect) and insulin resistance, leading to elevated blood glucose levels. Various disturbances in biochemical parameters are associated with T2DM, including dyslipidemia, which involves elevated fasting and postprandial TG, decreased levels of HDL-C, increased levels of LDL-C, and a prevalence of small, dense LDL-C particles (71). Liver enzymes play a crucial role in regulating metabolism, particularly in maintaining normal blood glucose levels during fasting and after meals. Insulin resistance in the liver leads to increased glycogenolysis and lipolysis, resulting in

elevated hepatic glucose production and abnormal triglyceride and fatty acid synthesis. These abnormalities, including elevated levels of AST, ALT, and ALP, are indicative of liver dysfunction and can precede the onset of fasting hyperglycemia. The elevation of these enzymes may be attributed to the direct hepatotoxic effects of excess fatty acids, which can disrupt cell membranes and impair mitochondrial function (72). Additionally, oxidative stress, peroxisomal beta-oxidation, and inflammation mediated by pro-inflammatory cytokines like TNF-α contribute to hepatic injury. Furthermore, the increased activity of ALT, a gluconeogenic enzyme suppressed by insulin, suggests a disruption in insulin signaling rather than solely hepatocyte injury (73, 74). Prolonged high blood glucose levels lead to increased oxidative stress, inflammation, and dysfunction of microvascular endothelial cells, which are common underlying mechanisms in both diabetic nephropathy (DN) and diabetic retinopathy (DR). These conditions often coexist, with elevated blood urea nitrogen (BUN) levels indicating their presence. BUN levels are also linked to the body's catabolic activity and may reflect reduced blood flow and increased oxidative stress. Additionally, microvascular hypoperfusion and oxidative stress contribute to the development of DR, potentially explaining the association between elevated BUN levels and DR (75). Serum creatinine, primarily metabolized by skeletal muscle, correlates with total skeletal muscle mass. Low serum creatinine levels are considered a risk factor for T2DM and dysglycemia, as they reflect reduced skeletal muscle mass. Skeletal muscle plays a crucial role in glucose uptake, with reduced uptake contributing to insulin resistance and the development of T2DM long before hyperglycemia becomes apparent. The decrease in skeletal muscle mass is thus associated with increased insulin resistance and the risk of developing T2DM (76, 77).

We next determined the histopathological alterations in the studied groups, the livers of the T2DM-induced rats showed significant changes, including fat accumulation, cell death, inflammation, and abnormal cell morphology, in addition to an increase in the adipocyte cell size. Treatment with Rosavin at a higher dose restored the liver structure to normal, while Z-Biotic and isorhamnetin showed moderate improvements. caffeic acid had some positive effects but to a lesser extent. The administration of rosavin, particularly at a high dosage, significantly decreased the severity of liver inflammation grades. This outcome aligns with our previous findings in a rat model of non-alcoholic steatohepatitis (NASH), where rosavin treatment improved liver functions, and lipid profile, and mitigated hepatic inflammation, fibrosis, and cell death (78). Overall, the drugs Rosavin, Z-Biotic, isorhamnetin, and Caffeic acid exhibited varying effects on the destructive liver architecture induced by diabetes, with higher doses generally demonstrating a more restorative effect and this was also obvious in decreasing the adipocyte cell diameter and liver inflammation grades.

Inflammation and autoimmunity play significant roles in the development of diabetes, and hence, targeting the inflammatory response has shown therapeutic benefits (79, 80). The NOD signaling pathway is involved in the inflammation triggered by the cGAS-STING pathway (81, 82). Perturbations in the gut microbiota in diabetic patients can, in turn, activate the cGAS-STING-NOD pathway, leading to inflammation (83). Paradoxically, we found that the probiotics Z-Biotic 1mg significantly modulated most of the inflammatory-enriched mRNAs (*DDX58*, *NFKB1*, *CHUK*, *RET*) that were implicated in the STING/NOD/IR pathways and made them decrease significantly to be close to the normal group ratios, interestingly, the high dose of caffeic acid behaved similarly.

The cytoplasmic DNA sensor known as cyclic GMP-AMP synthase (cGAS) directly binds to DNA, including mitochondrial DNA (mtDNA) and abnormal bacterial or viral DNA, leading to its activation. Upon activation, cGAS triggers the synthesis of a secondary messenger called 2′,3′-cGAMP, which then binds to and activates the stimulator of the interferon gene (STING). STING, a transmembrane protein primarily found in the endoplasmic reticulum (ER), undergoes translocation to the Golgi and recruits the downstream TANK-binding kinase 1 (TBK1) to form a complex. This complex, in turn, phosphorylates and activates interferon regulatory factor 3 (IRF3) and nuclear factor kappa B (NF-κB), initiating a cascade of signals that activate various innate immune-related genes, including type I interferon (IFN) (84). Recent studies have implicated the cGAS-STING pathway in the development of diabetic cardiomyopathy, a condition characterized by aseptic inflammatory activation. Notably, increased mtDNA in the cytosol and the activation of the cGAS-STING signaling pathway, along with its downstream targets such as IRF3, NF-κB, IL-18, and IL-1β, have been observed in the context of diabetic cardiomyopathy (85). A previous study discovered that activating *STING* resulted in an induction of the *NLRP3* inflammasome and pyroptosis, which culminated in an inflammatory response observed in diabetic mice (86). Qiao et al. found that *STING* plays a unique role in regulating insulin action in peripheral metabolic tissues and insulin secretion from β-cells (87).DDX58 participates in innate immune responses through the NOD-like receptor signaling pathway, detecting cytoplasmic DNA and triggering the production of interferon 1 and inflammatory cytokines (88, 89). Moreover, the cGAS-STING1 and DDX58-MAVS pathways are connected to the innate immune response (90).In a study conducted by Frietze et al. using a NASH model, it was shown that activation of DDX58 leads to the cleavage of LC3, a marker linked to autophagosome formation, DDX58 interacts with the autophagy receptor protein SQSTM1 to degrade itself selectively after viral stimulation. Activation of DDX58 enhances autophagic responses, aiding in the removal of harmful lipid inclusion bodies associated with inflammation and cell death. Excessive fatty acids hinder DDX58 activity, reducing crucial autophagic responses and worsening lipotoxicity. The study revealed that DDX58 directly influences SQSTM1 gene expression, protein accumulation, and targeted autophagic degradation. Furthermore, sustained overexpression of DDX58 markedly reduces inflammation mediated by JAK-STAT signaling (91).Studies have demonstrated that ZBP1, a cytosolic nucleic acid sensor, plays a pivotal role in coordinating innate immune responses by triggering both NF-κB and interferon regulatory factors (IRFs) signaling pathways (92). Additionally, ZBP1 activation leads to the expression of inflammatory cytokines and induces various forms of

inflammatory cell death, including necroptosis, pyroptosis, apoptosis, and PANoptosis, in response to different host-derived nucleic acids (93, 94). Moreover, *ZBP1* acts as a regulator of IFN-1-mediated disease progression, sensing mitochondrial DNA instability through the cGAS-STING pathway and sustaining IFN-1 signaling, which is involved in heart failure and cardiac cell remodeling (95, 96).

Stimulation of NOD and TNF receptors in intestinal epithelial cells activates *CHUK*, which stabilizes *ATG16L1*, preventing endoplasmic reticulum stress during inflammation (97). It also inhibits Kappa Beta kinases that suppress *NFKB1* (98). High glucose promotes proliferation and invasiveness in pancreatic cancer cells by upregulating *RET*, a proto-oncogene encoding a receptor tyrosine kinase (99). *ZBP1* acts as a regulator of IFN-1-mediated disease progression, sensing mitochondrial DNA instability through the cGAS-STING pathway and sustaining IFN-1 signaling, which is involved in heart failure and cardiac cell remodeling (95, 96) A previous study discovered that activating *STING* resulted in an induction of the *NLRP3* inflammasome and pyroptosis, which culminated in an inflammatory response observed in diabetic mice (86). Qiao et al. found that *STING* plays a unique role in regulating insulin action in peripheral metabolic tissues and insulin secretion from β-cells (87).

Intense evidence supports the involvement of miRNAs in the intricate regulation of glucose homeostasis, making them potential contributors to the development of diabetes (100). These small molecules exert their influence by impacting various aspects of insulin levels, including insulin production, and exocytosis (101) Additionally, lncRNAs can act as miRNA sponges by binding to miRNAs, thus preventing them from interacting with their mRNA targets (102). This regulatory mechanism plays a crucial role in diabetes pathogenesis, influencing beta-cell function, apoptosis, insulin secretion, glucose metabolism, and insulin resistance (103, 104).

We previously reported that miRNAs (has-miR-1976 and has-miR-611) acted as sponges on lncRNAs (AC074117.2 and RP4–605O3.4), decreasing the expression of mRNA (*CHUK* mRNA). Notably, these findings demonstrated the potential of has-miR(-1976 and 611) miRNAs as distinguishing factors between insulin-resistant and insulin-sensitive patients, and their involvement in modulating the STING/NOD/IR pathways (105). These results were consistent with our observations in animal models. Previous studies have highlighted the role of miR-1976 as a tumor suppressor in non-small cell lung cancer (106). *In vitro* experiments demonstrated that the suppression of miR-1976 resulted in a significant acceleration of wound healing and cell migration. Furthermore, it stimulated cell proliferation, decreased cell apoptosis, and increased the populations of CD44+/CD24− cells (107).

Our results suggested that RP11–773H22.4 could bind to miR-1, and miR-3163 and serve as a competing endogenous RNA (ceRNA) to upregulate *m-TOR*, *IGF1-R*, and downregulate *AKT2* expression, thus contributing to increased autophagy and the progression of T2DM, consistent with our previous results (28). Previous studies have indicated that insulin-like growth factor-1 (*IGF-1*) hinders the process of autophagy by inhibiting *AKT*. This inhibition is believed to be mediated by *AKT*'s activation of rapamycin complex 1 (*mTORC1*), a known inhibitor of autophagy, there for Inhibition of *IGF-1R* signaling cascade reduces autophagy, impacting autophagosome precursor formation and suggests that targeting the IGF-1R receptor or its downstream pathway may have implications for therapeutic purposes (108). Moreover, *Akt2* can inhibit the expression of the cGAS-STING pathway and suppress the inflammatory response in diabetes (109). Autophagy is crucial for maintaining cellular balance during stressful conditions, excessive or uncontrolled autophagy can trigger autophagy-dependent apoptosis, cardiac injury, and impaired function, primarily through autophagic cell death (110–112). MiR-1, which has been studied extensively, is often suppressed in various biological samples from patients with T2DM (113). Overexpression of miR-1 has been shown to inhibit cardiac fibrosis and apoptosis by altering the expression levels of *Bcl-2*, *TGFb1*, and *Bax* (114). Additionally, *mTOR* plays a significant role in cardioprotection, diabetes, cellular metabolism, apoptosis, autophagy, and mitochondrial biogenesis (115–117) Studies have demonstrated that inhibiting *mTOR* with rapamycin (*RAPA*) can reduce cardiomyocyte apoptosis following myocardial infarction (MI) stress (118). Moreover, in retinoblastoma cancer stem cells, miR-3163 influences cell proliferation, apoptosis, and drug resistance (119). Additionally, miR-3163 has been shown to enhance the sensitivity of hepatocellular carcinoma (HCC) cells to sorafenib by suppressing the cleavage of Notch protein (120).

The present study involved; i, Data preprocessing and feature selection: The dataset was carefully preprocessed to ensure data integrity and consistency with the study objectives. Null values and duplicate entries were carefully handled to maintain the quality of the dataset, which was essential for subsequent analysis. Targeted variables created following data correction methods 'standardization' are needed to predict response to type 2 diabetes mellitus (T2DM) treatment Based on 'fat cell diameter' and '. Inflammation (liver)' features used to divide the sample into "unimproved" and "improved" categories. Categorical features of the dataset were adjusted to facilitate their incorporation into the modeling pipeline. Robust coding techniques such as one-hot coding were used to ensure compatibility with machine learning algorithms. Feature selection was performed using cross-validation (RFECV) method and recursive feature elimination, which is the cornerstone of predictive modeling. This approach systematically identified factors that contribute to understanding T2DM drug response patterns. Notably, the selected molecules include ZBP1 (A), STING1(L), DDX58 (L), mTOR (L), NFKB1 (A), CHUK (A), RET (L), RET (A), miR-1. (A), miR-611 (L), miR-611 (A), LncRNA-RP11–773H22.4 (L), and LncRNA-RP11–773H22.4 (A). Furthermore, biological parameters such as glucose, insulin, HOMA-IR, total cholesterol, triglycerides, AST, ALT, creatinine, BUN, and ACR were identified as important contributors to the prediction of T2DM treatment response. ii, Training and evaluation model: The trained machine learning models, including K-Nearest Neighbors (KNN) and Light Gradient Boosting Machine (LGBM), were subjected to rigorous evaluation to assess their predictive prowess. Leveraging cross-validation techniques, the models demonstrated commendable performance, achieving an impressive accuracy of 80%. These

findings underscore the robustness and efficacy of the selected features in discerning intricate patterns inherent in T2DM treatment response. Moreover, the systematic approach adopted in this study holds promise for enhancing therapeutic strategies and optimizing patient outcomes in clinical settings.

In this study, a feature selection approach based on the RFECV technique was adopted to select the top molecular and biochemical features that had the highest prediction accuracy for T2DM drug response in the dataset. The selected molecular features were *ZBP1* (A), *STING1* (L), *DDX58* (L), *mTOR* (L), *NFKB1* (A), *CHUK* (A), *RET* (L), *RET* (A), miR-1976 (A), miR-611 (L), miR-611 (A), LncRNA-RP11–773H22.4 (L), and LncRNA-RP11–773H22.4 (A). While the biochemical features were Glucose, Insulin, HOMA-IR, Total cholesterol, Triglycerides, AST, ALT, Creatinine, BUN, and ACR. The utilized molecular and biochemical models using these features combined or separately maintained decent prediction performance with top classifiers KNN and LGBM at an accuracy of 80%.

While our study provides valuable insights into the potential therapeutic efficacy of medicinal plant-based drugs and probiotics in treating T2DM, there are several limitations that should be acknowledged. Our study focused on a limited number of medicinal plant-based drugs and a single probiotic, which may not fully represent the spectrum of potential therapeutic interventions for T2DM. Future research incorporating a broader range of pharmacological agents and therapeutic modalities could provide a more comprehensive understanding of effective treatment strategies for this complex condition. Further larger studies addressing the possibility of multiple dose and long-term treatment regimens and their impact on the evaluation of drug safety and efficacy should be explored. Also, Further future validation through independent datasets is strongly needed to ensure the findings' applicability in human T2DM treatment. Moreover, while our study assessed various molecular and biochemical features associated with T2DM pathogenesis, it is important to recognize that these chosen parameters may not capture the full complexity of the disease process. Additional factors such as genetic predisposition, environmental influences, and lifestyle factors may also contribute to individual variability in drug response and treatment outcomes. Further research is needed to address the limitations and translate these findings into clinically meaningful interventions for patients with T2DM. Researchers stressed the pivotal role of all members of brain, kidneys, pancreatic cells, alpha cells, and the gastrointestinal tract in the development of glucose intolerance besides the four cell types(liver, muscle and adipose tissues) (121). Thus further larger validation in other tissues is strongly recommended to ensure the generalization of the results.

6 Conclusion

We developed a prediction system for identification of potential therapeutic targets using machine learning algorithms with feature selection using mRNAs-miRNAs-LncRNAs implicated in autophagy and STING/NOD/IR pathways that directly correlated with T2DM pathogenesis in addition to biochemical features. Our results demonstrated that the KNN algorithm outperformed other classifiers in both the molecular and combined models, for the biochemical model, the LGBM Classifier exhibited the highest performance with AUC values of 0.9177, 0.9, and 0.9397, respectively. Notably, our machine learning approach successfully identified 20 significant features out of the total 44 features in the combined model with an accuracy of 80%.

Data availability statement

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

Ethics statement

The animal study was approved by Research Ethics Committee of the Faculty of Medicine at Ain Shams University under federal-wide assurance NO. FWA000017585. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

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Conflict of interest

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

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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.2024.1384984/full#supplementary-material

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Association between remote resistance exercises programs delivered by a smartphone application and skeletal muscle mass among elderly patients with type 2 diabetes– a retrospective real-world study

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Objective: We aimed to explore the relationship between remote resistance exercise programs delivered via a smartphone application and skeletal muscle mass among elderly patients with type 2 diabetes, utilizing real-world data.

Methods: The resistance exercises were provided through Joymotion®, a web-based telerehabilitation smartphone application (Shanghai Medmotion Medical Management Co., Ltd). The primary outcome was the changes in skeletal muscle index (SMI) before and after the remote resistance exercises programs. The secondary outcomes were changes in skeletal muscle cross-sectional area (SMA), skeletal muscle radiodensity (SMD) and intermuscular adipose tissue (IMAT).

Results: A total of 101 elderly patients with type 2 diabetes were analyzed. The participants had an average age of 72.9 ± 6.11 years for males and 74.4 ± 4.39 years for females. The pre- and post-intervention SMI mean (± SE) was 31.64 ± 4.14 vs. 33.25 ± 4.22 cm^2/m^2 in male, and 22.72 ± 3.24 vs. 24.28 ± 3.60 cm^2/m^2 in female respectively (all $P < 0.001$). Similarly, a statistically significant improvement in SMA, IMAT, and SMD for both male and female groups were also observed respectively ($P < 0.001$). Multiple linear regression models showed potential confounding factors of baseline hemoglobin A1c and duration of diabetes with

changes in SMI in male, while hemoglobin A1c and high density lipoprotein cholesterol with changes in SMI in female.

Conclusion: Remote resistance exercises programs delivered by a smartphone application were feasible and effective in helping elderly patients with type 2 diabetes to improve their skeletal muscle mass.

KEYWORDS

resistance exercises, smart phone application, skeletal muscle mass, diabetes mellitus, remote rehabilitation, elderly

Introduction

Elderly patients with type 2 diabetes (T2D) are a distinct and rapidly expanding group, confronting a wide array of health challenges, including a heightened risk of developing sarcopenia (1). Sarcopenia, defined by the loss of muscle mass, strength, and function, significantly diminishes quality of life, functional independence, and healthcare outcomes in this demographic (2). The relationship between T2D and sarcopenia in elderly adults is intricate and reciprocal. T2D propels the aging process via several mechanisms, such as chronic inflammation, oxidative stress, and endothelial dysfunction, all of which contribute to the development and progression of sarcopenia. In turn, the presence of sarcopenia can exacerbate diabetes management, complicating glycemic control, increasing the likelihood of hypoglycemia, and elevating the risk of hospital admissions, falls and fractures, and even death (3, 4). Additionally, there is an increasing body of evidence indicating that both sarcopenia and T2D independently and together play a role in cognitive deterioration, elevating the risk of developing dementia, including Alzheimer's disease (5–7).

Resistance exercise, also known as strength training, is crucial in managing T2D and addressing sarcopenia, especially among the elderly population (8–10). This physical activity entails exercises that force muscles to contract against an external force, aiming for improvements in strength, tone, mass, and/or endurance. The advent of remote resistance exercise programs available through smartphone applications marks a significant progression in healthcare technology (11, 12). These innovations provide accessible, personalized, and scalable exercise solutions, featuring real-time feedback and instructions, some of which can integrate with wearable technology. While several clinical trials have shed light on the effectiveness of such interventions in clinical scenarios (13–15), home-based real-world evidence, particularly within the Chinese population, remains scarce. Our objective is to explore the relationship between remote resistance exercise programs delivered via a smartphone application and skeletal muscle mass among elderly patients with T2D, utilizing real-world data.

Methods

Study design and participants

The Department of Rehabilitation at the Third Affiliated Hospital of Jinzhou Medical University offers a comprehensive array of services, including a rehabilitation medicine clinic and specialized clinics. It is recognized as the most expansive and technologically advanced rehabilitation facility among the large comprehensive hospitals in western Liaoning, boasting expertise in several key areas such as exercise prescriptions, neurological rehabilitation, trauma rehabilitation, and traditional medicine rehabilitation. We extracted data from the electronic health records (EHRs) from the Third Affiliated Hospital of Jinzhou Medical University. Eligible patients were (1) aged 65 years or older; (2) confirmed diagnosis of T2D; (3) using remote resistance exercises programs for at least 3 months; (3) available data on clinical characteristics and medical history. Exclusion criteria included: (1) patients without available images in the CT scan or with poor image quality; (2) patients with loss of rehabilitation record; (3) without complete clinical data (see Figure 1 in detail). The analytic plan was approved by the Institutional Review Board of the Third Affiliated Hospital of Jinzhou Medical University (JYDSY-KXYJ-IEC-2021–009). Our study did not require obtaining informed consent from individual participants as it utilized retrospective anonymized data extracted from EHRs.

Data source and measurements

Using the Chinese government-issued unique personal identification numbers, we developed an electronic database. This database compiled information such as date of birth, sex, age at diabetes diagnosis, smoking status, and medication use, including antihypertensive, glucose-lowering, lipid-lowering, and antiplatelet or anticoagulant drugs. Data was gathered via a standardized form for collecting electronic inpatient and outpatient medical record information. Additionally, at every inpatient admission or

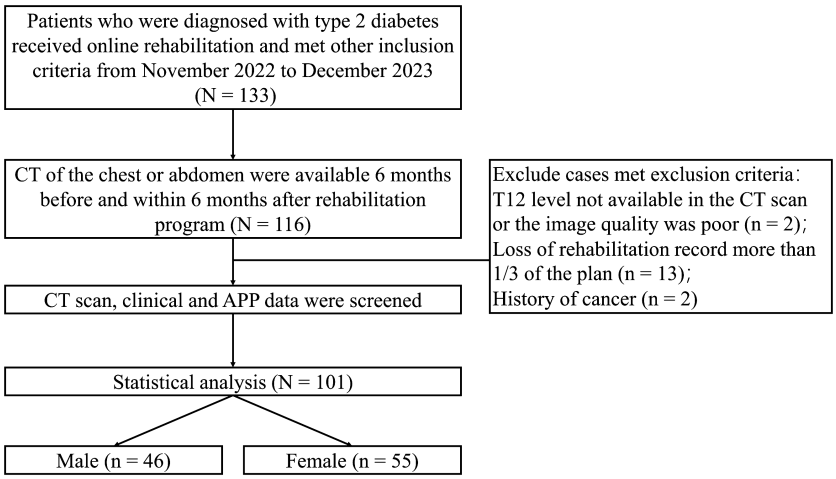

FIGURE 1
Participant flow diagram.

outpatient visit, standardized methods were used to measure patients' height, weight, blood pressure, plasma glucose levels, C-peptide, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, hemoglobin A1c (HbA1c), serum creatinine, and C-reactive protein. The body mass index (BMI) was calculated using the formula weight in kilograms (kg) divided by the square of height in meters (m^2). The estimated glomerular filtration rate (eGFR) was determined using the formula from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (16). Comorbidities and history of diseases were coded using the International Classification of Diseases 10th version (ICD-10).

Remote resistance exercises programs delivered by smartphone application

The resistance exercises were provided through Joymotion®, a web-based telerehabilitation smartphone application (Shanghai Medmotion Medical Management Co., Ltd) (17). Joymotion®; is a remote rehabilitation and exercise prescription monitoring device designed for treating musculoskeletal diseases. It integrates wearable sensor hardware with an app that features a library of standardized exercise prescriptions based on evidence-based practices. These can be tailored by doctors to create personalized treatment plans. The app guides patients through exercises with video and written instructions, monitors performance in real-time, and offers interactive communication with online physiotherapists. It also pushes educational content tailored to patients' conditions, enhancing understanding and engagement in their rehabilitation. Key features include the ability to facilitate easy follow-ups for doctors and automatically push tele-rehabilitation as "daily tasks" and targeted educational videos, improving patient education and compliance. Through real-time tracking, messaging, and video consultations, Joymotion® facilitates continuous personalized care and supports comprehensive disease management, even after hospital discharge. Within the app, immediate feedback on the completion of exercises within a session is recorded, determining success based on whether the patient fully viewed or skipped the instructional videos.

In this study, a 12-week progressive elastic band resistance training program was delivered via the Joymotion®. Participants engaged in a structured series of resistance exercises employing elastic bands (Thera-Band®, The Hygenic Corporation, Akron, OH, USA). These bands, differentiated by color (yellow, red, green, blue, black, or silver), provided varying levels of resistance, with about 20% increase in resistance intensity. The training protocol was meticulously designed to encompass all major muscle groups, incrementally elevating both the volume and intensity of the exercises. Training intensities were meticulously tailored to the individual's clinical profile and historical health data, ensuring a bespoke rehabilitation process. Adherence to the resistance training guidelines established by the American College of Sports Medicine for elderly adults was ensured (18).

Participant compliance and safety were paramount; thus, participants were instructed to report the perceived exertion and any difficulties encountered during each session through the application. Weekly virtual consultations with the physical therapist were mandated to evaluate training load, ascertain the presence of any adverse reactions, and adjust training intensity and exercises progressively optimizing the intervention protocol based on these evaluations. A series of elastic bands with varying levels of resistance were provided, allowing for progression based on participants' training capacity. In instances where participants were unable to tolerate the increased intensity of the next resistance level, the resistance intensity of the elastic band was maintained at the previous level for an additional session. However, in such cases, the number of repetitions per set might be increased to continue challenging the participants and promoting strength development. This maintenance continued until participants could successfully achieve a 20% increase in resistance intensity, signaling readiness to progress to the next color-coded elastic band. The program stipulated

a thrice-weekly engagement over 12 weeks, culminating in 36 sessions. Each session was structured to last 50 minutes, comprising a 5-minute general warm-up, 40 minutes of targeted elastic band resistance exercises, and a concluding 5-minute cool-down and stretching phase. The exercise component was designed to target specific muscle groups—including the lower limbs, core, arms, and shoulders—through 1 or 2 exercise variations. For each exercise, participants were instructed to perform 2–3 sets of 8–12 repetitions, focusing on controlled concentric and eccentric muscle contractions across the full movement range, facilitated by the resistance offered by the elastic bands.

Evaluation of skeletal muscle mass

We used computed tomography (CT) images at the thoracic 12 (T12) vertebral level to assess the muscle area and quality. This method is commonly used in many other studies for assessing sarcopenia or the loss of skeletal muscle mass and function (19–21). Since the COVID-19 pandemic in 2019, chest CT scanning is routine at every clinical visit and the reports and images were stored in the EHR systems. The T12 vertebra is identified on the CT scan by locating the last rib's attachment point, as T12 is the last thoracic vertebra to which ribs attach. We used SliceOmatic 6 (TomoVision, Magog, Canada) to analyze the images. The skeletal muscle cross-sectional area (SMA) at the T12 level is delineated manually. The muscles analyzed include the paraspinal muscles (erector spinae and multifidus), and intercostal muscles. The software calculated the total cross-sectional area of skeletal muscle in square centimeters (cm^2) and we further adjusted these measurements for height to derive a skeletal muscle index (SMI). Skeletal muscle radiodensity (SMD) and intermuscular adipose tissue (IMAT) were determined using the images at T12 level based on the Hounsfield Unit (HU) values. The SMD and IMAT were reported as the mean HU value within the erector spinae muscle area.

Outcomes

The primary outcome was the changes in SMI before and after the remote resistance exercises programs. The secondary outcomes included the changes in SMA, SMD and IMAT.

Statistical analysis

For the primary outcome measure of SMI, we determined that a sample size of 44 patients in each gender would grant the study 90% statistical power, with a two-sided alpha level of 0.05, in a two-sided paired t-test, to detect a treatment difference of 2 cm^2/m^2 in male and 1.5 cm^2/m^2 in female, assuming a standard deviation of 4 in male and 3 in female. G*power version 3.1 (Heinrich-Heine-Universität Düsseldorf Universitätsstr, Germany) was employed in the calculation (22). To accommodate potential exclusion, we increased the target enrollment to 133 patients.

Data with a normal distribution were described using the mean and standard deviation, while skewed data were presented as the median alongside interquartile ranges. Frequencies and percentages were used to describe categorical variables. To compare between groups, Student's t-tests were applied to normally distributed data, the Wilcoxon rank-sum test was used for skewed data, and the $\chi 2$ test was utilized for categorical variables. Baseline variables that were considered clinically relevant or that showed a univariate relationship with outcome were entered into multiple regression model (Table 1). Variables for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final model. Stepwise multiple linear regression models (*lmtest, caret* in R) were used to estimate the confounding factors associated with the outcomes (Table 2). The primary analysis was performed according to sexes separately. The model employed the Breusch-Pagan test to assess the homoscedasticity of the residuals for the validity of Ordinary Least Squares (OLS) regression. A P-value of less than 0.05 was considered of statistical significance. The R software version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria) was utilized to carry out all the statistical analysis.

Results

Baseline characteristics

From November 2022 to December 2023, 133 patients were screened for eligibility, and 101 were analyzed, with 46 male (45.5%) and 55 female (54.5%) patients (Figure 1). The demographic and

TABLE 1 Univariable regression analysis to explore the associations of baseline characteristics with ΔSMI.

	Male	R^2	P-value	Female	R^2	P-value
	β			β		
Age	-0.389	0.152	0.007	0.006	0.019	0.967
BMI	0.138	-0.003	0.360	0.057	-0.016	0.681
HbA1c	0.922	0.847	<0.001	0.954	0.908	<0.001
LDL	0.031	-0.022	0.837	0.168	0.010	0.220
HDL	0.256	0.044	0.086	-0.321	0.086	0.017
TG	-0.321	0.022	0.161	-0.321	0.012	0.203
eGFR	0.164	0.005	0.276	-0.132	-0.001	0.336
Insulin	-0.145	-0.001	0.336	0.417	0.159	0.002
Oral glucose lowering drugs	0.095	-0.014	0.530	0.225	0.033	0.098
Anti-hypertension drugs	-0.205	0.020	0.171	0.144	0.002	0.294
Statins	-0.029	-0.022	0.847	0.135	0.000	0.325
Aspirin	-0.100	-0.012	0.507	-0.025	-0.018	0.858
Duration	0.800	0.631	<0.001	-0.063	-0.015	0.648

R^2, adjusted R^2.

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TABLE 2 Multiple linear regression analysis for ΔSMI.

	Variable	Co-efficient	95% CI	P- value
Male	HbA1c	0.208	0.164, 0.251	<0.001
	Duration	0.030	0.014, 0.047	<0.001
Female	HbA1c	0.349	0.320, 0.378	<0.001
	HDL	-0.004	-0.006, -0.002	<0.001

clinical characteristics of the patients at baseline are shown in Table 3. The participants had an average age of 72.9 ± 6.11 years for males and 74.4 ± 4.39 years for females (P < 0.05). The mean diastolic blood pressure (DBP) was 72.3 ± 5.62 mmHg for males and 70.8 ± 5.60 mmHg for females. Systolic blood pressure (SBP) was 132 ± 9.08 mmHg for males and 136 ± 10.8 mmHg for females. BMI was balanced across genders, with males at 28.0 ± 3.76 kg/m^2 and females at 28.2 ± 4.43 kg/m^2. Medication usage varied across the cohort, with higher percentages using insulin (male 50%, female 47.2%) in male and metformin (male 54.3%, female 70.9%) in female. Anti-hypertensive drug use was prevalent, with over 89% of each gender using these medications. Statin use was also high, with 76.1% of males and 78.2% of females on these cholesterol-lowering drugs. Smoking status was reported by 34.8% of males and 27.3% of females (P < 0.05).

The primary and secondary outcomes

The primary outcome assessed in this study was the change in SMI following participation in a remote resistance exercise program (Figure 2). A statistically significant improvement in SMI for both male and female groups were observed after the program when compared to the SMI at baseline (P < 0.001). The pre- and post-intervention mean SMI was 31.64 ± 4.14 vs. 33.25 ± 4.22 cm^2/m^2 in male, and 22.72 ± 3.24 vs. 24.28 ± 3.60 cm^2/m^2 in female respectively (all P < 0.001). The secondary outcomes were the changes in SMA, IMAT, and SMD (Figure 2). Similarly, a statistically significant improvement in SMA, IMAT, and SMD for both male and female groups was also found respectively (P < 0.001).

Multiple linear regression models

We further explored the correlations between the changes in SMI before and after the resistance training program (ΔSMI), and various baseline characteristics of patients were analyzed separately in univariate models (Table 1), then a forward stepwise approach used to inform the final variables for inclusion into the multiple regression model (Table 2). The analysis was conducted separately for male and female groups to identify variables significantly associated with ΔSMI within each gender. In the male group, HbA1c and duration of diabetes showed significant positive association with ΔSMI (HbA1c, coefficient 0.208 (0.164, 0.251), P < 0.001; duration of diabetes, coefficient 0.030 (0.014, 0.047), P < 0.001). In the female group, HbA1c was also found to have a significant positive correlation with ΔSMI (coefficient 0.349 (0.320, 0.378), P <0.001). HDL cholesterol levels were negatively associated with ΔSMI (coefficient -0.004 (-0.006, -0.002), P <0.001).

TABLE 3 Baseline characteristics of the patients.

	Male (n = 46)	Female (n = 55)
Age, yrs	72.9 (6.11)	74.4 (4.39)*
Height, cm	170 (6.31)	154 (6.33)
Weight, kg	80.8 (12.8)	67.4 (11.5)
DBP, mmHg	72.3 (5.62)	70.8 (5.60)
SBP, mmHg	132 (9.08)	136 (10.8)*
BMI, kg/m^2	28.0 (3.76)	28.2 (4.43)
LDL, mmol/L	2.32 (0.64)	2.47 (0.80)
HbA1c, %	7.28 (1.38)	7.15 (1.02)
HDL, mmol/L	1.08 (0.29)	1.33 (0.35)
Tg, mmol/L	1.50 (0.73)	1.34 (0.52)
eGFR, mL/min/1.73m^2	70.4 (27.2)	85.4 (28.7)*
Duration of diabetes, yrs	10.8 (3.59)	11.0 (4.26)
insulin, n(%)	23 (50.0)	26 (47.2)*
SUs, n(%)	13 (28.3)	23 (41.8)
metformin, n(%)	25 (54.3)	39 (70.9)*
DPP 4, n(%)	11 (23.9)	9 (16.4)
AGI, n(%)	0 (0.00)	1 (1.82)
SGLT 2 inhibitors, n(%)	1 (2.17)	0 (0.00)
GLP 1, n(%)	3 (6.52)	4 (7.27)
TZD, n(%)	3 (6.52)	1 (1.82)
Oral glucose lowering drugs, n(%)	40 (87.0)	49 (89.1)
Beta Blockers, n(%)	30 (65.2)	33 (60.0)
Calcium Channel Blockers, n(%)	24 (52.2)	34 (61.8)*
ACE Inhibitors, n(%)	27 (58.7)	31 (56.4)
ARBs, n(%)	14 (30.4)	17 (30.9)
Anti-hypertension drugs, n(%)	41 (89.1)	51 (92.7)
Statins, n(%)	35 (76.1)	43 (78.2)
Aspirin, n(%)	13 (28.3)	14 (25.5)*
Smoking, n(%)	16(34.8)	15(27.3)*

Data were mean (SD) or number (percentage).
*P < 0.05.

Discussion

In this study, we demonstrated the significant improvements in SMI, SMA, IMAT, and SMD for both males and females by a

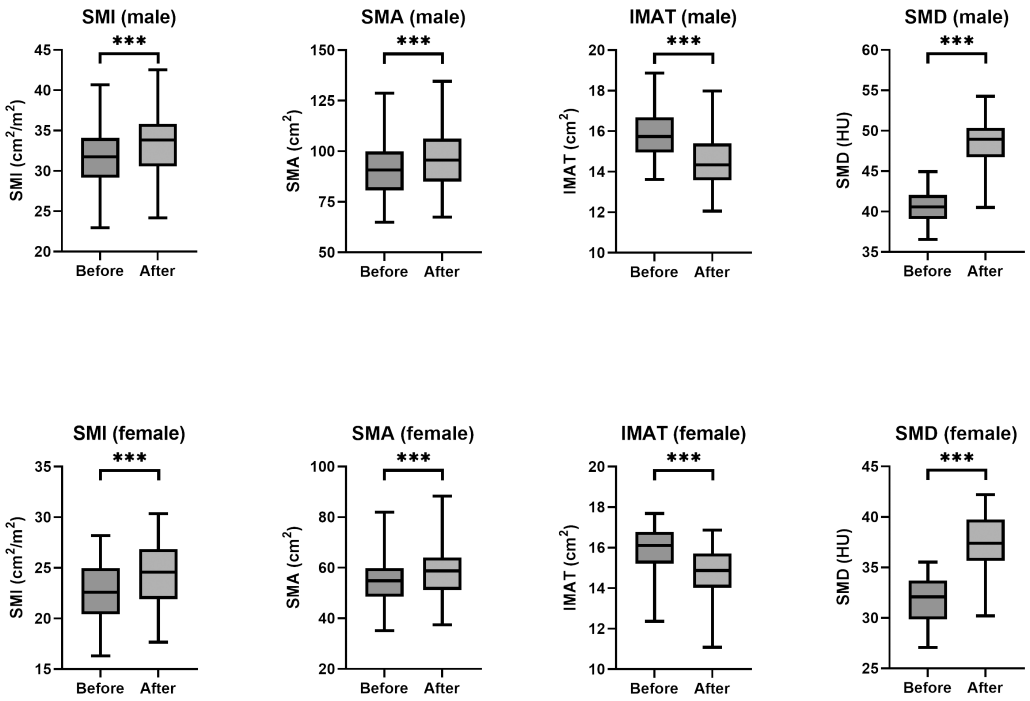

FIGURE 2
Box plots of SMI, SMA, IMAT, and SMD values before and after training by sex. HU, Hounsfield unit. (*** $P < 0.001$).

remote resistance exercise program. Multiple linear regression analysis highlighted significant correlations between post-interventional SMI and various factors. These findings underscore the effectiveness of resistance training in enhancing muscle metrics among older adults, along with the complex interplay of metabolic health factors in modulating these outcomes.

The effectiveness of resistance exercises in addressing sarcopenia, particularly among elderly patients with T2D, has been substantiated by some clinical trials and studies. One prospective study (23) aimed to assess the impact of combined strength and aerobic exercises on frailty levels in elderly diabetic patients over 70 years of age with relatively high functional and cognitive capacities. The study demonstrated that a 6-month regimen of strength exercises with elastic bands and aerobic activities can effectively reduce frailty prevalence among elderly diabetic patients. Another randomized clinical trial (24) assessed the impact of high-protein diets both with and without resistance exercise training on weight loss, body composition, and cardiovascular disease risk factors over a 16-week period. The study found significant group effects for body weight, fat mass, and waist circumference, with the most substantial reductions observed in the low fact hypocaloric diet + resistance exercise group. Specifically, this group experienced the largest decrease in body weight (-13.8 ± 6.0 kg), fat mass (-11.1 ± 3.7 kg), and waist circumference (-13.7 ± 4.6 cm). Bouchi et al (25) also assessed the impact of combining resistance training, with the sodium-glucose cotransporter 2 inhibitor dapagliflozin on body composition and metabolic health in type 2 diabetes patients over a 24-week period of intervention. While this trial revealed no significant difference between the two groups in terms of changes in fat-free mass and SMI, a notable reduction in trunk fat mass was observed in the combination group. Our study showed notable improvements in the SMI following participation in remote resistance exercise programs, alongside a reduction in IMAT. These findings indicate the effectiveness of such a remote program, though further research is required to substantiate these results.

Certain gaps between clinical trials and real-world evidence may limit the interpretation of the findings above. Differences in population diversity, intervention adherence, data collection and outcomes, and study design and flexibility were huge (26). Evidence from real world setting of resistance exercises on skeletal muscle mass is few. Remote resistance exercise programs thus offer a series of advantages for real world use (27). Remote programs can be accessed from any location at any time, eliminating the need for transportation to a gym or fitness center. This is especially beneficial for individuals with mobility issues or those living in areas with limited access to fitness facilities. Remote exercise programs can be highly personalized to meet the specific needs and limitations of elderly individuals. This ensures that exercises are both safe and effective, contributing to improvements in strength, balance, and functional ability without risking injury. By reducing or eliminating the need for clinical visits, personal trainers, or specialized equipment, remote resistance exercises can provide a cost-effective way to combat sarcopenia. This is particularly important for those on a fixed income, such as many elderly individuals. The Joymotion®; incorporates elements of gamification, social interaction, and progress tracking, which can significantly enhance motivation and adherence. Being part of a virtual

community or having the ability to share achievements with friends and family can provide additional encouragement to continue with the program. The programs and instructions within the Joymotion®; are designed based on the Standards of Care in Diabetes by the American Diabetes Association (28), and the consensus statement on exercises/physical activity in individuals with T2D from the American College of Sports Medicine (18), which provides interventions that are scientifically proven to be effective in improving strength, mobility, and frailty among elderly patients with T2D. This study with real world evidence provided a flexible, personalized, and accessible means of engaging in remote resistance exercises, representing a valuable tool in the fight against frailty, empowering individuals to maintain and improve their health and independence.

In our study, we also analyzed the potential confounding factors associated with the improvement of skeletal muscle mass. We found that elderly patients with long duration of diabetes may have a great improvement in SMI. Interestingly, high hemoglobin A1c level may also contribute to a significant improvement in SMI. Although we did not observe any association between insulin use and changes in skeletal muscle mass, insulin plays a critical role in muscle protein synthesis and glucose uptake in muscle tissues (29, 30). Therefore, individuals who manage diabetes without insulin might have a metabolic environment more conducive to gaining muscle mass when engaged in resistance training. The positive correlation between the duration of diabetes, as well as the hemoglobin A1c levels at baseline and SMI improvement might seem counterintuitive, as long-term diabetes along with poor glycemic control is often associated with complications that could impair muscle function. However, this finding could indicate that individuals with a longer history of diabetes and poorer glycemic control have more to gain from engaging in a resistance exercise program. It's possible that these individuals had greater initial muscle loss or more pronounced muscle quality deterioration, thereby experiencing more significant gains when exposed to resistance training. Engaging in resistance exercise can lead to various metabolic adaptations that improve muscle protein synthesis, increase glucose uptake by muscles, and enhance insulin sensitivity (31, 32). These adaptations could be more pronounced in individuals who start with higher levels of metabolic dysfunction. Further studies are needed to validate these hypotheses.

The association between resistance exercises and sarcopenia is underpinned by several biological mechanisms and physiological adaptations that contribute to improved health outcomes and a reduction in frailty indicators. As aging is associated with sarcopenia, resistance training can stimulate muscle protein synthesis and inhibits protein degradation through the activation of the mammalian target of rapamycin (mTOR) pathway (33), leading to increases in muscle mass and strength. Resistance exercises also enhance neuromuscular efficiency, improving the recruitment of muscle fibers, and increasing motor unit activation. The mechanical stress applied to bones during resistance training stimulates osteogenesis (34), helping to prevent or reverse osteopenia and osteoporosis, which contributes to sarcopenia through increased fracture risk. Resistance exercises have been shown to reduce systemic inflammation (35), through the downregulation of pro-inflammatory cytokines and the enhancement of anti-inflammatory mediators. Meanwhile, AMP-activated protein kinase (AMPK) can be activated by resistance training in response to changes in cellular energy status (36). AMPK activation further promotes glucose uptake, fatty acid oxidation, and mitochondrial biogenesis by upregulating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) (37). Research also supports the hypothesis that resistance exercises can increase the levels of IGF-1 (38), which binds to its receptor on muscle cells, activating the Akt pathway. This also leads to increased protein synthesis and muscle cell growth, as well as decreased protein degradation. Other benefits from resistance exercises may include the reduction of myostatin and modulating the activity of NF-kB, further reducing muscle loss and dysfunction associated with sarcopenia (39).

This study underscores the potential of emerging digital technologies in managing T2D in the elderly population, along with precise quantification of skeletal muscle mass through CT imaging. However, several limitations should be fully addressed. Firstly, the study's reliance on a self-control design may restrict the strength of the evidence provided. Secondly, it was conducted with a small participant group at a single center, suggesting the need for a larger, multi-center study to validate the findings. Lastly, the omission of dietary data, a significant confounding factor, was noted, although all participants were local residents likely sharing similar dietary habits. In future research, we plan to employ food recall questionnaires to meticulously document nutrient intake, with a focus on protein consumption, to address this limitation.

Conclusion

Remote resistance exercises programs delivered by a smartphone application were feasible and effective in helping elderly patients with type 2 diabetes to improve their skeletal muscle mass. Future prospective randomized controlled trials are warranted to provide further evidence on this digital technology-based intervention.

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 humans were approved by Institutional Review Board of the Third Affiliated Hospital of Jinzhou Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants

or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JY: Writing – original draft, Data curation. HT: Writing – original draft. HY: Writing – original draft, Software, Formal analysis. JL: Writing – review & editing, Data curation. YC: Writing – review & editing, Data curation. YL: Writing – review & editing. XL: Writing – review & editing. QC: Writing – review & editing. DZ: Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

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Conflict of interest

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

Publisher's note

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Tele-rehabilitation for Type II diabetics with heart failure with preserved ejection fraction

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Objective: This study aims to determine whether tele-rehabilitation has similar effects to conventional face-to-face physical rehabilitation for diabetic patients with heart failure with preserved ejection fraction (HFpEF).

Materials and methods: Demographic, laboratory, diagnostic and rehabilitation information for patients with type 2 diabetes with HFpEF were extracted from disease-specific databases. Outcome measures, including the Short Physical Performance Battery (SPPB), 6-minute walk distance, frailty status, European Quality of Life 5-Dimension 5-Level questionnaire (EQ-5D-5L) and reduction in HbA1c from admission, patients who received tele-rehabilitation therapy were compared to those received face-to-face rehabilitation.

Results: In this study, 90 patients with type 2 diabetes and HFpEF using tele-rehabilitation were matched with 90 patients with type 2 diabetes and HFpEF using face-to-face physical rehabilitation. Improvements in the results of the SPPB scores, 6-min walk distance and gait speed and EQ-5D-5L were noted from the follow-up time point 3 months to 6 months in both two groups. There were no significant differences in functional tests and quality of life between the two groups.

Conclusion: Our study proved that mobile-based tele-rehabilitation programs are non-inferior to face-to-face physical rehabilitation for diabetes patients after HFpEF. In addition, adherence to the telerehabilitation program showed that the novel technology was accepted well and could be an alternative to the conventional face-to-face rehabilitation program.

KEYWORDS

tele-rehabilitation, diabetes, HFPEF, Propensity score matching, outcome

Introduction

Heart failure, a prevalent condition among elderly individuals globally, stands as a primary reason for hospital admissions. It correlates with diminished health-related quality of life, frequent readmissions to hospitals, and significant mortality rates (1, 2). There are a number of reasons why a person with diabetes may be at risk for heart failure: 1) Chronic high blood sugar, one of its main features, damages blood vessels and the nerves that control the heart. In the long run, these damages may cause cardiovascular diseases including heart failure. High glucose levels can lead to the formation of plaques in the arteries (atherosclerosis), reducing blood flow and increasing the risk of heart attacks (3). 2) Insulin resistance in type 2 diabetes mellitus (4). Insulin is a hormone that helps regulate blood glucose levels. Insulin resistance not only contributes to hyperglycemia but is also associated with a cluster of cardiovascular risk factors, including hypertension, abnormal cholesterol levels, and obesity. These conditions, often called "metabolic syndrome," can greatly increase the risk of heart disease and heart failure. 3) Diabetes is accompanied by a higher inflammatory response and more oxidative stress, which can lead to damage to the cardiovascular system. Inflammatory cytokines and oxidative stress can lead to endothelial dysfunction, a condition in which the inner lining of blood vessels does not function normally, further increasing the risk of cardiovascular disease. 4) People with diabetes often have hypertension, which can put extra strain on the heart, leading to heart muscle thickening (hypertrophy) and eventually heart failure.

In patients with heart failure, there is a significant decline in body function and a high incidence of debilitation, which is exacerbated by the presence of concurrent diseases (5–8). Even in elderly patients with stabilized heart failure who are well cared for, body functions are often severely impaired by aging, cardiovascular dysfunction, and musculoskeletal dysfunction (9, 10). In patients with heart failure who convert to acute decompensated heart failure, the organism functions worse and can be exacerbated by hospital admissions and bed rest (8). The deficits are usually long-lasting. Many patients fail to return to basic functioning, have reduced self-care, and are at higher risk for readmission and death after discharge.

The Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial was a multicenter, single-blinded, randomized controlled trial, which focused on an early, personalized, progressive rehabilitation intervention encompassing various aspects of physical function. The study demonstrated that for older adults admitted to the hospital due to acute decompensated heart failure, receiving transitional, tailored and progressive rehabilitation interventions (covering various aspects of physical function) for 12 weeks after admission resulted in significant improvements in physical function compared to usual care (11).

Due in part to the trend in the aging of the populations in big cities in China, which result in a high prevalence of heart failure, the number of patients has steadily increased over the past decades while hospital stays have decreased. This patient group has consequently become a growing workload for physical therapists (PT) either in the community or hospital. In some communities in the author's home city (Shanghai, China), these patients group approximately accounts for over 30% of PT's caseload, and this number is increasing year by year. Since the growing rehabilitation needs of heart failure cannot be met by the current labor force of PT in China, the exploration for new effective alternatives to ensure reliable and accessible postoperative physical rehabilitation is vital and urgent (12).

Another treatment model is to use telerehabilitation technology to deliver rehabilitation programs directly to the patient's home. This intervention may mitigate access challenges for patients residing in both rural and remote areas, as well as those in urban settings facing transportation difficulties (13, 14). Many patients might encounter difficulties accessing healthcare services following hospital discharge. Access to rehabilitation programs is complex with patients' financial costs and health sectors providing in-home services in conjunction with or substitute with community care. For patients living in rural areas, the problem of access is compounded by long distances and time spent by patients or treating doctors. Home-based programs facilitated by technology might motivate patients to engage in more frequent physical activity, which could help mitigate the strength deficits commonly observed in older individuals with diabetes and heart failure. It not only provides convenience for patients, but also saves healthcare costs.

This study aims to determine whether tele-rehabilitation has similar effects to conventional face-to-face physical rehabilitation for diabetic patients with HFpEF.

Materials and methods

Study participants

Data on patients with HFpEF were obtained in "Heart Failure database", which is one of the disease-specific databases in Renhe Hospital, Baoshan District, Shanghai. The Heart Failure database included electronic health record data from March 1, 2018. For the present study, data from the Heart Failure database were included in the analysis. Full details of the inclusion and exclusion criteria of the data base are provided in the Supplementary Appendix S1.

The definition of type 2 diabetes in the present study was formulated according to the SUPREME-DM criteria (15) as follows: a) One or more International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes and Tenth Revision, Clinical Modification (ICD-10-CM) codes for type 2 diabetes associated with an inpatient hospitalization; b) Two or more ICD codes associated with outpatient visits on different dates within a 2-year period; c) Two or more codes associated with outpatient visits on different dates within a 2-year period. combinations of: 1) ICD codes associated with outpatient visits; 2) fasting glucose levels ≥ 126 mg/dl; 3) 2-hour glucose level ≥ 200 mg/dl; 4) random glucose ≥ 200 mg/dl; 5) HbA1c ≥ 6.5%; and 6) prescriptions for antidiabetic medications.

Although different cut points have been defined in the literature (16), and EF <50% could be sub-divided into midrange (40% to 49%) and reduced (<40%) classifications (17). We defined HFpEF

by an EF ≥ 50%, in consistency with previous analyses of hospital readmissions in patients discharged with heart failure.

A total of 694 patients with type 2 diabetes mellitus combined with HFpEF were identified in this study. After excluding patients with incomplete data, a total of 576 patients with type 2 diabetes mellitus combined with HFpEF were included in this study (Figure 1). The study and analysis plan were approved by the Institutional Review Board (Research Ethics Committee) of Renhe Hospital, Baoshan District, Shanghai, China (KY2023–18). As we used anonymized data from electronic medical records, informed consent was not obtained from the participating researchers.

Interventions

Face-to-face physical rehabilitation

If possible, intervention is provided in the hospital and then transferred to an outpatient facility as soon as possible after discharge. If necessary, interventionists will provide in-home treatment until the patient is physically able to participate in outpatient treatment, if the patient is physically able to do so. Outpatient therapy lasted 60 minutes, 3 days per week, for 12 weeks (or 36 sessions), with an interventionist-to-patient ratio of 1:1. Outpatient therapy was accompanied by home exercise on non-treatment days (low-intensity walking gradually increased to 30 to 45 minutes per day and rehabilitation exercises). Each session included approximately 15 to 20 minutes of rehabilitation exercises including four domains tailored to the patient's condition. For patients in the face-to-face physical rehabilitation group, exercises were conducted at the outpatient facility with one-on-one guidance from a PT. For patients in the tele-rehabilitation group, exercises were conducted at home, monitored via an APP and sensors. Every two weeks, patients were reassessed at the PT outpatient clinic to determine if their exercise prescriptions needed adjustments. For the tele-rehabilitation group, these assessments were conducted by the PT through real-time bidirectional video and audio interactions online. Detailed information was provided in Supplementary Appendix S2. The home exercise component of the intervention was initiated after the home environment was evaluated through remote video assessment by a PT and deemed suitable for rehabilitation exercises (11).

The primary purpose of the first 3 months (outpatient phase) of the intervention is to prepare patients for the transition to the independent maintenance phase (months 4 to 6). At the 3-month visit, patients are provided with an individualized exercise prescription and then followed up every 4 weeks via telephone contact. Retention rates and adherence to the intervention sessions for patients in the intervention group are reviewed and discussed every 2 weeks by a special committee, as recommended by the National Institutes of Health Behaviour Change Consortium Treatment Fidelity Workgroup (18).

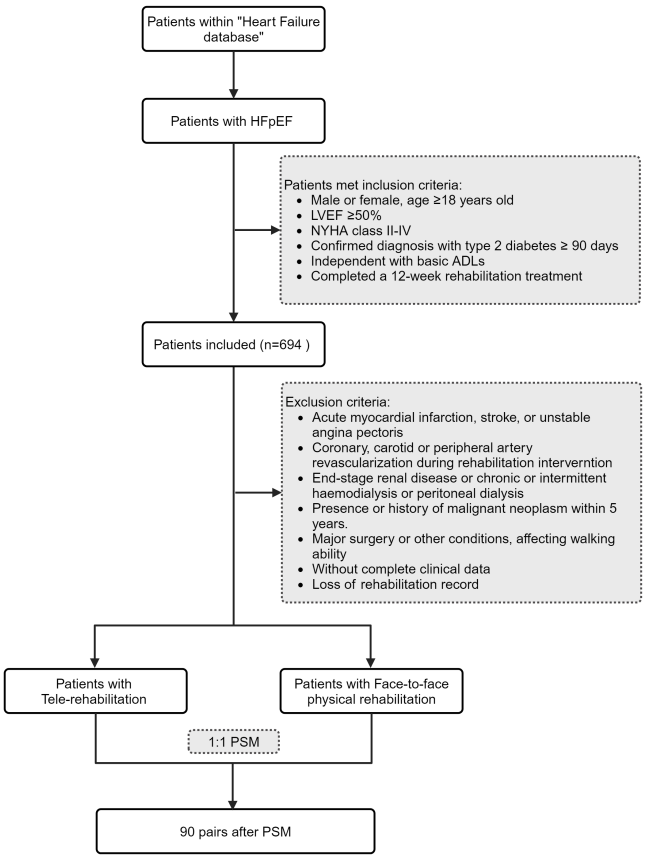

FIGURE 1
Flowchart of the study.

Tele-rehabilitation

Remote rehabilitation interventions were carried out through the mobile application Joymotion® software (developed by Shanghai Medmotion Medical Management Co., Ltd., Shanghai, China). This application facilitated the provision of exercise guidelines, feedback on training performance, and enabled real-time bidirectional video and audio interactions between patients and PTs (19).

Originally developed for the rehabilitation of musculoskeletal disorders, the Joymotion® APP has expanded its scope through advancements in telemedicine, remote sensing rehabilitation technologies, and the accumulation of a diverse exercise database. Due to the substantial overlap between the rehabilitation needs of patients with heart failure, metabolic diseases, and those with musculoskeletal disorders, this APP has been co-developed and upgraded in collaboration with cardiology and orthopedic departments to tailor rehabilitation programs specifically for cardiac and metabolic conditions. The APP, installed by a technician on the day of the patient's discharge, connected through the patient's home Wi-Fi. PTs at the rehabilitation center would initiate weekly scheduled teleconference sessions with the patients. The APP provided daily rehabilitation exercises with comprehensive instructions and tracked exercise completion rates. The rehabilitation protocol, prescribed by the supervising PT, was conveyed to patients as "daily tasks". The intervention content mirrored that of the face-to-face group. Adherence to the prescribed regimen and retention of patients within the intervention group were monitored through the APP by the supervising PTs, with the completion of daily tasks being trackable via the APP's website.

Baseline measurement

Patients' data extracted from the Heart Failure database for this study included birth date, sex, body mass index (BMI), insurance type, date of diagnosis of heart failure, date of diagnosis of diabetes mellitus, blood pressure, smoking status, diagnosis of various medical conditions, laboratory tests, ejection fraction from cardiac ultrasonography, NYHA (New York Heart Association) class, median N-terminal pro–B-type natriuretic peptide. Based on smoking status reported at each clinical visit, we categorized patients into three groups: never smokers, former smokers, and current smokers.

Tele-rehabilitation interventions started on 15 January 2021 at Renhe Hospital, Baoshan District, Shanghai. Tele-rehabilitation users (Group TELE) were defined as patients who used tele-rehabilitation immediately after discharge from hospital, and no face-to-face physical rehabilitation visit was recorded. Non-users of tele-rehabilitation (Group PT) were defined as patients who regularly visited physical rehabilitation departments or clinics 3–4 times per week as required by doctors.

Propensity score matching (PSM)

Patients included in this study were required to have a follow-up period of no less than six months post-hospital discharge. Initially, patients with type 2 diabetes and HFpEF who received tele-rehabilitation were identified. Propensity score matching was performed using the nearest neighbor algorithm, with a caliper set at 0.01. Matching covariates included age, sex, baseline BMI, systolic blood pressure, smoking status, insurance type, NYHA (New York Heart Association) class, and median N-terminal pro-B-type natriuretic peptide levels. Based on these propensity scores, patients undergoing traditional physical rehabilitation were matched in a 1:1 ratio with those receiving tele-rehabilitation interventions (Figure 1).

Ultimately, 90 patients with type 2 diabetes and HFpEF who utilized tele-rehabilitation were matched with 90 patients who underwent in-person physical rehabilitation, resulting in a total cohort of 180 patients. The baseline characteristics between the groups were well balanced (Table 1).

Outcomes measures

Patients' outcome data at day of discharge (baseline), 3 months (3 mo) and 6 months (6 mo) after discharge were extracted, including score on the SPPB, 6-min walk distance, frailty status [assessed according to modified Fried criteria (5)], and EQ-5D-5L visual-analogue scale, and decreased HbA1c from admission.

TABLE 1 Demographic and clinical characteristics of the patients at baseline*.

Characteristic	Total (n=180)	Group PT (n=90)	Group TELE (n=90)	P-value
Age -yr, mean (SD)	64.04 (10.60)	63.43 (11.15)	64.64 (10.05)	0.445
Female sex — no (%)	74 (41.11)	38 (42.22)	36 (40.00)	0.880
Body mass index -kg/m^2, mean (SD)	24.28 (3.67)	24.26 (3.53)	24.31 (3.83)	0.934
NYHA class — no (%)				0.629
II	33 (18.33)	19 (21.11)	14 (15.56)	
III	114 (63.33)	55 (61.11)	59 (65.56)	
IV	33 (18.33)	16 (17.78)	17 (18.89)	
HbA1c at admission (%)	7.46 (1.67)	7.37 (1.62)	7.56 (1.71)	0.446
Median N-terminal pro–B-type natriuretic peptide -pg/ml, median [IQR]	636.75 [561.16, 953.20]	613.00 [559.23, 792.20]	677.55 [570.31, 1134.20]	0.208
Smoking status— no (%)				0.971
Never	95 (52.78)	47 (52.22)	48 (53.33)	
Ever	64 (35.56)	32 (35.56)	32 (35.56)	
Current	21 (11.67)	11 (12.22)	10 (11.11)	
Insurance — no (%)				0.463
None	21 (11.67)	13 (14.44)	8 (8.89)	
Social	145 (80.56)	71 (78.89)	74 (82.22)	
Commercial	14 (7.78)	6 (6.67)	8 (8.89)	

(Continued)

TABLE 1 Continued

Characteristic	Total (n=180)	Group PT (n=90)	Group TELE (n=90)	P-value
Coexisting conditions				
Total no. of coexisting conditions	2.64 (0.98)	2.67 (0.89)	2.62 (1.08)	0.763
Hypertension — no (%)	167 (92.78)	83 (92.22)	84 (93.33)	1.000
History of myocardial infarction — no (%)	17 (9.44)	7 (7.78)	10 (11.11)	0.606
History of coronary revascularization, including PCI and CABG — no (%)	36 (20.00)	17 (18.89)	19 (21.11)	0.845
Atrial fibrillation — no (%)	92 (51.11)	51 (56.67)	41 (45.56)	0.185
Hyperlipidemia — no (%)	133 (73.89)	67 (74.44)	66 (73.33)	1.000
Depression, according to electronic medical record — no (%)	31 (17.22)	15 (16.67)	16 (17.78)	1.000
Geriatric conditions				
Dementia or cognitive impairment, according to electronic medical record — no (%)	6 (3.33)	1 (1.11)	5 (5.56)	0.221
Frail, as defined by the presence of at least three Fried criteria† — no (%)	84 (46.67)	40 (44.44)	44 (48.89)	0.658
Prefrail, as defined by the presence of one or two Fried criteria† — no (%)	96 (53.33)	50 (55.56)	46 (51.11)	0.658
Urinary incontinence — no (%)	23 (12.78)	8 (8.89)	15 (16.67)	0.211

Continuous variables were expressed as mean ± standard deviation (SD), or median [interquartile range] and were compared utilizing either independent t test or Mann-Whitney U test. Categorical variables were presented as the number of cases (percentage) and were compared utilizing Chi-square test.
*CABG denotes coronary artery bypass graft, IQR interquartile range, NYHA New York Heart Association, and PCI percutaneous coronary intervention.
†The five Fried criteria include weight loss, exhaustion, low physical activity, slow gait speed, and weak hand-grip strength.

The primary outcome of this study was SPPB score, a standardized and reproducible measure of overall physical function. The SPPB has been validated in frail older adults and is known to predict a broad spectrum of clinical outcomes (20–22).

Statistical analysis

The groups were first compared on baseline characteristics. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) and were compared utilizing either the paired t test or the Wilcoxon sign rank test, depending on the Shapiro-Wilk test. The categorical variables were presented as the number of cases (percentage) and statistically analyzed with McNemar or McNemar-Bowker test. The main research hypothesis verified that the mean SPPB score gain from baseline to the last follow-up in the Tele-rehabilitation group would not be inferior compared with that in the control group. Only patients who participated in all assessments and attended the required number of intervention sessions, as specified in the inclusion criteria in S1, were included in the analysis. All statistical analyses were performed by SPSS 27.0 with a significance level of 0.05 (two-sided).

Results

In this study, 90 patients with type 2 diabetes mellitus combined with HFpEF using telerehabilitation and 90 patients using face-to-face physical rehabilitation were matched, totaling 180. The baseline characteristics of the two groups were well matched (Table 1).

For primary outcome and major secondary outcome, improvements in the results of the SPPB scores, 6-min walk distance and gait speed were noted from the follow-up time point 3 months to 6 months in both two groups, patients using tele-rehabilitation had similar SPPB scores and 6-min walk distance (and gait speed) with patients using face-to-face physical rehabilitation at both 3 months and 6 months after discharge. The gains from 3 months to 6 months showed no significant differences with regards to SPPB scores and 6-min walk distance (and gait speed) (Table 2).

The other secondary outcome, frailty status, quality of life and clinical events also improved from 3 months to 6 months, patients using tele-rehabilitation noted similar EQ-5D-5L scores with patients using face-to-face physical rehabilitation at 6 months (Table 2). Decreased HbA1c from baseline were similar for two groups at both 3 months and 6 months after discharge.

For clinical events, the number of events was similar among two groups, and the number of days of rehospitalization for any cause also noted no significant difference (Table 3).

Discussion

The "Heart Failure database", founded on March 1, 2018, is one of the disease-specific databases in Renhe Hospital, Baoshan District, Shanghai. The inclusion criteria were provided in the Supplementary Appendix S1. Using real-world disease-specific database information, this study found that patients with type 2 diabetes mellitus combined with HFpEF using tele-rehabilitation therapy was comparable to the efficacy of face-to-face physical rehabilitation. Studies in terms of debilitating conditions and quality of survival also demonstrated the clinical effectiveness of tele-rehabilitation.

Our trial sought to fill significant evidence gaps in tele-rehabilitation for patients with diabetes with heart failure. Unlike previous early heart failure rehabilitation trials, which typically started patient enrollment and intervention about seven weeks post-discharge and primarily used traditional endurance exercise training (23, 24), our trial began earlier and included a more diverse and frail patient population (24). For instance, the EJECTION-HF trial (Exercise Joins Education: Combined Therapy to Improve Outcomes in Newly-Discharged Heart Failure) found no advantage of the intervention over

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TABLE 2 Heart failure and diabetes mellitus related outcomes.

Outcomes	Group PT (n=90)	Group TELE (n=90)	P-value
SPPB score, primary outcome†			
At baseline	5.30 (1.62)	5.26 (1.55)	0.860
At 3 mo	8.09 (0.79)	8.12 (0.72)	0.781
At 6 mo	9.21 (0.61)	9.21 (0.66)	1.000
Change from baseline			
To 3 mo	2.79 (1.53)	2.87 (1.52)	0.745
To 6 mo	3.91 (1.63)	3.96 (1.56)	0.862
Balance score			
At baseline	1.92 (0.88)	1.89 (0.90)	0.805
At 3 mo	2.81 (0.58)	2.89 (0.59)	0.409
At 6 mo	3.10 (0.37)	3.09 (0.36)	0.820
Change from baseline			
To 3 mo	0.89 (0.64)	1.00 (0.73)	0.283
To 6 mo	1.18 (0.91)	1.20 (0.93)	0.870
4-M walk score			
At baseline	1.91 (0.82)	1.98 (0.83)	0.574
At 3 mo	3.26 (0.49)	3.22 (0.51)	0.671
At 6 mo	3.90 (0.30)	3.87 (0.34)	0.470
Change from baseline			
To 3 mo	1.34 (0.81)	1.24 (0.96)	0.424
To 6 mo	1.99 (0.83)	1.89 (0.74)	0.378
Chair rise score			
At baseline	1.47 (0.97)	1.39 (0.94)	0.621
At 3 mo	2.02 (0.15)	2.01 (0.11)	0.567
At 6 mo	2.21 (0.41)	2.26 (0.44)	0.530
Change from baseline			
To 3 mo	0.56 (1.01)	0.62 (0.95)	0.681
To 6 mo	0.74 (1.00)	0.87 (1.02)	0.470
6-min walk distance — m			
At baseline	193.00 (54.66)	197.53 (52.95)	0.555
At 3 mo	285.43 (27.23)	279.69 (29.87)	0.187
At 6 mo	327.70 (20.50)	323.56 (18.85)	0.148
Change from baseline			
To 3 mo	92.43 (54.42)	82.16 (57.84)	0.165
To 6 mo	134.70 (55.39)	126.02 (48.52)	0.248
Frailty status — no. of modified Fried criteria met‡			
At baseline	2.42 (0.81)	2.47 (0.81)	0.710
At 3 mo	1.67 (0.52)	1.62 (0.57)	0.558
At 6 mo	0.86 (0.46)	0.83 (0.50)	0.734
Change from baseline			
To 3 mo	-0.76 (0.77)	-0.84 (0.73)	0.417
To 6 mo	-1.57 (0.90)	-1.63 (0.76)	0.602
EQ-5D-5L visual-analogue scale score ††			
At baseline	0.52 (0.10)	0.51 (0.09)	0.678
At 3 mo	0.64 (0.07)	0.65 (0.05)	0.145
At 6 mo	0.72 (0.05)	0.72 (0.04)	0.968
Change from baseline			
To 3 mo	0.12 (0.08)	0.14 (0.10)	0.162
To 6 mo	0.20 (0.10)	0.21 (0.09)	0.719
Decreased HbA1c from admission — % †††			
At 3 mo	-0.71 (0.18)	-0.70 (0.22)	0.951
At 6 mo	-1.01 (0.25)	-1.04 (0.24)	0.367

(Continued)

TABLE 2 Continued

Continuous variables were expressed as mean ± standard deviation (SD) and were compared utilizing paired t test.

† Total scores on the Short Physical Performance Battery (SPPB) range from 0 to 12, with lower scores indicating more severe physical dysfunction; each component (the standing balance test, the gait-speed test [as assessed by a 4-m walk], and the strength test [as assessed by the time needed to rise from a chair five times]) is scored on a scale of 0 to 4.

‡ Frailty status was assessed according to modified Fried criteria[5].

†† Scores on the European Quality of Life 5-Dimension 5-Level questionnaire (EQ-5D-5L) visual analogue scale range from 0 to 1, with higher scores indicating better health status.

††† Decreased HbA1c are presented as HbA1c at 3 mo or 6 mo minus HbA1c at admission.

usual care regarding 6-minute walk distance, rehospitalization, and mortality, with adherence at only 43% (23, 24). In contrast, the REHAB-HF trial, focusing on frail, older patients hospitalized for acute decompensated heart failure, showed that an early, tailored, and progressive rehabilitation approach led to significantly better physical function outcomes than usual care (11).

Tele-rehabilitation is widely used for glycemic control, exercise capacity, physical fitness, muscle strength and psychosocial status in people with type 2 diabetes mellitus (25). Tele-rehabilitation was commercially available in Renhe Hospital, Baoshan District, Shanghai on 15 January 2021 and was applied to patients with heart failure after discharge. To our knowledge, our analyses were the first study to evaluate the clinical effects of tele-rehabilitation in diabetes with heart failure with preserved EF, and the results supported our hypothesis of non-inferiority of tele-rehabilitation in function, frailty status and quality of life compared with traditional physical rehabilitation. The data in this study provide an essential reference for a more comprehensive and in-depth study on the effectiveness of telerehabilitation in different countries and regions, especially in the fields of rehabilitation after heart failure.

Several limitations in the current study are acknowledged. Firstly, the sample size of patients participating in tele-rehabilitation in our study was relatively small compared to other real-world studies. Secondly, the PSM process was not optimal for certain covariates, as

TABLE 3 Clinical events.

Clinical events at 6 mo	Group PT (n=90)	Group TELE (n=90)	P-value
Rehospitalization for any cause, secondary outcome — no. of events (rate)	24 (0.27)	18 (0.20)	0.400
Death — no. of events (rate)	0	0	1.000
Rehospitalization for heart failure — no. of events (rate)	6 (0.07)	7 (0.08)	1.000
No. of patients with ≥2 rehospitalizations for any cause (%)	4 (4.44)	3 (3.33)	1.000
No. of patients with ≥2 rehospitalizations for heart failure (%)	2 (2.22)	2 (2.22)	1.000
No. of days of rehospitalization for any cause	1.11 (2.20)	0.94 (2.55)	0.639
No. of patients with ≥1 fall (%)	24 (26.67)	19 (21.11)	0.484
No. of patients with ≥1 fall that resulted in injury (%)	1 (1.11)	3 (3.33)	0.613

some socioeconomic variables, such as education level and family income, were absent in the electronic medical records (EMR) data. Thirdly, the long-term effects of this rehabilitation program are unknown, the limited follow-up period of 6 months has implications for the interpretation of the results. Further randomized controlled trials with larger samples are needed to evaluate telerehabilitation in patients after acute heart failure. Lastly, the inherent limitations of a single-center study particularly restricted the generalizability. Differences in medical standards, economic levels, infrastructure, and patients' awareness of rehabilitation treatments across different cities can potentially impact rehabilitation outcomes. Our study is an initial step in establishing the feasibility and effectiveness of tele-rehabilitation. We hope that future researchers will consider conducting multi-center studies that encompass multiple cities and hospitals in subsequent clinical trials.

Conclusion

Our study proved that mobile-based tele-rehabilitation programs are non-inferior to face-to-face physical rehabilitation for diabetes patients after acute heart failure. In addition, adherence to the telerehabilitation program showed that the novel technology was accepted well and could be an alternative to the conventional face-to-face rehabilitation program.

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 humans were approved by Institutional Review Board (Research Ethics Committee) of Renhe Hospital, Baoshan District, Shanghai. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this study is a retrospective study, and there is no identifiable patient information involved.

Author contributions

MY: Formal Analysis, Methodology, Software, Writing – original draft. HX: Data curation, Funding acquisition, Methodology, Writing – original draft. DZ: Investigation, Methodology, Writing – original draft. DS: Software, Writing – original draft. LS: Data curation, Writing – original draft. HZ: Methodology, Writing – original draft. SL: Supervision, Validation, Writing – review & editing. JW: Conceptualization, Funding acquisition, Project administration, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1433297/full#supplementary-material

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Walking away from depression: the mediating role of walking activity in depression impacting blood glucose levels of people with diabetes or prediabetes

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Introduction: Depression can exacerbate diabetes by impairing self-care behaviors and increasing the risk of complication; however, the underlying mechanism is still unclear. Given the suggested associations between walking activity, depression status, and blood glucose levels this study explores the intricate relationship between depression and blood glucose (BG) control, with a focus on walking activity as a behavioral mediator. The purpose of this study is to examine walking activity's mediating role in depression's impact on BG levels, investigating and validating the non-linear association between BG levels and walking activity. This retrospective real-world study demonstrates the potential of regular walking activity as a simple and accessible intervention to mitigate the negative effects of depression on BG levels in T2D and prediabetes.

Methods: A cohort of 989 users with T2D and prediabetes, who regularly tracked their steps levels and BG levels for 12 months using the Dario digital health platform was evaluated. The mediating role of the monthly average number of steps on the relationship between the self-reported depression status and lagged monthly average BG was assessed. Additionally, the association between monthly walking activity and monthly average BG was tested using a piecewise linear mixed effects model.

Results: Users with self-reported depression demonstrated increased BG levels compared to users without depression (B=8.00, P=.01). The association between depression and monthly average number of steps was significant (B=-.27, P<.005) and monthly average number of steps significantly predicted the following months' average BG (B=-.81, P=.001), adjusting for depression. The monthly average number of steps significantly mediated the effect of self-reported depression on the following month's average BG (M=.22, P<.005). Further sensitivity analysis demonstrated model robustness over various

periods. Finally, non-linear dynamics of walking activity over time was validated using unseen data showing a decrease in monthly average BG for users with over an average of 400 steps per day (B=-1.87, P<.01).

Discussion: This study shows how regular walking may reduce the negative impact of depression on BG levels in people with T2D. Our findings advocate for the integration of walking activity into treatment protocols as a cost-effective, accessible intervention strategy to improve glycemic management and depressive symptoms in this population.

KEYWORDS

blood glucose, physical activity, steps counting, depression, mediation effect, digital health, diabetes

1 Introduction

The co-occurrence of depression in individuals with T2D is a well-documented phenomenon, with about 18%–25% of patients with T2D experience significant depressive symptoms (1, 2). This interrelation poses a significant challenge to the management of diabetes, as depression can exacerbate diabetes outcomes by undermining self-care behaviors and increasing the risk of diabetes-related complications (2–4). The intricate relationship between mental health and metabolic regulation in diabetes highlights the critical need for comprehensive strategies that address both psychological and physiological components of diabetes management through mindset shifts and behavior modifications. The capacity for physical activity can be behaviorally regulated by adopting a positive mindset and modifying daily habits, fostering a proactive approach to incorporating exercise into daily routines (5). Physical activity is a cornerstone in the management of type 2 diabetes (T2D) and prediabetes, recognized for its capacity to improve glycemic control, facilitate weight management, and enhance overall well-being (6–10). Exercise is beneficial to the general population and in people with prediabetes as it lowers the risk of developing T2D (10, 11). Among various forms of physical activity, walking is one of the easiest applicable forms of exercise due to its accessibility, low cost, and minimal requirement and may represent, for many, a first step towards lifestyle change (12). Focusing on walking aligns with the study's aim to explore how this accessible, low-cost and easily integrated physical activity can mediate the relationship between depression and blood glucose levels among users with T2D and prediabetes. It underscores the potential of walking as a feasible and effective intervention strategy in promoting both physical and mental health in this population. Walking has been associated with significant health benefits, including improved blood glucose levels and reduced cardiovascular risk factors (13). The American Diabetes Association recommends that people with diabetes start exercising slowly by gradually progressing to a brisk walk, and monitoring both the duration and number of steps taken. Regular walking reduces A1C, triglycerides, blood pressure, and insulin resistance and intensive walking promotes rapid enhancement of skeletal muscle oxidative capacity, insulin sensitivity, and glycemic management (fasting blood glucose) (14, 15). Even a moderate level of walking can show long-term effects on glycemic improvement, as measured by HbA1c (16, 17). There is limited knowledge on the relationship between number of steps walked and diabetes risk or clinical outcomes, as well as on how the number of daily steps walked impacts blood glucose levels over time (18, 19). Most of the existing data were derived from self-report or survey tools or RCTs that, suffered from a number of limitations such as generalizability (20, 21). More longitudinal research on the association of daily step counts with clinical outcomes using real-life data are required (18, 20, 22).

Furthermore, walking activity has been proposed as a therapeutic strategy not only for its physical health benefits but also for its potential psychological benefits, including alleviating symptoms of depression (23–25). Evidence for the efficacy of walking as an intervention for depressive symptoms has been found in several meta-analyses (23, 26, 27). A variety of mechanisms have been suggested as to why physical activity and might reduce depressive symptoms (23) such as biochemical, physiological, psychological and psychosocial (28). Nevertheless, previous studies have not been able to identify the optimal characteristics for the design and delivery of a walking intervention that can benefit depressive symptoms (29).

Studies have shown that engagement with digital health apps and using activity trackers for walking activity have positive effects on physical activity, physiological metrics and psychosocial outcomes (30). Previous evidence demonstrated that using smartphone apps for tracking and promoting physical activity and using pedometers can enhance engagement and increase efficacy of interventions. However, limited knowledge is available

about the effect of long-term walking on diabetes outcomes in real-life settings (31, 32).

Specifically, previous research highlights the effect of depression on glycemia (3, 30, 31). However, walking activity may potentially modulate this effect in T2D based on the biopsychosocial model, which posits that biological, psychological, and social factors have significant, interdependent impacts on health (33). Depression, a common comorbidity in T2D, is known to negatively affect self-management behaviors, including adherence to dietary recommendations, medication regimens, and physical activity guidelines. This reduction in self-care activities can lead to poor glycemic management, creating a vicious cycle of worsening depressive symptoms and diabetes management (3, 34, 35).

In this complex interplay, walking activity emerges as a promising behavioral intervention that might bridge the gap between mental and physical health. The act of walking could potentially counteract the negative effects of depression on diabetes management by improving mood, enhancing self-efficacy, and directly contributing to better blood glucose levels through increased physical activity. These effects are likely to be mediated by a range of biological and psychological mechanisms, including the release of endorphins, improvements in insulin sensitivity, and the establishment of a routine that fosters a sense of accomplishment and control over one's health (36–39).

This study aims to assess the relationship between depressive symptoms and blood glucose levels in individuals with T2D over time, with a specific focus on walking activity as a potential behavioral mediator. In addition, the study aims to investigate the association between monthly aggregated blood glucose (BG) measurements and walking activity (number of steps), by testing potential non-linearity.

2 Methods

2.1 Platform

This study used the Dario digital therapeutics platform (Dario Health) for chronic conditions to support self-management of diabetes. The glucose meter consists of a small, pocket-size holder for strips, a lancet, and the meter. The BG meter is removed from the holder and plugged directly into a smart mobile device, effectively converting the smart mobile device into a display screen for the meter (Figure 1). Data is uploaded to the cloud for backup and further analysis. Step counts were recorded within the app through either the integrated pedometer of a smart mobile device or by interfacing with Apple Health.

2.2 Measures

The monthly average blood glucose was the first measure. The monthly average blood glucose was defined as the mean of all blood glucose measurements taken over a 30-day interval for each user. It was used as the core outcome metric to reflect the monthly aggregated interval changes over 12 months. As part of the app's intake questions, we also gathered demographic information, including gender, age, weight, and height. Additionally, we collected self-reported medical data through the digital health platform. This data included diabetes type and other comorbid conditions such as depression, by having users select the relevant condition from a comprehensive dropdown list of comorbidities. By utilizing a user-friendly dropdown list we ensured consistent data

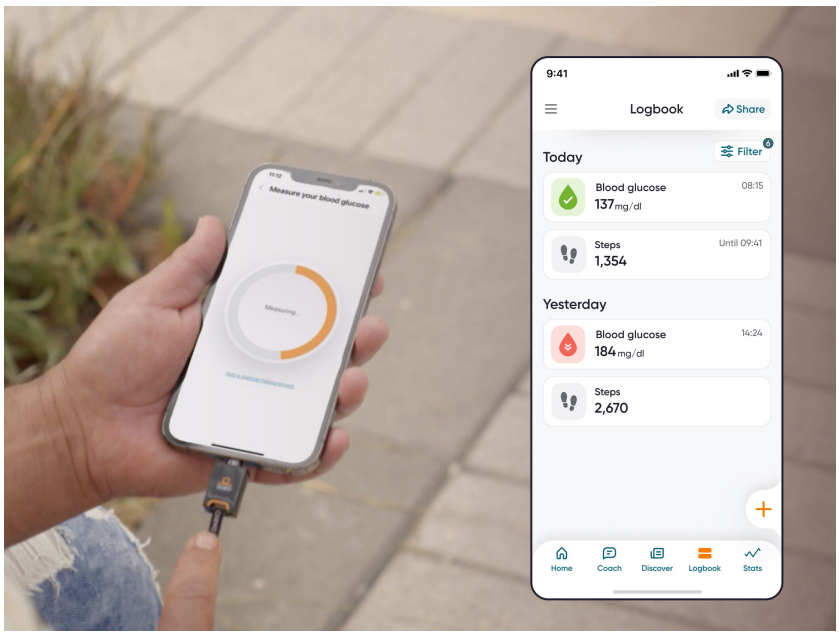

FIGURE 1
A BG measurement taken on the Dario mobile app platform via the glucose meter and a logbook screen presenting BG measurements and daily number of steps.

collection, enabling robust analysis of the interplay between diabetes, comorbid conditions, and overall health outcomes.

2.3 Study population

The inclusion criteria required Dario platform users to have consistently measured their blood glucose every week for a full year between 2019 to 2023 and to have reported type 2 or prediabetes in their diabetes type within the app. Additionally, users were required to have an average daily step count exceeding 10 steps. No exclusion criteria were applied. Subpopulation included users who reported Depression in the app. This study is based on an analysis of an existing database already collected in the digital platform. All data were anonymized before extraction for this study. Ethical and Independent Review Services, a professional review board, issued the institutional review board exemption for this study (18032-06#) (40).

2.4 Study design

We applied a retrospective longitudinal cohort study design utilizing a database containing previously recorded follow-up data from the Dario Health users.

2.5 Statistical analysis

In this study, we used a mediation model based on a mixed model framework to infer quasi-causal relationships between depression status and BG levels through walking activity. To ensure the robustness of our findings, we carefully controlled for potential confounding variables and considered the temporal relationships among the variables.

Firstly, we identified and included relevant confounding variables in the mediation model, such as age, gender, diabetes type, diabetes duration, insulin treatment, and weight. By including these confounders, we aimed to isolate the specific pathways through which depression status may affect BG levels.

Secondly, our mediation analysis uses longitudinal data to account for temporal relationships. By analyzing data collected at multiple time points, we were able to establish the temporal sequence of events, which is crucial for causal inference using 1 month lag in the measures of walking activity and BG levels. This approach helps to ensure that the mediator precedes the outcome, thereby supporting the causal interpretation of the mediation effects.

Furthermore, we used sensitivity analyses to assess the robustness of our mediation findings, exploring the mediation effect across various time points. The results of these sensitivity analyses suggested that our mediation model is stable over time, further strengthening our causal inferences.

Overall, by controlling for relevant confounders, considering temporal relationships, and conducting sensitivity analyses, we aimed to ensure the validity and reliability of our mediation analysis and the quasi-causal inferences drawn from our study.

Here, we applied the following models: (a) examining the effect of depression status on the monthly average number of steps; and (b) examining the association between monthly average number of steps a day and 1-month lagged monthly average blood glucose, conditioned on the depression status. The mediation effect was defined as the a*b and statistical inferences were made based on the approach described above. The mediation effect was tested using a quasi-Bayesian–Monte Carlo method with 5,000 simulations. A quasi-Bayesian–Monte Carlo method for testing the mediation effect is particularly suited for longitudinal data due to its ability to incorporate prior information and handle complex data structures. This method involves generating random samples from the posterior distribution of the mediation effect through Monte Carlo simulations, allowing for accurate estimation of the mediation effects while accounting for uncertainties and potential biases.

The quasi-Bayesian–Monte Carlo method offers several advantages:

1. It effectively deals with the longitudinal nature of the data, allowing for time-varying exposures and mediators. For example, Mittinty and Vansteelandt (2020) demonstrated the robustness of Bayesian methods to unmeasured confounding in longitudinal mediation analysis (41).
2. The Bayesian approach allows us to incorporate prior knowledge into the analysis, improving the robustness and interpretability of the estimates. Studies like those by Gao and Albert (2019) have shown the advantages of Bayesian methods in handling complex data structures for longitudinal mediation models (42).
3. The Monte Carlo simulations provide accurate approximations of the mediation effects and their uncertainties, even with complex models and data distributions. Vansteelandt et al. (2019) successfully applied Bayesian dynamic mediation analysis to account for time-varying exposures and mediators, supporting the method's suitability for longitudinal studies (43).

Furthermore, a sensitivity analysis to the mediation effect was performed to evaluate stability in time. We used moderated mediation models assuming fluctuations of the mediation effect over time by adding interaction effects between time and depression. We first tested whether the association between depression and monthly average number of steps varied across time. Then we tested whether the previous month's average number of steps is associated with the monthly average BG across time, conditioned on the depression effect modulated by time. Finally, we tested the mediation effects at specific time points: months 2, 5, 10 and 12.

A classic linear longitudinal model assumes a single-slope growth pattern for changes in an outcome variable across time. In contrast, piecewise-based mixed-effects models allow for the modeling of variable change trajectories across time, accommodating potential non-linear relationships between walking activity and blood glucose levels. Here, a piecewise linear mixed effects model was applied to model the trajectories of monthly average BG levels and monthly average number of steps a day over a year among users with and without depression.

The monthly average number of steps was distributed right skewed; therefore, a log transformation was applied to fit the models' assumptions. In the field of physical activity, outcome variables are often count variables (a non-negative integer) and therefore are commonly positively skewed (44). When fitting a linear mixed-effects model, assuming a normal distribution for this type of data can be problematic (45), as it does not match the characteristics of the model and may affect the interpretation and conclusions (44). Therefore, it is common to analyze this type of data on a transformed scale that yields an approximately normal distribution, and a log transformation is reported as the most popular due to its ease of use and interpretability (44, 45).

The threshold of 400 steps per day was selected based on a detailed exploratory data analysis, which included visualizing the relationship between average monthly steps and BG levels. The visualization revealed a noticeable inflection point at approximately 400 steps per day, beyond which the association between steps and BG levels appeared to change. This threshold was chosen to account for this observed non-linearity and to improve the model's ability to detect meaningful patterns in the data. Following a visualization of the association between monthly average steps and BG, the average steps were divided into 2 segments (<400 steps a day/>400 steps a day), assuming a change in BG levels at >400 steps a day. Overfitting is a condition that occurs when a model that shows a good fit for a specific data set then cannot be generalized to a new data. Therefore, the data set was randomly partitioned (by users) into 70% train set, which will actually be used to adjust the parameters of the models, and 30% test set which will be used to measure the predictive validity of the chosen model during the training.

3 Results

3.1 Users

In total, a group of 989 users were included in this analysis. The study cohort comprised 55% (546/989) of men, the average age was 62.5 (SD ±12.7) and average BMI was 32.5 (SD ±6.9). The average diabetes duration was 9.4 years (SD ±8.9). A total of 14% (140/989) of the users reported having depression, 82% (808/989) have T2D and 18% (181/989) have prediabetes. Of the users, 78% (771/989) reported not using insulin, 22% (216/989) reported using an insulin pen and only 2 users reported using an insulin pump.

3.2 Effect of depression on blood glucose levels and walking activity over time

Figure 2 demonstrates a similar time-associated behavior in the monthly average BG among users with and without depression yet the BG levels in the depression group are higher across the 12-month period.

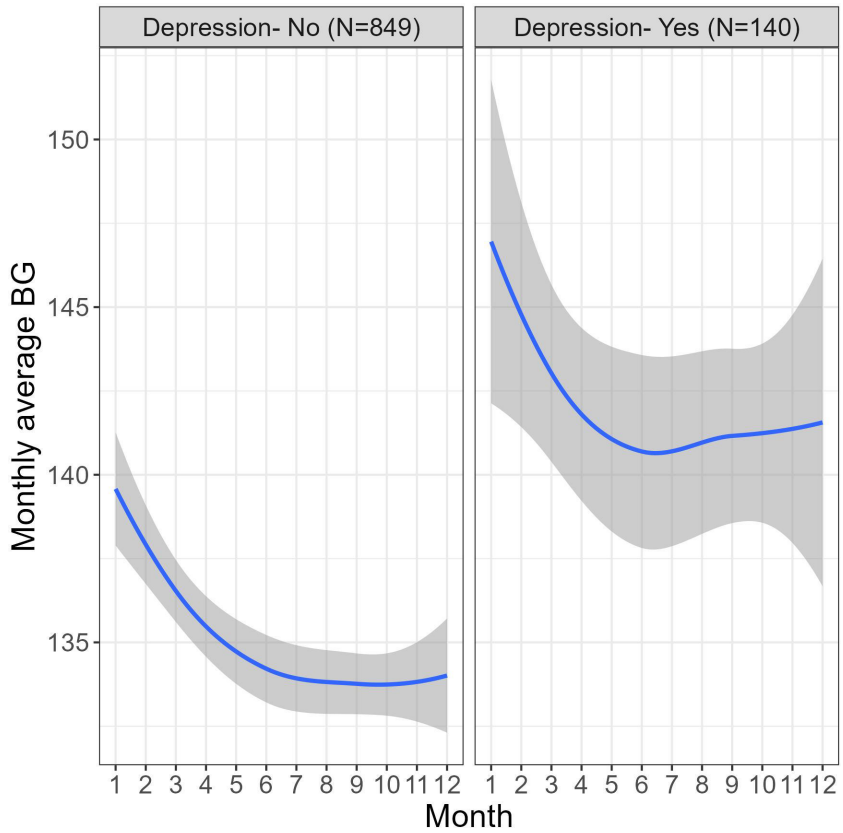

FIGURE 2
Differences in monthly average BG (mg/dL) fluctuations across 12 months of platform usage in users with and without depression.

Piecewise mixed model analysis was used to test the differences in the trajectories of the monthly average BG during two periods- 1-4 months and 4-12 months. A significant decrease in the BG levels was found during the first 4 months of platform usage (B=-1.83, 95% CI [-1.71, -1.06], P<.001), in months 4-12 there was no significant change in the BG levels (B=.00, 95% CI [-0.15, 0.15], P=.99). Fifty-nine percent of users showed significant overall decrease in their BG levels over the 12 months of platform usage (t(989) = –8.03, P<.001). Moreover, the ratio of users with monthly average BG below 117mg/dL (equivalent to A1c 5.7, indicating a cut-off of normal blood glucose levels (46)) increased by 33% over a year.

Also, a statistically significant association was found between the depression status and BG levels (B=8.00, 95% CI [1.93, 14.06], P=.01), meaning that users with depression have higher avg BG levels than users without depression over a 12-month period. The follow-up time did not moderate the effect, meaning that the trajectories of the monthly average BG in both periods were similar in both users with and without depression (months 1-4: B=-.39, 95% CI [-1.25, 0.46], P=.37 and months 4-12: B=.25, 95% CI [-0.16, 0.66], P=.23).

Another piecewise mixed model analysis was conducted to test the differences in the trajectories of the monthly average number of steps (following a natural log transformation) during two periods- 1-7 months and 7-12 months, in users with and without depression. Also, a statistically significant association was found between the depression status and monthly average number of steps (B=-.57, 95% CI [-0.78, -0.36], P<.001), meaning that users with depression have significantly lower average number of steps than users without depression over a 12-month period. A significant interaction effect was found between depression status and the first trajectory, 1-7 months (B=.03, 95% CI [0.01, 0.04], P<.001), the interaction between depression and the second trajectory, 7-12 months was insignificant (B=-.02, 95% CI [-0.04, 0.], P=.05). No significant changes in the monthly average number of steps were found during the first 7 months of platform usage (B=.00, 95% CI [-0.00, -0.01], P=.07), in months 7-12 a significant decrease was found (B=-.01, 95% CI [-0.02, -0.01], P=.001).

3.3 Mediating role of walking activity

The association between depression and monthly average number of steps was significant regarding the differences between the two groups (B=-.27, 95% CI [-0.44, -0.10], P<.005). Users with type 2 diabetes compared to users with prediabetes (B=-.17, 95% CI [-0.33, -0.01], P<.05) and those with insulin pens compared to those who do not use insulin (B=-.27, 95% CI [-0.42, -0.13], P<.001) had significantly lower monthly average number of steps, while users with insulin pumps did not have significant differences in monthly average number of steps (B=-.08, 95% CI [-1.35, 1.18], P=.90) compared to non-insulin users. In addition, a negative association was found between age (B=-.02, 95% CI [-0.03, -0.02], P<.001) diabetes duration (B=-.27, 95% CI [-0.42, -0.13], P<.001) and weight (B=-.01, 95% CI [-0.01, -0.01], P<.001) with the monthly average number of steps. It was also found that men had more monthly average number of steps compared to women (B=.61, 95% CI [0.49, 0.74], P<.001).

Adjusting for the previous months' average number of steps is negatively associated with the monthly average BG (B=-.82, 95% CI [-1.31, -0.32], P=.001), conditioned on the effect of the depression (B=2.73, 95% CI [-2.33, 7.79], P=.29) which was not significant. Users with type 2 diabetes compared to users with prediabetes (B=14.3, 95% CI [9.52, 19.04], P<.001) and users with insulin pens compared to non-insulin users (B=16.55, 95% CI [12.22, 20.88], P<.001) had significantly increased monthly average BG levels, while users with insulin pumps compared to non-insulin users did not have significant differences in monthly average BG (B=20.77, 95% CI [-17.06, 58.61], P=.28). In addition, it was found that diabetes duration (B=0.03, 95% CI [0.01, 0.05], P<.005) and weight (B=0.17, 95% CI [0.10, 0.25], P<.001) were associated with increased monthly average BG. Age and gender were not significantly related to monthly average BG (B=-.04, 95% CI [-0.20, 0.11], P=.59 and B=-3.26, 95% CI [-6.93, 0.40], P=.08, respectively).

Finally, the results of the mediation analysis demonstrated that there was a significant indirect effect of the depression status on the monthly average BG levels through the monthly average number of steps (M=.22, 95% CI [0.05, 0.45] P<.005) (Figure 3). The direct effect of depression status on the monthly average BG levels was insignificant (M=2.75, 95% CI [-2.2, 7.7], P=.29), indicating a full mediation.

Furthermore, a sensitivity analysis was conducted for the purpose of testing whether the mediation effect is stable over time. It was revealed that there was a significant indirect effect of the depression status on the monthly average BG levels through the monthly average number of steps at month 2 (M=.49, 95% CI [0.21, 0.82] P<.001); month 5 (M=.43, 95% CI [0.18, 0.74] P<.001); month 10 (M=.33, 95% CI [0.12, 0.61] P<.001) and month 12 (M=.29, 95% CI [0.09, 0.57] P<.005), stating that the mediation effect is stable over time.

3.4 The association of monthly average number of steps and monthly average blood glucose

Figure 4A demonstrates time-related fluctuations of the Z-transformed monthly average BG and monthly average number of steps, across 12 months of platform usage. Figure 4B visualizes the association between the monthly average BG with the monthly average number of steps. Piecewise mixed model analysis on the training data revealed a significant decrease in monthly average blood glucose for users with monthly average number of steps a day above 400 (B=-1.87, 95% CI [-3.17, -0.57], P<.01), while for users with monthly average number of steps a day less than 400 there were no significant changes in monthly average BG (B=.30, 95% CI [-0.24, 0.83], P=.28). Figure 5 demonstrates the nonlinear association between the variables and predictive values of the piecewise mixed model applied on the training and test dataset. Training and test data have a similar temporal pattern, especially regarding the change-point in the slope and our model reflects it. The slight differences at the first slope (below 400 steps a day) can be explained by high variability due to the limited amount of data.

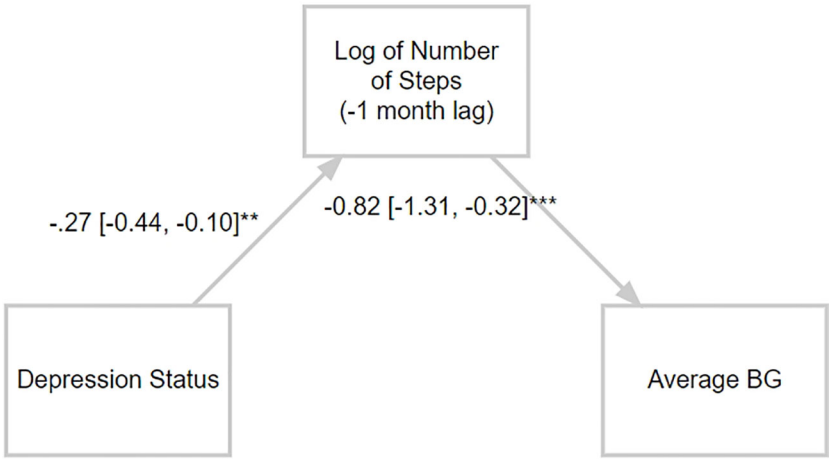

FIGURE 3
Mediation model. Self-reported depression is associated with the monthly average number of steps, which in turn predicts the following month's average BG levels. The monthly average number of steps fully mediates the association between self-reported depression and monthly average BG (mg/dL).

4 Discussion

Our analysis sheds light on the effect of self-reported depression status on BG levels over time. As shown in Figure 2, the monthly average BG levels were consistently higher in users with self-reported depression compared to those without. The ratio of people with depression in this study is 14% reflecting how the high prevalence of depressive disorders in people with diabetes, which ranges from 10% to 15% and is approximately twice as high as the prevalence of depression in people without diabetes (47–49). The piecewise-based model indicated that during the short-term adoption phase, while both users with depression and without depression show declines in average blood glucose levels, users who reported depression exhibited higher average BG levels compared to those without depression. In both cases we observed a significant decrease in BG levels during the initial 4 months of platform usage, followed by a stable period during months 4-12 of the monitoring. This finding underscores the importance of considering mental health factors in diabetes and prediabetes management. As with most chronic diseases, many factors contribute to the occurrence and treatment of diabetes, including depressive conditions (50).

Depression may contribute to poorer glycemic levels and necessitate tailored interventions to address both physical and psychological health needs (51–53). People living with diabetes and depressive disorders are at increased risk for earlier all-cause

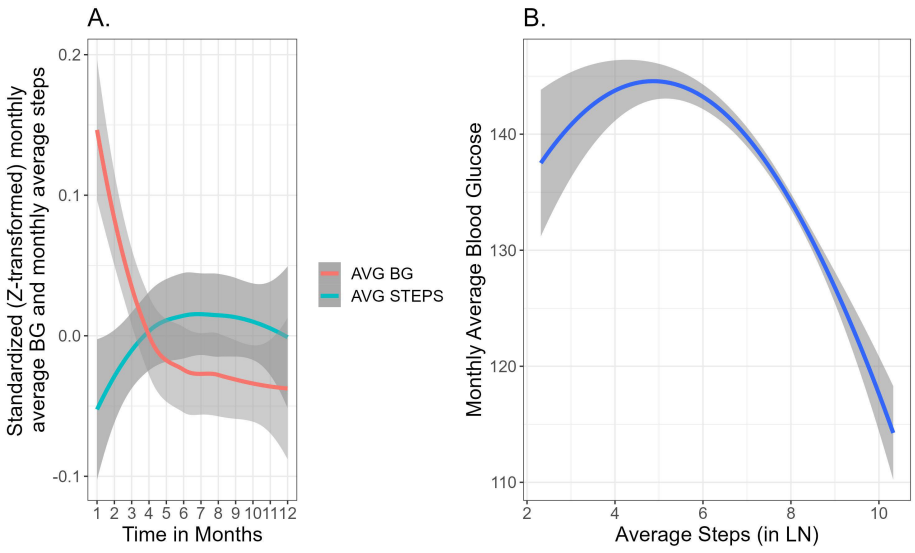

FIGURE 4
(A) Smoothed Standardized (Z-transformed) fluctuation of the monthly average BG and monthly average steps across 12 months of platform usage. Grey area represents 95% confidence intervals **(B)** Visualizes the association between the monthly average BG and monthly average steps a day (following a log transformation). The grey area around the lines represents 95% confidence intervals.

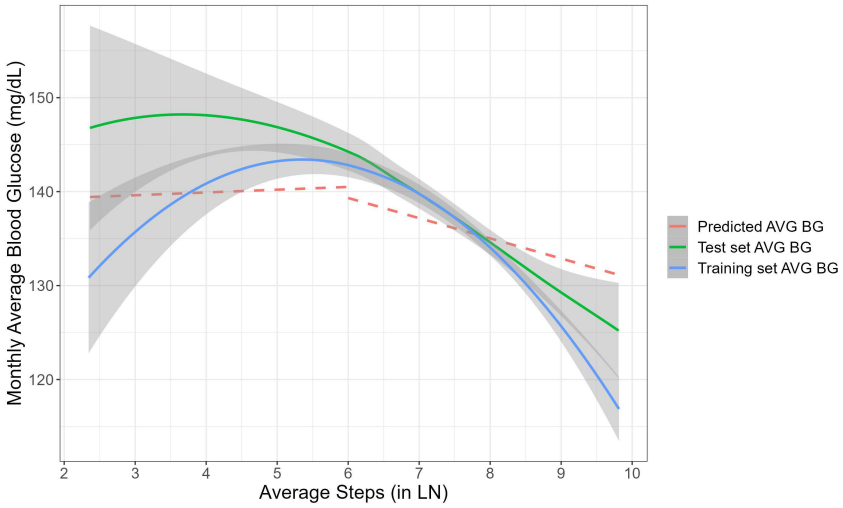

FIGURE 5
The non-linear association between the monthly average number of steps to the monthly average BG. Blue and green lines represent smoothing association between the variables for the training and test datasets. The grey area around each curve represents 95% confidence intervals. The red line shows the predictive piecewise mixed model applied on the test dataset.

mortality compared to people living with diabetes without a history of depression (54, 55). Digital well-being interventions have the potential to mitigate prevalent barriers to psychological support in both non-clinical and clinical populations, including cost, stigma, and accessibility challenges (56, 57).

While depression can worsen diabetes outcomes by hindering self-care behaviors and increasing the risk of complications, having T2D might also contribute to the development of depression. Individuals with either type 1 or type 2 diabetes have a higher risk of developing depression and depressed people have a greater chance of developing type 2 diabetes (49, 58). Furthermore, the study found that the monthly average number of steps significantly mediated the effect of self-reported depression status on the following month's average BG levels. The mediation effect reveals compelling insights into the complex interplay between depression, physical activity (measured by monthly average number of steps), and BG levels among individuals with diabetes or prediabetes and depression (Figure 3).

While there is a potential bidirectional relationship between depression and type 2 diabetes, the steps were not analyzed for their mediating effect on BG levels influencing depression levels in the following month. This analysis provides valuable insights into the mechanisms through which depression influences BG levels, highlighting the role of physical activity as a potential mediator. By promoting physical activity, interventions targeting depression may indirectly impact BG levels and improve diabetes management outcomes. Including both diabetes and prediabetes populations in a study analyzing the mediating role of walking activity in depression impacting blood glucose levels offers a beneficial factor. Prediabetes represents a stage where individuals have higher than normal blood glucose levels but not high enough to be classified as diabetes. Studying both prediabetes and diabetes allows us to examine the continuum of glucose metabolism. This holistic approach can provide insights into how early interventions (like physical activity) may impact blood glucose levels across different stages, potentially influencing preventive strategies for diabetes (59, 60). Moreover, individuals with prediabetes often share similar risk factors with those diagnosed with diabetes. Studying both populations together provides better understanding of common pathways linking depression, physical activity (such as walking), and blood glucose levels. This knowledge can aid in risk stratification and personalized interventions to prevent diabetes progression (61, 62). Individuals with diabetes and prediabetes frequently experience comorbidities such as depression, which can significantly impact their overall health outcomes. Analyzing the mediating role of walking activity in depression across both populations can inform integrated health management strategies that address mental health, physical activity, and glucose control simultaneously.

Firstly, the study identified a significant association between self-reported depression and the monthly average number of steps. This highlights the impact of depression on physical activity levels, suggesting that individuals with depression may engage in fewer steps compared to those without depression. This finding aligns with existing literature linking depression to decreased physical activity and highlights the importance of addressing mental health issues in promoting an active lifestyle among individuals with diabetes (63, 64).

Secondly, the analysis revealed a negative association between previous month physical activity and monthly average BG levels, conditioned on the effect of depression. This suggests that higher levels of physical activity are associated with lower BG levels underscoring the importance of regular exercise and walking activity as a key component of diabetes management that contributes to improved glycemic outcomes and overall health outcomes (65). Addressing the non-constant variance and the asymmetric error bars (Figure 4, 5), we applied mixed-effects models which inherently indicate heteroscedasticity by modeling the variance structure at multiple levels simultaneously (66). They

accommodate varying levels of variability across groups or conditions by estimating both fixed effects (mean structure) and random effects (variance structure) jointly. This approach provides valid estimates even when there are unequal variances across different groups or conditions (e.g. time points), ensuring robustness against heteroscedasticity in the data. Additionally, the non-constant variability between time points is also related to the fewer data points collected at certain time intervals, which can lead to increased variability in those estimates.

Indeed, experimental evidence has shown the effectiveness of mobile phone–based physical activity program on depression symptoms, through improvement of accessibility and encouragement of participation (67). Physical activity and exercise offer an effective alternative for treating depression by inducing interdependent changes in the brain, which foster a protective environment against depressive symptoms (68, 69). Moreover, the sensitivity analysis conducted to test the stability of the mediation effect over time revealed consistent findings. The moderated mediation model suggested that the mediation effect of physical activity on the relationship between self-reported depression and BG levels remains stable across various time points. This implies that the beneficial effects of physical activity on glycemic management persist over time. Physical activity is a key component of the therapeutic approach for people with diabetes (70). Regular involvement of individuals with diabetes in exercise programs could become a potential way to improve their quality of life reducing the economic expenditure for diabetes treatment and reducing complications that result from it (70, 71). Elevated physical activity and improved physical fitness have been shown to alleviate symptoms of depression and enhance health-related quality of life among individuals diagnosed with type 2 diabetes (72). This study highlights how management of physical activity with digital steps count targeting improved glycemia may work synergistically to enhance glycemic management and overall well-being and mental health in individuals with diabetes.

The presented results offer valuable insights into the dynamic relationship between physical activity, represented by monthly average number of steps, and improved glycemia, as reflected in the monthly average BG levels among users with diabetes. Previous research assumed this association to be linear, relying on limited sample size data (73) or real-life data with limited follow-up period (73, 74). The present study relied on a real-world larger sample size showing the negative association between monthly average BG levels and the monthly average number of steps exceeding 400 steps a day. This suggests a beneficial effect of higher levels of physical activity on blood sugar management, wherein increased step counts are associated with improved blood glucose levels. Conversely, no significant changes in the monthly average BG were observed among users with a monthly average number of less than 400 steps a day. This divergence in outcomes underscores the importance of achieving a certain threshold of physical activity to elicit favorable effects on blood glucose levels. The temporal patterns observed in both the training and test data, particularly regarding the change-point in the slope, indicate consistency and reliability in the model's predictive capacity.

These findings hold significant clinical implications, emphasizing the pivotal role of physical activity in diabetes management. Healthcare providers should consider incorporating walking programs into routine diabetes care, particularly for patients with comorbid depression, to enhance both mental and physical health outcomes. Encouraging individuals to engage in performance and digital tracking of regular physical activity and, aiming to surpass the identified threshold of 400 steps a day may confer tangible benefits in terms of improved blood glucose levels for both depressed and non-depressed users. The non-linear effect that was tested revealed the minimum level of daily steps for a significant effect in blood glucose in population with average BMI of 32.5 (SD ±6.9) (Figure 5). Previous studies have published recommendations for daily steps accumulation that resulted in decreased blood glucose as well as systolic blood pressure in overweight population (75). Furthermore, the nonlinear nature of the association underscores the importance of personalized interventions tailored to individual activity levels and needs. Future research should investigate the impact of different speeds, durations, and rhythms of walking activity on blood glucose levels to enhance our understanding and application of mediation models and personalized behavioral interventions.

4.1 Limitations

As in all studies involving retrospective real-world data, groups were not randomly assigned, and treatment protocols were not prescribed. In addition, users who actively engaged with the Dario platform and consistently measured their blood glucose levels for a year likely represent a more motivated and engaged group compared to the general population of individuals with diabetes. This could limit the generalizability of the findings. Our analysis did not fully control for potential confounding factors such as socio-economic status and other lifestyle variables, which could have influenced both the likelihood of engaging with the Dario platform and the observed health outcomes. However, we included potential confounding factors collected on the platform in our model, such as age, gender, diabetes type, diabetes duration, insulin treatment, and weight. In this study, we relied on self-reported data regarding users' comorbid conditions, specifically depression. While self-reporting is a common practical method in many observational and digital health studies, assessing depression solely through self-reporting without a clinically validated survey, has its limitations and may introduce misclassification bias. Nevertheless, studies have shown that self-reported diagnoses of depression are generally reliable (76–78). Though self-report measures should not replace in-person clinical evaluations, they can offer valuable supplemental information in a clinical setting and are likely to be increasingly utilized in the future (79). Moreover, the data collected in the study may not fully represent all patients with depression, and the timeliness of self-reporting can also vary. Nevertheless, for all users included in the analysis, we gathered self-reported medical data, including comorbid conditions such as depression, by having users select from a dropdown list of comorbidities.

In addition, there is a lack of information on whether users were taking antidepressant and antidiabetic medications. Future studies should incorporate clinically validated depression assessments and consider medication use to provide a more comprehensive

understanding. There may be other physical activities besides walking that influence blood glucose levels and are not accounted for in the study. In addition, steps were synced weekly, daily activity levels were not fully captured in the analysis. We addressed this limitation by focusing on active users who consistently measured their blood glucose every week for a full year, their steps were consistently recorded on the platform and analyzed alongside blood glucose levels. Steps were synced to the platform weekly whenever the app was opened. It is certainly possible that people who chose to use pedometer and complete medical profile in the app were those who were the most motivated to change. Our inclusion criteria were designed to ensure that all participants in the analysis demonstrated commitment to managing their diabetes. This was evidenced by their consistent weekly blood glucose measurements throughout the 12-month study period, allowing for comprehensive analysis.

4.2 Conclusion

In conclusion, these findings emphasize the dynamic nature of BG management over time and highlight the importance of early intervention and ongoing support in diabetes management. Additionally, our findings underscore the importance of integrating physical activity, such as walking, into diabetes management protocols to improve both glycemic control and mental health in individuals with T2D and prediabetes. Further research is warranted to explore the neurophysiological mechanisms underlying the relationship between depression and glycemia and to develop targeted interventions aimed at improving health outcomes in this population. Future research could explore the effectiveness of integrated interventions targeting depression and physical activity in improving diabetes outcomes and long-term health trajectories.

Data availability statement

The datasets generated during and/or analyzed during this study are not publicly available due to company privacy policy but are available from the corresponding author on reasonable request according to the subject to company policies. Requests to access the datasets should be directed to yifat@dariohealth.com.

Ethics statement

This study is based on an analysis of an existing database already collected in the digital platform. All data were anonymized before extraction for this study. Ethical and Independent Review Services, a professional review board, issued the institutional review board exemption for this study: Ethical & Independent Review Services (E&I) part of the Salus IRB organization. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YF-H: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. IB: Formal analysis, Methodology, Validation, Visualization, Writing – original draft. HK: Data curation, Formal analysis, Visualization, Writing – review & editing. SR: Data curation, Formal analysis, Visualization, Writing – review & editing. MR: Conceptualization, Writing – review & editing. DH: Conceptualization, Writing – review & editing. OM: Writing – review & editing. PG: Conceptualization, Investigation, Methodology, Writing – review & editing.

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Conflict of interest

YF-H, IB, and OM are employees at Dario Health. MR and DH serve as Dario Health scientific advisory board members. PG has received a consulting fee to assist with analyses but otherwise has no conflict of interest.

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

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Different intensities of aerobic training for patients with type 2 diabetes mellitus and knee osteoarthritis: a randomized controlled trial

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Objective: The purpose of this study was to compare different intensities of aerobic exercise for patients with knee osteoarthritis (KOA) and type 2 diabetes mellitus (T2DM) in terms of glycemic control, pain relief, and functional outcomes.

Methods: A prospective randomized open-label parallel multicenter clinical trial conducted at two hospitals in Shanghai and Sichuan that included 228 patients with type 2 diabetes mellitus (T2DM) and knee osteoarthritis (KOA). Enrollment occurred between January 2021 and February 2023, and follow-up was completed in September 2023. Participants were randomized to threshold training/high-intensive stationary cycling training (n=76), intensive endurance/moderate-intensive stationary cycling training (n=77), and regular rehabilitation programs (n=75). The primary outcome at the 6-month follow-up was the HbA1c level. Key secondary outcomes included the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscale of pain and quality of life.

Results: Of 228 patients, 212 (93%) completed the trial. The mean adjusted (sex, baseline BMI, and baseline outcome measures) HbA1c level at the 6-month follow-up decreased significantly in the high-intensive training group compared with other groups (high-intensity group vs. control group; difference, 0.51%, 95% confidence interval, 0.05% to 1.15%). Mean KOOS subscales of pain and quality of life were statistically significantly different between the control group and moderate-intensity or high-intensity groups, but no statistical differences were noted between the different intensities of aerobic exercise. Patients in all groups achieved a greater reduction in BMI but no significant differences were observed between groups.

Conclusion: In KOA and T2DM patients, high-intensity stationary cycling can significantly improve glycemic control compared with moderate-intensity and regular rehabilitation programs. However, high-intensity stationary cycling does not exert a superior effect on pain relief and functional improvement for KOA compared with moderate-intensity and regular rehabilitation programs.

KEYWORDS

aerobic training, type 2 diabetes mellitus, knee osteoarthritis, KOOS, HbA1c

Introduction

Multimorbidity is a rising public health challenge with important implications for health management and policy. The most common multimorbidity pattern is the combination of cardiometabolic and osteoarticular diseases, exemplified by the highly prevalent co-occurrence of type 2 diabetes mellitus (T2DM) and osteoarthritis (1). The relationship between T2DM and knee osteoarthritis (KOA) has garnered attention due to the overlapping prevalence and shared risk factors, such as obesity and advanced aging. Research indicates a significant association between T2DM and KOA. A study that included populations with type 1 DM (T1DM) and T2DM observed a notably higher association of KOA with T2DM, with an odds ratio (OR) suggesting a more than double likelihood of individuals with T2DM developing KOA compared with those without T2DM. Interestingly, this association was stronger among non-obese individuals, highlighting the potential impact of diabetes beyond the effects of obesity alone (2). There were other studies that collectively underscored the significant correlation between T2DM and KOA, suggesting that the mechanisms linking these conditions go beyond simple risk factors like obesity (3, 4).

Exercise is considered a cornerstone of treatment for T2DM alongside diet and medication of proven efficacy (5, 6). Although the effectiveness of exercise in improving glycemic control, blood lipid profiles, and other outcomes in this group is well documented (7–9), there is less certainty about the relative effects of different types of exercise. Aerobic exercise is traditionally the most studied exercise (8) and recruits large groups of muscles and includes brisk walking, cycling, swimming, and jogging.

For KOA, the most common form of aerobic land-based exercise found in the literature was stationary bicycle (10), as it is a low weight bearing and non-impact form of physical activity. It has been shown that stationary cycling performed over 10 to 12 weeks leads to a reduction in knee pain and stiffness, and an improvement in walking speed and distance in individuals with KOA (11, 12). Positive benefits of rehabilitation caused by cycling could be attributed to improvements in leg muscular power output and the dynamic range of motion (13). For individuals with KOA, both low- and high-intensity cycling are reported to be therapeutically beneficial (11, 12).

Patients with both KOA and T2DM present unique pathophysiological challenges. KOA leads to joint pain and reduced mobility, making exercise more difficult, and T2DM requires effective glycemic control, which is often achieved through physical activity. Understanding the appropriate exercise intensity can help tailor interventions that effectively manage both conditions without exacerbating either.

Exercise is a cornerstone in the management of both KOA and T2DM (14–17). However, the optimal intensity of aerobic exercise that maximizes benefits for both conditions simultaneously is not well-established. Research in this area could identify exercise protocols that improve joint function, reduce pain, and enhance insulin sensitivity, leading to better overall health outcomes (14–17). In addition, incorrect exercise intensity may lead to increased joint pain or injury in KOA patients or inadequate glycemic control in T2DM patients. Establishing evidence-based guidelines for aerobic exercise intensity can prevent these adverse effects, ensuring that exercise regimens are safe and effective.

To our knowledge, no studies have examined the intensity of aerobic exercise in patients with multimorbidity of both KOA and T2DM. The purpose of this study was to compare different intensities of aerobic exercise for patients with KOA and T2DM in terms of glycemic control, pain relief, and functional outcomes.

Methods

Study design

This is a prospective randomized open-label parallel multicenter clinical trial. Eligible participants were recruited from the Shanghai Sixth People's Hospital Affiliated to the Shanghai Jiao Tong University School of Medicine, Deyang Hospital Affiliated to the Chengdu University of Traditional Chinese Medicine, and Fuzhou Second General Hospital and were divided into the intervention group and the control group. The allocation ratio was 1:1:1 (two intervention groups and one control group). This

trial was registered at chictr.org.cn before participants were recruited (ChiCTR2100042872) and was approved by the Institutional Review Board of the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine [IRB No: 2019-KY-063(K)]. Other trial sites acknowledged the approval. All participants provided written informed consents.

Study participants

KOA was confirmed according to the criteria from the National Institute for Health and Clinical Excellence (18): patients can be diagnosed with KOA if they are 45 years or older, have movement-related joint pain, and either no morning knee stiffness or stiffness of 30 min or less.

The definition of type 2 diabetes in the present study was formulated according to the SUPREME-DM (19) criteria as follows: a) one or more of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes and Tenth Revision, Clinical Modification (ICD-10-CM) codes for type 2 diabetes associated with in-patient encounters; b) two or more ICD codes associated with outpatient encounters on different days within 2 years; c) a combination of two or more of the following associated with outpatient encounters on different days within 2 years: 1) ICD codes associated with outpatient encounters; 2) a fasting glucose level ≥126 mg/dl; 3) a 2-h glucose level ≥200 mg/dl; 4) random glucose ≥200 mg/dl; 5) HbA1c ≥6.5%; and 6) a prescription for an antidiabetic medication.

Interventions

The participants in the intervention group were instructed to undertake regular rehabilitation plus stationary cycling exercises every day for at least 30 min at different targeted heart rates. All participants in this study were asked to complete a graded exercise test (GXT) (19, 20) before the intervention. Submaximal anchor measurements were derived from the GXT result to prescribe exercise intensity. The submaximal anchor measurement model we used in this study included five exercise intensity levels (L1–L5) (20, 21) (Table 1). In this study, intensity levels 2 (extensive endurance/moderate-intensive group) and 3 (intensive endurance/high-intensive group) were used for our evaluation for patients with KOA and T2DM in terms of glycemic control, pain relief, and functional outcomes. For the control group, the participants were only instructed on regular rehabilitation. A professional healthcare group provided a comprehensive rehabilitation program to the participants in the intervention and control groups (Supplementary Figure 1). The rehabilitation program was delivered through a smartphone app (22–24) (device: Joymotion software, Shanghai Medmotion Medical Management Co., Ltd., Shanghai, China.), which provided participants with exercise instructions, feedback on their training performance, and real-time two-way video and audio interaction with the physical therapists (PTs). The app was installed by a technician on the day of the first visit. PTs at the rehabilitation center initiated the conference at the appointed time scheduled with the participants every week. The app provides daily rehabilitation exercises with detailed instructions and records the exercise completion rates. The rehabilitation program was prescribed by the supervising PTs and assigned to the participants as "daily tasks". The content of the rehabilitation program is illustrated in the Supplementary Table 1.

Outcomes

The primary outcome was the pre-post changes of HbA1c. The major secondary outcome was changes in the Knee Injury and Osteoarthritis Outcome Score (KOOS) from baseline. The KOOS is a patient-reported outcome measurement system used to evaluate short-term and long-term symptoms and function in individuals with knee injuries and osteoarthritis. The score consisted of five separately scored subscales: pain, symptoms, function in daily living (ADL), function in sport and recreation (Sport/Rec), and knee-related quality of life (QoL). The score ranges from 0 to 100 with 0 representing extreme problems and 100 representing no problems. Other secondary outcomes included changes in the body mass index (BMI).

Sample size

We aimed to detect a difference of 0.5% in HbA1c change from baseline to achieve an 80% power at a significance level of 0.05, and

TABLE 1 The five aerobic training levels based on the first and second lactate threshold (LT1/LT2) derived from a graded exercise test.

Aerobic training zone	Level 1 - recovery	Level 2 - extensive endurance	Level 3 - intensive endurance	Level 4 - threshold training	Level 5 - interval training
Heart rate (% of HRmax)	65–75%	75–80%	80–85%	85–92%	> 92%
Blood lactate (mmol.L^{-1})	< 2.0	2.0–2.5	2.5–3.5	3.5–5.0	> 5.0
Rating of perceived exertion (RPE) (6–20)	< 11	11–12	13–14	15–16	17–19
Relative to sub-maximal anchor	< LT1	LT1 < LT2	LT1 < LT2	> LT2	> LT2

Each level is characterized by a percentage of the maximum heart rate (% of HRmax), an absolute blood lactate value, a rating of perceived exertion, and the relationship with a submaximal anchor[15,16].

considering a 10% dropout rate, approximately 70 participants were required per arm.

Randomization, treatment, and follow-up

The participants were randomly assigned to the intervention and control groups in a 1:1:1 ratio. The randomization sequence was generated by the institutional staff and was concealed from the PTs during follow-up. Anthropometric and clinical data were collected from the participants at baseline and at the third and sixth months after the intervention; these data included sex, marital status, family income, use of a walking aid, BMI, and history of diseases and medications. Height and weight were measured using standardized methods. BMI was calculated as the weight in kilograms divided by the squared height in meters. Other data were collected from questionnaires.

The follow-up period lasted for 6 months. During the follow-up period, participants in the intervention group were instructed by Joymotion on how to carry out the rehabilitation program plus stationary cycling for at least 30 min every day. The PTs were directed to evaluate the methods and provide additional help to the participants to correct and improve their rehabilitation program based on the online platform provided by Joymotion. The timing of stationary cycling was also monitored and the records were requested to be uploaded. The participants in the control group only used Joymotion for the rehabilitation program without further instruction and demands with regard to the cycling training. The rehabilitation goal for all the participants in this trial was prespecified as a significant improvement in symptoms.

Blinding

No blinding was performed in this trial. Only the analyst who assessed the outcomes was blind to this trial.

Statistical analysis

The analysis was conducted according to the intention-to-treat principle, with multiple imputed data for participants with missing data under the assumption that data were randomly missing. Continuous outcomes were reported as the least squares means and standard errors. Mixed linear models for repeated measures adjusted for sex, age, and KL grade were employed to analyze the change from baseline, including participants as random effects, with fixed effect factors for the group and week, and the corresponding interaction. Sensitivity analyses were performed for the primary and key secondary outcomes at month 6 by repeating the primary analyses on the per-protocol population predefined as participants with satisfactory adherence and without major protocol deviations. The group differences between least squares means were reported with two-sided 95% confidence intervals (CIs), and a two-tailed $P < 0.05$ was defined as significant. False discovery rate correction was conducted for multiple testing. Counting data were reported as a percentage. Statistical significance was analyzed using a chi-square test, and $P < 0.05$ was defined as significant. All data were analyzed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the study participants

Of the 234 participants who underwent screening in this study, 228 were enrolled into the final analysis and randomized. Of these, 77 were in the intensive endurance/moderate-intensive group, 76 were in the threshold training/high-intensive group, and 75 were in the control group. Of these, 212 (93%) completed the full follow-up visits. Sixteen participants (five in the high-intensity group, five in the moderate-intensity group, and six in the control group) failed to complete the entire study due to unplanned surgery and injury (n=9) and reasons unrelated to the study (n=6) (Figure 1).

The baseline characteristics are shown in Table 2. The mean age was 61.5 ± 5.8 years. The mean BMI at baseline was 30.4 ± 4.5 kg/m^2.

Changes in HbA1c

Pre-post changes in HbA1c were significant at the 6-month follow-up in each group. Participants in the threshold training group achieved a significant decrease in HbA1c compared with participants in the intensive endurance group and control group (Table 3), exceeding the minimal clinically important difference of 0.5% (25).

Changes in the KOOS

A multivariate generalized linear model defined KOOS improvement as a dependent variable and the control group as the reference. After adjustments in age, gender, and KL grade, the results showed that the patients with high intensity were statistically significantly different between the control group and moderate-intensity group with regard to the pain subscale of the KOOS. In addition, patients in the moderate-intensity group showed statistically superior results to patients in the control group (Table 3).

The average changes in the KOOS QoL score from baseline to 6 months were 6.0 (95% CI, 3.9 to 8.0) in the high-intensity group, 4.7 (95% CI, 3.4 to 5.0) in the moderate-intensity group, and 2.5 (95% CI, 1.7 to 3.3) in the control group (Figure 2). The high-intensity and moderate-intensity groups exhibited significant improvements compared with the control group, as shown in Table 3. However, no significant inter-group difference was noted. Regarding other KOOS subscales (KOOS symptoms, KOOS ADL, and KOOS sport/Rec), patients undergoing high-intensity training (HIT) demonstrated significantly better outcomes than those in the control group. However, no significant differences were observed between the

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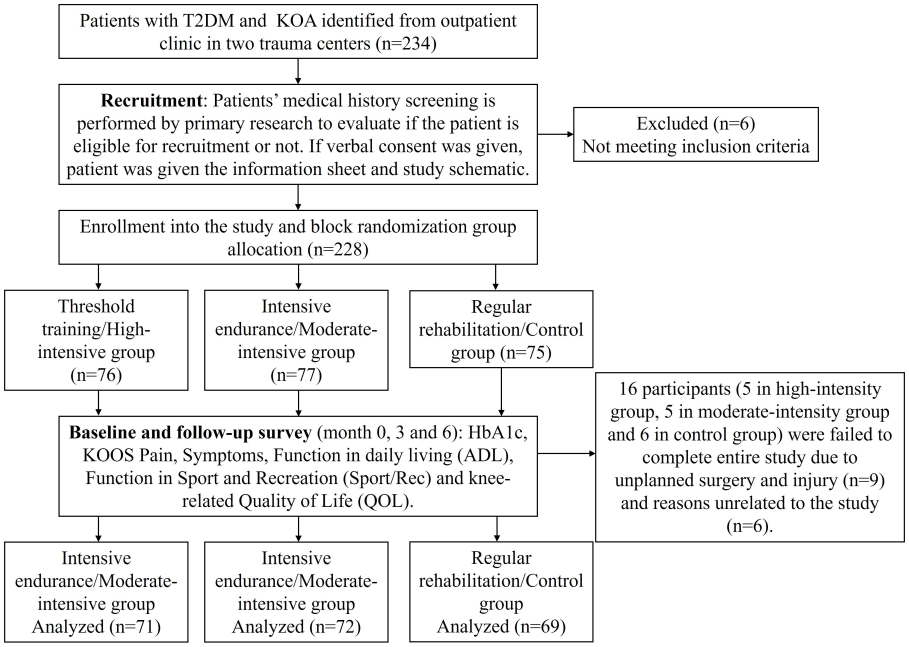

FIGURE 1
Flowchart of the study.

high-intensity and moderate-intensity groups (Table 3). Participants undertaking moderate-intensity stationary cycling exhibited similar results to those on the regular rehabilitation program with regard to KOOS symptoms, KOOS ADL, and KOOS sport/Rec.

Changes in BMI

Health outcomes are also presented in Table 3. Patients in all groups achieved a greater reduction in BMI but no significant differences were observed between groups.

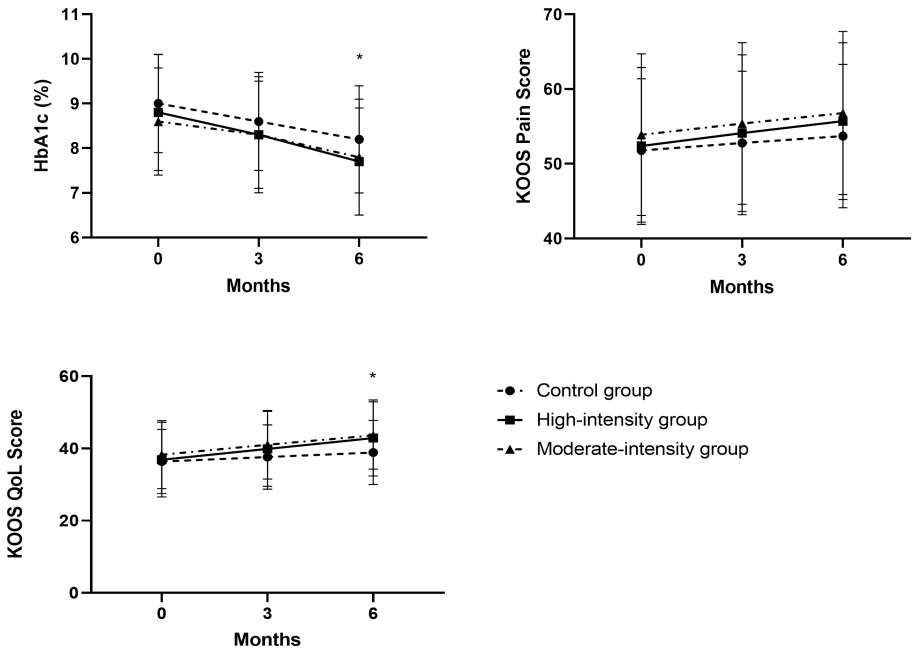

FIGURE 2
Trajectories of HbA1c and the KOOS subscales of pain and QoL in the PP population. For the KOOS subscales, high values represent better outcomes. Data points represent means at each follow-up time point (error bars indicate standard deviation). *$P < 0.05$. KOOS, Knee Injury and Osteoarthritis Outcome Score; PP, per protocol; QoL, quality of life.

TABLE 2 Demographic and clinical characteristics of the study participants at baseline.

Characteristics	High-intensity group (N=76)	Moderate-intensity group (N=77)	Control group (N=75)
Age (years), mean (SD)	61.4 (5.2)	61.7 (6.2)	61.2 (6.0)
Gender, male (%)	36 (48.0)	37 (48.7)	39 (50.6)
BMI (kg/m^2), mean (SD)	30.8 (4.3)	30.3 (5.0)	30.1 (4.2)
Obesity (BMI ≥30, %)	43 (57.3)	39 (51.3)	39 (50.6)
Education level			
≥ High school (%)	41 (54.7)	46 (60.5)	40 (51.9)
Insurance type (%)			
Government	60 (80.0)	58 (76.3)	61 (79.2)
Commercial	4 (5.3)	5 (6.6)	4 (5.2)
Self-financial	12 (14.7)	13 (17.1)	12 (15.6)
HbA1c level (%)	9.0 (1.1)	8.8 (1.3)	8.6 (1.2)
Comorbid illness* (%)			
Hypertension	52 (69.3)	47 (61.8)	51 (66.2)
Cardiovascular disease	14 (18.7)	16 (21.1)	13 (16.9)
Arthritis in other joints	16 (21.3)	18 (23.7)	17 (22.1)
Kellgren–Lawrence grade**			
2	35 (46.7)	36 (47.4)	37 (48.1)
3	32 (42.7)	27 (35.5)	29 (37.7)
4	8 (10.7)	13 (17.1)	11 (14.3)
Patellofemoral OA, severity 1,2 (mild-moderate)***	61 (81.3)	60 (78.9)	58 (75.3)
Paracetamol and NSAID (%)	53 (70.7)	57 (75.0)	56 (72.7)
Walking aid used	1 (1)	0	1 (1)

*Reported on a self-administered health history questionnaire (with the exception of patellofemoral OA) as conditions diagnosed by a health care professional. With comorbid illnesses that could exclude patients from participation, final approval or denial for participation provided after patient evaluation by a study physician.
**The Kellgren–Lawrence scale ranges from 0 to 4. A grade of 2 or greater indicates definite osteoarthritis on a posteroanterior weight-bearing radiograph. A grade of 2 indicates definite osteophytes and possible joint space narrowing; grade 3, multiple osteophytes, definite joint space narrowing, sclerosis, and possible bony deformity; and grade 4, large osteophytes, marked definite joint space narrowing, severe sclerosis, and definite bony deformity.
*** Patellofemoral OA measured from a skyline view radiograph using the OARSI scale (0, none; 1, mild; 2, moderate; 3, severe). Patients with severe (JSW, 3) patellofemoral OA were excluded. One patient was missing baseline skyline view radiographs.

TABLE 3 Primary, key secondary, and other outcomes at 6 months in the intention-to-treat population.

Outcome	High-intensity group (N=76)	Moderate-intensity group (N=77)	Control group (N=75)	Mean difference (95% CI)	*P* value
Primary outcomes					
HbA1c level					
6-month adjusted means from baseline (95% CI)*	1.13 (0.93, 1.33)	0.72 (0.50, 0.94)	0.61 (0.40, 0.83)		
High-intensity vs. control				0.51 (0.05, 1.15)	.01
High-intensity vs. moderate-intensity				0.38 (0.05, 0.74)	.04
Moderate-intensity vs. control				0.10 (-0.22, 0.43)	.10

(Continued)

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TABLE 3 Continued

Outcome	High-intensity group (N=76)	Moderate-intensity group (N=77)	Control group (N=75)	Mean difference (95% CI)	*P* value
Key secondary outcomes					
KOOS pain					
6-month adjusted means from baseline (95% CI)	3.3 (2.8, 3.8)	2.9 (2.0, 3.8)	1.6 (0.9, 2.3)		
High-intensity vs. control				1.7 (0.4 to 2.8)	.02
High-intensity vs. moderate-intensity				0.6 (-0.8 to 1.8)	.45
Moderate-intensity vs. control				1.3 (0.3 to 2.3)	.02
KOOS QoL					
6-month adjusted means from baseline (95% CI)	6.0 (3.9, 8.0)	4.7 (3.4, 5.0)	2.5 (1.7, 3.3)		
High-intensity vs. control				3.5 (1.0 to 6.0)	.01
High-intensity vs. moderate-intensity				1.2 (-0.7 to 3.0)	.48
Moderate-intensity vs. control				2.3 (0.1 to 4.5)	.04
Other secondary outcomes					
KOOS symptoms					
6-month adjusted means from baseline (95% CI)	7.9 (6.3, 9.5)	6.5 (4.7, 8.3)	5.1 (3.6, 6.6)		
High-intensity vs. control				2.8 (0.1 to 5.9)	.04
High-intensity vs. moderate-intensity				1.4 (-1.3 to 4.3)	.65
Moderate-intensity vs. control				1.4 (-1.7 to 4.5)	.79
KOOS ADL					
6-month adjusted means from baseline (95% CI)	13.6 (10.8, 16.4)	10.9 (8.3, 13.5)	8.7 (6.9, 10.5)		
High-intensity vs. control				4.9 (1.1 to 8.7)	.02
High-intensity vs. moderate-intensity				2.7 (-2.5 to 7.9)	.61
Moderate-intensity vs. control				2.2 (-2.0 to 6.4)	.85
KOOS sport/Rec					
6-month adjusted means from baseline (95% CI)	5.1 (3.7, 6.5)	3.6 (2.4 to 4.8)	2.2 (1.5 to 2.9)		
High-intensity vs. control				2.9 (0.8 to 5.0)	.02
High-intensity vs. moderate-intensity				1.5 (-1.0 to 4.0)	.79
Moderate-intensity vs. control				1.4 (-0.4 to 3.2)	.65
BMI					
6-month adjusted means from baseline (95% CI)	2.8 (1.9 to 3.7)	2.3 (1.5 to 3.1)	1.8 (1.1 to 2.5)		
High-intensity vs. control				1.0 (-0.4 to 2.4)	.63
High-intensity vs. moderate-intensity				0.5 (-0.9 to 1.9)	.70
Moderate-intensity vs. control				0.5 (-0.8 to 1.8)	.88

KOOS, Knee injury and Osteoarthritis Outcome Score; QoL, quality of life; Rec, recreation; ADL, ability of daily life.
Analyses were conducted to multiply imputed data for participants with missing data under the assumption that data were randomly missing.

Adverse events and other outcomes

During the follow-up, no adverse events were reported.

Discussion

Our randomized controlled trial involving T2DM patients indicated that stationary cycling improved the physical function of KOA, by improving muscle strength, compared with a regular rehabilitation program. Although participants in high-intensity stationary cycling had better functional results than participants in the control group, participants in different intensities of stationary cycling had similar results with regard to pain relief and functional improvement. We also found that high-intensity stationary cycling was more effective in glycemic control than moderate-intensity stationary cycling.

Osteoarthritis and T2DM are complex diseases influenced by genetic, demographic, and lifestyle factors, such as older age and obesity (26). Lifestyle intervention is considered a cornerstone in the treatment of osteoarthritis and T2DM (4–8, 10, 11). Among different types of lifestyle interventions, stationary cycling is primarily considered an aerobic activity. It involves continuous rhythmic movements of large muscle groups and is designed to improve cardiovascular fitness by increasing the heart rate and oxygen consumption over a sustained period. Additionally, it can help with muscle endurance in the lower body and does not add an extra burden on the knee joint. However, the standard for determining effective activity intensity remains controversial for patients with T2DM and KOA. In most studies of healthy individuals and diabetic populations, it is evident that a positive dose-response relationship exists between a higher exercise dose and improved physiologic changes, physical capacity, and performance (27, 28). In contrast, a different mechanism seems to be involved in patients with musculoskeletal pain, with previous studies showing inconsistent intensity-response relationships (29, 30).

Submaximal and maximal anchors have also been used in different models to define different training intensities (20, 31). The model we used in this study has five exercise intensity levels derived from GXT (19, 20). These levels can be further characterized by percentages of HRmax, blood lactate values, and ratings of perceived exertion (RPE) (Table 1). Participants were supposed to reach an 80–85% of HRmax and 85–92% of HRmax in two intervention groups, which resulted in a different effect of glycemic control in our study. In line with other studies, patients with a higher percentage of HRmax when participating in aerobic exercise had a better effect in glycemic control. In a previous systematic review by Umpierre et al., aerobic and resistance exercises decreased HbA1c by 0.73 and 0.57%, respectively (32). However, different intensities of aerobic exercise did not lead to different effects on pain relief or functional improvement in KOA in our study. There were some statistical differences favoring the high-intensity group in the domain of knee function at the end of the treatment and 3 months after intervention; however, none of these differences persisted at the 6-month follow-up. Notably, most variables numerically favored the high-intensity group, albeit not in a statistically or clinically meaningful way. Other reports have found similar results to our study with regard to the intensity-response relationships of aerobic training and KOA (33, 34).

Studies have shown that HIT increases insulin sensitivity and glycemic control through various mechanisms. For instance, HIT has been reported to improve muscle metabolic adaptations, regulate inflammation, and ameliorate lipid metabolism, all contributing to improved glucose homeostasis and insulin sensitivity (35–39). Additionally, although our study primarily focused on the short-term effects (6 months), it is essential to consider the potential long-term impact and safety of HIT, especially on joint health in KOA patients. Long-term HIT may lead to sustained improvements in insulin sensitivity but it is crucial to monitor for potential joint wear and injury risks. Thus, future studies should focus on the long-term adherence and safety of HIT programs in KOA patients to ensure they can benefit from the training without adverse effects.

Englund suggested that the modest benefits of exercise interventions for KOA could largely be attributed to the placebo effect, the disease's natural progression, and statistical regression to the mean (40). The considerable sample size and extended duration of the study likely heightened the placebo response, particularly regarding the subjective experience of pain (41). Additionally, the significant pain reduction observed in the control group might explain why there was no substantial difference between the high-intensity strength training group and the control group (41). Some authors considered the use of exercise treatment in chronic pain conditions should be viewed as a form cognitive therapy, in which the goal is to modulate the feeling of pain and thus patients' thoughts and feelings about it rather than increasing muscle strength and endurance (33, 41, 42). In a previous trial, placebo treatment matched the efficacy of exercise therapy[31]. Our study found no significant differences among high-intensity, moderate-intensity, and control groups over a 6-month intervention, possibly due to placebo effects increased by close supervision via an online platform. The attentive interaction between patients and the online platform may have overshadowed the expected dose-response benefits of exercise, which only became apparent when this direct attention ceased.

This study has several limitations. First, the results may be more generalizable to individuals who are comparable with the study sample, the majority of whom were men, obese, and had more than a high school education. Second, submaximal anchors have been used to define the domains of exercise, even though the majority of these methods have not been confirmed to elicit domain-specific physiological responses. Third, a trial with a larger sample size and long-term follow-up period is required to evaluate the effectiveness of exercise therapy in KOA and T2DM patients.

Conclusion

Among KOA and T2DM patients, high-intensity stationary cycling has a significantly greater glycemic control capability than

moderate-intensity stationary cycling and a regular rehabilitation program. However, high-intensity stationary cycling does not have a superior effect on pain relief and functional improvement in KOA compared with moderate-intensity stationary cycling and a regular rehabilitation program.

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 humans were approved by Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CS: Formal Analysis, Methodology, Software, Writing – original draft. LH: Data curation, Investigation, Methodology, Writing – original draft. ST: Supervision, Validation, Writing – review & editing. SL: Conceptualization, Project administration, Writing – review & editing.

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Conflict of interest

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

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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.2024.1463587/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Rehabilitation program.

SUPPLEMENTARY TABLE 1
Primary and key secondary outcomes at 6 months in the per-protocol population.

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The critical elements of digital health in diabetes and cardiometabolic care

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Digital innovations provide novel opportunities to individualize a person's care to best match their lifestyle needs and circumstances and to support them as they live their daily lives with diabetes. These innovations also serve to provide actionable data and insights for the care team giving them a "Webb telescope-like" view into their individual self-management journey, allowing them to see what cannot be seen during infrequent and limited office visits, thereby facilitating collaboration and communication to optimize the care plan on a timely basis. Technology advances are enabling diabetes care to transition from episodic, synchronous, primarily in-person care to include synchronous virtual care options and to continuous, on-demand, data-informed, asynchronous digital care better matching the demands of living with a relentless 24/7 chronic condition. In this paper we will discuss the critical elements and considerations in designing and implementing successful diabetes digital health tools in clinical practice.

KEYWORDS

diabetes, digital health, artificial intelligence, connected health, digital therapeutics, self-management, quintuple aim

1 Introduction

The rising global burden of diabetes and related cardiometabolic conditions (1, 2), combined with a worsening global shortage of healthcare professionals (3), necessitates new approaches to expand access to care, lessen the burden on individuals living with these conditions, improve efficiencies and reduce unsustainable medical costs. Diabetes is a condition that heavily relies on self-management on the part of individuals, requiring them to perform and track multiple daily tasks as outlined in the Association of Diabetes Care and Education Specialists' self-care behaviors framework (ADCES7 Self-Care Behaviors®). These behaviors include the management of medications, glucose, activity, diet, coping,

risk, and problem solving (4). As such, diabetes self-management can be complex and challenging; only about half of individuals diagnosed with diabetes meet the American Diabetes Association (ADA) treatment targets (5, 6). Each person may have unique physical characteristics, emotional concerns and environmental circumstances that could impact their ability and sometimes willingness to self-manage their condition (7). Digital innovations provide novel opportunities to individualize a person's care to best match their lifestyle needs and circumstances and to support them as they live their daily lives with diabetes. These innovations also serve to provide actionable data and insights for the care team giving them a view into their individual self-management journey, allowing them to see what otherwise cannot be seen during infrequent and limited office visits, thereby facilitating collaboration and communication to optimize the care plan on a timely basis.

Digital advancements enable going beyond the current and traditional glycemic-centric approach to diabetes care to address an expanded set of risk factors (hypertension, hyperlipidemia, obesity, sleep, cardiac function), which are collectively referred to as cardiometabolic health management. Digital health capabilities lend themselves well to the free-living, behavioral aspects of self-care as many of the challenges of managing complex cardiometabolic conditions, such as diabetes and obesity occur in daily life, not when the individual is with their clinical team. Having a common, ubiquitous personal device on hand, which also doubles as a coach for helping manage diabetes, and to track, measure, advise, connect to others, and to nudge toward better health behaviors just-in-time and right when needed, can better support individuals between healthcare encounters.

2 What is digital health?

The Food and Drug Administration (8) defines the broad scope of digital health including categories such as mobile health, health information technology, wearable devices, telehealth and telemedicine, and personalized medicine. This includes mobile medical apps, clinical decision support software, and artificial intelligence (AI). Digital technology has led to a revolution in health care and has the potential to help clinicians more accurately diagnose and treat disease and improve the health care experience for the individual. Digital health technologies use mobile computing platforms, connectivity, software, and health care sensors spanning a wide range of uses, from general wellness applications to technologies intended for use as a medical product, in a medical product, as companion diagnostics, or as an adjunct to other medical products [devices, drugs, and biologics] (8). A digital therapeutic is health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient's health. Digital therapeutics meet the following criteria: Incorporate design, manufacturing, and quality best practices; engage end users in product development and usability processes; incorporate patient privacy and security protections; apply product deployment, management, and maintenance best practices; publish trial results inclusive of clinically meaningful outcomes in peer-reviewed journals; are reviewed and cleared or certified by regulatory bodies as required to support product claims of risk, efficacy, and intended use; make claims appropriate to clinical evaluation and regulatory status; collect, analyze, and apply real-world evidence and/or product performance data (9).

3 How is healthcare evolving with connected technologies and digital health?

The availability of a growing variety of connected technologies such as continuous glucose monitoring systems (CGMs), blood pressure monitors, smart scales, digital stethoscopes, automated insulin delivery, connected insulin pens, and other digital health devices including consumer-facing fitness trackers are enabling individuals with diabetes to measure and self-manage their health directly using the data collected as they live their daily lives (10). Data aggregators such as Tidepool (Palo Alto, California, USA) and Glooko (Palo Alto, California, USA) can be used to integrate data from various sources for people with diabetes and their care team. The goal of AI-powered digital healthcare is to collect and analyze the various data generated by an individual person and to support them by providing software-driven personalized coaching and insights, but to implement this "n=1 solution" at scale and across diverse populations and geographies.

A vital element of success with digital health tools is strengthening the individual digital health user connection to their clinical care team. Digital health tools generate population- and person-level data, enabling healthcare teams to remotely monitor the health of populations more efficiently (11). With the increasing use of text messaging, regulated digital health apps, patient portals, digital social networks and video telehealth, it has become easier for clinicians to interact remotely with patients (12). A population health management approach that informs more effective and timely touchpoints with the clinical team when needed has the potential to help address health disparities and improve outcomes for individuals and populations (13). AI-powered digital health technology can be harnessed to realize practice efficiencies and to improve access to and effectiveness of care (7, 10, 11) as illustrated in Figure 1.

A public-private-industry partnership in the frontier state of Montana illustrated this concept. As part of a collaborative agreement between the Montana Diabetes Program (MDP) and the Centers for Disease Control (CDC), the MDP sought to identify opportunities to expand access and participation in diabetes self-management and education services (DSMES) across the large, mostly rural state. The goal was to explore and test innovative digital tools to eliminate barriers to participation and retention in underutilized DSMES services. The Montana Diabetes Digital Health Learning Network was formed as a collaborative project among the Montana public health department, Montana Coordinating Body of the ADCES, and Welldoc, a

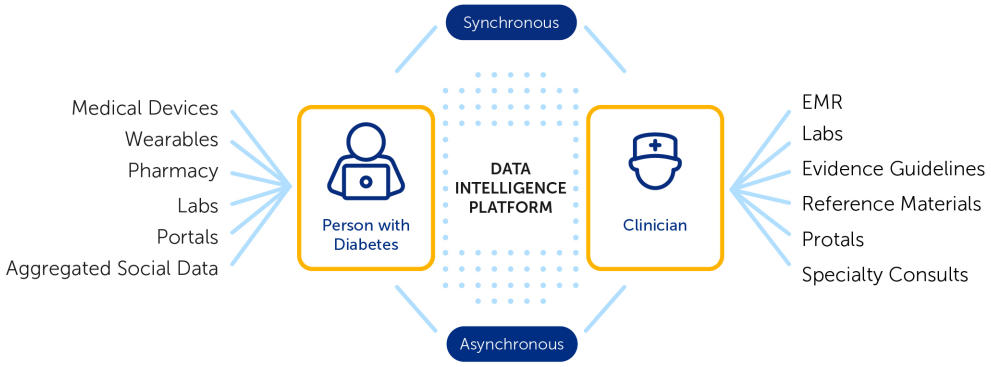

FIGURE 1
AI-Powered Digital Health Technology.

cardiometabolic digital health company. Eleven diabetes care and education specialists (DCESs) enrolled 198 patients with T1D or T2D in using the BlueStar® digital health solution per its associated indications for use. Engaged participants achieved improvements in glycemia, blood pressure and weight (14). The DCESs were able to extend their DSMES services remotely including automated digital self-management support and iteratively develop best practices for remote physiological monitoring and population management.

An umbrella review sought to identify the active ingredients and mechanisms of action of technology enabled solutions for diabetes care (15). Here we list the mechanisms of action for digital health and digital therapeutic solutions:

- Lifestyle or behavioral modification, particularly for diabetes and obesity but also with associated comorbidities in mind (hypertension and hyperlipidemia) and/or smoking cessation and physical activity recommendations.
- Therapeutics, both insulin-based therapies (basal and basal/bolus) and non-insulin agents
- Biometrics, either to monitor vital information and to track progress with an intervention (glucose, blood pressure, heart rate, weight, etc.)
- Safety, addressing hypoglycemia, side effects with incretin therapies, sick day management, diabetes ketoacidosis, pancreatitis, etc.

Diabetes care is transitioning from episodic, synchronous, primarily in-person care to include synchronous virtual care options and to continuous, on-demand, data-informed, asynchronous digital care better matching the demands of living with a relentless 24/7 chronic condition (10, 12). Many digital health solutions for diabetes provide live coaching on-demand for example, MySugr (Vienna, Austria) integrated with the Roche Diabetes Care Platform, Livongo by Teladoc Health (Purchase, New York, USA), Virta Health (San Francisco, California, USA) and Verily Onduo (San Francisco, California, USA). Others, such as the Welldoc application (Columbia, Maryland, USA) don't rely on live human-based coaching but rather, provide automated, scalable AI-powered coaching in real-time for individuals with integrated population-level and person-level data available to the care team, thus enabling remote monitoring and establishing criteria for clinical team intervention as needed. It is important to establish clear roles and responsibilities for clinical team members regarding who will receive, review and respond to population and person level data as digital-powered care models evolve.

Numerous challenges will need to be addressed as digital health advances. Expanding access to technology will require public-private partnerships to address the digital divide and technology literacy limitations. Additional clinical and economic evidence is needed to continue to demonstrate the value of digital health. Making digital health a mainstream aspect of care delivery requires significant buy-in from care teams and other healthcare stakeholders. To help build the case, leaders must outline digital health's benefits for all stakeholders, describe how to attain those benefits, and back up the claims with clinical and real-world evidence.

Workflow integration best practices are essential. Digital solutions must be seamless components of care delivery, and solutions should be incorporated into the workflow, so they don't create additional work or cause inefficiencies. The goal is to integrate digital health into mainstream care delivery, so it becomes as routine as in-person visits. Person-generated health data should be incorporated into the data view that care managers have access to so that they can address gaps in care, care transitions, and readmission and gain deeper insights into the health of their population. Engaging and activating individuals in their own health journeys demands a coordinated effort across extended-care teams, all of them working with the same data and understanding of a person's health status. Through digital health, people become more empowered to self-manage their health and wellness when they have more meaningful interactions with their own personal care team. For individuals reluctant to engage, healthcare organizations should establish and implement support programs that walk people through their initial experiences, offer clear assurances that data is adequately encrypted, and make clear that they own their own data. Optimal engagement starts with clear support from a person's own care team—through either a provider including a digital solution as part of the treatment plan or through a strong recommendation from a health plan care manager, a coach, a technology champion within the practice or a physician. Providing initial and ongoing

support in use of the digital tool configured to the user's care plan is essential as discussed later.

Building AI-enabled digital health capabilities is complex, requiring diligence in operationalizing extensive and diverse data sets, clinical evidence, data governance, interoperability and the use of a robust data intelligence platform that ensures privacy, security and scalable application in real-world settings. Good data governance ensures the mitigation of potential harm and helps to build and maintain public trust. The General Data Protection Regulation (GDPR) was instituted in 2018 providing comprehensive and robust data protection regulation across the globe. While GDPR addresses general personal data, the Health Insurance Portability and Accountability Act (HIPAA) enacted in the United States in 1996, focuses specifically on protecting medical information. HIPAA sets standards for the protection of health information and requires healthcare providers, insurers, and their business associates to implement strict data security measures. HIPAA compliance is critical for healthcare organizations to ensure the confidentiality, integrity, and availability of protected health information (PHI).

Additionally, payment models will need to be redesigned to accommodate digital health. This will require digital health companies to quantify how digital solutions can lower costs and improve efficacy compared with other modes of care delivery or in combination with other modalities.

4 Does digital health require regulatory oversight and need to be prescribed?

As noted above, the FDA acknowledges the wide span of digital health uses from general wellness applications to technologies intended for use as, in or as an adjunct to a medical product or therapy (8). Diabetes digital health solutions offering basal insulin dose titration such as the Tempo system by Lilly (Indianapolis, Indiana, USA) require regulation and are prescribed. Digital health applications such as Dreamed insulin decision support system (Petah Tikva, Israel) are provider facing and require both regulatory oversight and a prescription. In some cases digital health tools include functions requiring regulation and prescriptions as well as general health and wellness functions not requiring regulation or prescriptions. For example, in smart insulin pens, such as the InPen system by Medtronic (Northridge, CA, USA) and the Tempo system by Lilly (Indianapolis, Indiana, USA), the insulin dose calculator is regulated while dose reminders and dose tracking functions are not regulated. Other digital health solutions, such as the Welldoc application for cardiometabolic conditions (Columbia, Maryland, USA) include specific features that require a prescription and regulatory oversight, such as the rapid and basal insulin dose titration functionality, while other features, such as food and activity tracking and coaching, do not require either a prescription or regulatory review. Both are critical for success.

The product code used by the FDA for CGM-informed insulin bolus calculators has additional FDA requirements such as data simulation and clinical safety trials. A study to demonstrate the safety of a CGM-informed insulin bolus calculator that applies trend arrow and exercise adjustments to bolus insulin dose recommendations and provides real-time coaching found that use of the CGM-informed insulin bolus calculator by individuals with diabetes was associated with significant improvement in time-in-range (TIR; 70-180 mg/dL) without an increase in hypoglycemia or diabetes distress (16). Recently over-the-counter CGMs have been approved by the FDA offering sensor platforms with a limited set of functions to serve a broader scope of the population.

Real-world data analysis from connected insulin injection technologies is shining the spotlight on injection therapy revealing significant gaps and opportunities to improve care in this population (17). Visibility to dose data enables health care professionals to have a more complete picture of the pharmaco-adherence of insulin dosing informing the need to either address barriers to taking insulin as prescribed or making adjustments in the insulin plan (18). The paper logbook with its inaccuracies and omissions is being replaced with automated dose and glucose capture and data sharing. Smart insulin pens that objectively track active insulin are making it possible to calculate and deliver more frequent correction doses to safely improve glycemia without compromising time-below-range, thus changing the treatment paradigm for insulin injection therapy (17). A retrospective cohort analysis was conducted in 5,135 smart insulin pens users with either T1D or T2D, pediatric and adult, with their smart insulin pen paired with a personal CGM. Researchers used a rate-of-change detection methodology to identify meal events and timeliness of insulin doses. A dosing frequency of three or more times per day (including correction-only doses) and a missed dose frequency of less than 20% were associated with improved glycemia.

For further examples of digital health in diabetes care, readers are referred to an annual review of the literature highlighting key papers written in the prior year in which digital health technologies were used to provide digitally driven care for people with diabetes or prediabetes (10). For a thorough review of commercially available digital health solutions for diabetes the reader is referred to Doyle-Delgado and Chamberlain, 2020 (19).

5 What are the essential elements of digital health in diabetes care?

Successful diabetes digital health solutions keep the person in the center engaging and empowering them in their own care. Essential elements include:

5.1 Going beyond A1C

Digital health is not a substitute but rather, an amplifier of current standards, supporting various behaviors beyond glucose (the ADCES7 self-care behaviors (4) and bringing this data to life to drive "whole person care." In addition, there is an opportunity to go beyond the usual ABCs of diabetes (A1C, blood pressure, and

cholesterol [lipids]) by monitoring activity, sleep, weight, psychosocial wellness and social determinants of health such as food security, diabetes distress, and depression. Recognizing that many live with more than one chronic metabolic condition, digital health can bring an integrated holistic approach to self-management and care. For example, Welldoc reported results from a real-world study examining the use of a digital health tool with AI-coaching for people with diabetes enrolled in a virtual diabetes program. Of the 71 participants, 77% had significant weight loss (average weight loss was 4.8% of body weight). In addition, the participants enjoyed an average systolic blood pressure reduction of 7 mmHg (p=.01) (20).

5.2 Regulatory oversight

Higher risk digital health features must embrace evidence-based guidelines and deliver tailored interventions to people living with diabetes in a safe and effective manner. Thus, regulatory oversight is critical, to ensure a discipline and rigor for safety and efficacy, and also the implementation and management of good manufacturing processes, that support scalability, repeatability and traceability of quality and cybersecurity standards throughout the digital health lifecycle. Regulated digital health solutions can be combined and work together with general health and wellness digital health tools to provide a comprehensive solution. The digital health field continues to evolve as new technology capabilities and regulations are considered. As the digital health industry continues to develop, flexibility, safety & risk and real-world feasibility will need to be assessed in determining the appropriate regulatory oversight and integration into care.

5.3 Device integration and addressing the digital divide and technology literacy

Smartly engineered digital health takes advantage of hardware that people with diabetes already have and use. Digital health solutions engineered to work with existing hardware maximizes the return from dollars already invested and avoids the need to purchase and train individuals on new devices. The digital divide has been identified as a social determinant of health and will need to be addressed to expand digital health access and adoption (21). Well-designed digital health architectures can help address the digital divide and allow for use offline with episodic connectivity. Off-line use is of particular importance to ensure compliance with patient safety best practices. When setting up a new digital health tool account, providing SMS versus email account confirmation increases access to those without an email account. Manufacturers of CGMs should continue to offer the option of a standalone receiver versus needing to rely on a smartphone to expand access. Having a designated digital champion or technology navigator in the clinic can further help build efficiencies in technology onboarding and data accessibility. It will also be critical to build health technology literacy and confidence among those living with chronic conditions (13). In addition, makers of digital technologies need to consider how to meet the needs of those with low literacy or numeracy and sensory or motor impairment. As the population ages, there is growing evidence demonstrating the efficacy of diabetes technology for adults in their sixties, though data is limited for the oldest populations (22). ADA standards of care are now recommending AID systems (for those with T1D) and other advanced insulin delivery devices such as connected pens for older adults to reduce the risk of hypoglycemia (23).

5.4 Connected ecosystems and clinical integration for practice efficiency

Digital health gives visibility to population health data enabling remote monitoring capability, enabling true person-centered care for populations at scale (one-to-one to one-to-many). Digital health enables identifying who in the population needs a human touchpoint or nudge and then uses the person-level data to inform the interaction. Digital health provides the capability to segment the baseline population by various vectors enabling a more effective bottom-up vs. top-down approach to population health (i.e., people are heterogenous, and aggregated data is more meaningful at a population level). Digital health, if properly deployed, brings individuals and clinical teams together; visibility to data gives a window into the individual's self-management journey since the last encounter and facilitates meaningful conversations and care plan adjustments.

5.5 Increasing role of artificial intelligence

Artificial intelligence, defined as software that learns, is revolutionizing diabetes care by providing advanced tools for monitoring, personalized treatment, and early detection of complications. By combining AI with human expertise, diabetes management can be transformed and improve outcomes for people living with diabetes. AI allows translation of general guidelines into consistent personalized delivery at scale with healthcare team oversight. It drives the translation of data to information, to knowledge, to action and ultimately, to outcomes. Simply put, right person, right place, right time, right instruction. AI democratizes access to diabetes management best practices in a manner that fits into a person's "life-flow" and a healthcare provider's workflow. AI capabilities are continuing to advance and allow us to pivot from a generalized (one-size-fits-all) approach to care and from technology guided by rules or algorithms to provide precise, holistic therapy recommendations that address the needs of each individual. Generative AI will be able to analyze a patient's specific health data to provide tailored prevention recommendations, interpreting their data in the context of each person's health history and treatment plans. The current evidence-based medicine represents the tip of the iceberg providing barely enough shallow evidence to care for a generic

patient. To achieve the next-generation of deep evidence-based medicine, it will be necessary to gather and analyze all available data (natural history data, genomic, all published clinical studies, real-world data, and amassed data from Internet of medical things) (24).

AI is already being used in diabetes-cardometabolic care. CGMs use AI algorithms to analyze data from the devices to provide real-time insights into blood glucose trends and patterns. AI can predict high and low blood glucose events before they occur, allowing for timely interventions) (16). AI is being used in optimizing insulin pump therapy in the form of Automated Insulin Delivery (AID). AI is used to automatically adjust insulin delivery based on CGM readings, improving blood glucose management. Personalized treatment plans and decision support tools use AI-driven applications to provide personalized recommendations for insulin dosing, food and physical activity based on individual data. AI enhances telemedicine platforms by facilitating remote monitoring of person-level data, allowing healthcare providers to make informed decisions remotely. In the future AI, using advanced predictive analytics could predict the progression of diabetes and related complications, allowing for earlier and more precise interventions. AI models could assess individual risk factors and predict the likelihood of complications such as neuropathy, retinopathy, and cardiovascular disease. AI will be able to integrate data from various sources (CGMs, insulin pumps, wearables, electronic health records) to provide comprehensive and personalized care recommendations. AI systems could make real-time adjustments to treatment plans, including medication dosages and lifestyle changes, based on continuous data analysis. AI could provide personalized education and support, helping patients manage their condition more effectively through tailored advice and motivation. Chatbots and Virtual Assistants could offer 24/7 support, answering questions and providing guidance on diabetes management. AI will help accelerate the discovery of new medications and treatment options by analyzing vast amounts of data and identifying potential therapeutic targets. AI can also help to optimize clinical trial design and subject recruitment, making the process more efficient and inclusive.

Areas of attention in the application of AI in healthcare include data privacy and security. AI systems collect and process a large amount of personal health data, and can raise concerns about data privacy and security. Good security practices such as SOC2 and HiTrust certifications can help alleviate these concerns. Accuracy and reliability must be addressed. AI algorithms are not infallible and can make errors in predictions and recommendations. AI hallucinations are incorrect or misleading results that AI models generate. These errors can be caused by a variety of factors, including insufficient training data, incorrect assumptions made by the model, or biases in the data used to train the model. Using well-represented data sets and testing models for data drift over time can help increase accuracy and reliability of models. The accuracy of AI depends on the quality of data it is trained on. Incomplete or biased data can lead to inaccurate outcomes. Needless to say, garbage in will lead to garbage out. While AI can provide valuable support, it is essential to have human oversight to interpret and validate AI-driven recommendations. Over-reliance on AI tools may lead to reduced patient autonomy in managing their own health. Partnership with the clinical team will be critical. Additionally there are important ethical considerations (bias, fairness, toxicity). AI systems can perpetuate existing biases if not carefully designed and monitored, potentially leading to disparities in care. Statistical methods and tools exist for managing such considerations. Ensuring transparency in AI decision-making processes is essential for trust and accountability.

5.6 Addressing the quintuple aim

Digital health should strive to improve patient outcomes, provider satisfaction, healthcare costs and quality of healthcare, along with an emergent and important theme from the IHI Quintuple Aim, with the new 5th aim addressing health inequity (25). This is foundational for value and sustainability and will involve a shift in focus from a downstream, reactive, disease management approach to an upstream proactive, preventive approach. Health inequities are estimated to cost the U.S. healthcare system approximately $83 billion annually (25). With social determinants of health (SDOH) driving 70% of health outcomes (26), efficient ways to assess then address SDOH through linking to local community resources are needed and could include, for example, AI-enabled geo-location capabilities to identify local food banks for food-insecure individuals. In addition, many risk factors for disease, disease severity and disease progression including SDOH are captured in medical records by clinicians in the free text but rarely translate to what exists in the structured data. Natural Language Processing (NLP) capabilities can be used to efficiently scan this text and thus help clinicians and healthcare systems identify at-risk patients. At the same time, it is important to test digital health tools that use generative AI to assure freedom from unfairness and bias which could be unintentionally introduced during the AI model training process.

Even before the pandemic, many rural, vulnerable, and underserved populations were, for a variety of reasons, struggling to keep in-person clinic visits, but compromised care resulted because of lack of regular contact. During the pandemic, those populations have largely embraced remote interactions. In fact, there is growing evidence that digital health can be a cost-effective and powerful tool for such populations (27). Digital health provides the continuity of care required to manage chronic conditions by reaching people who might otherwise feel reluctant to seek care for a condition because of privacy and confidentiality concerns or because of the stigma still often associated with certain behavioral health conditions or social situations. Digital health can also serve as a bridge to populations that are ethnically and linguistically diverse —not only patients and their families but also their care teams.

It's widely accepted that better management of chronic illness depends on improved collaboration across the healthcare continuum. Digital health solutions can help by creating a single source of rich and readily accessible person-generated health data. Consider, for example, that with diet as a key factor in many chronic health conditions, healthcare entities are examining ways to

prescribe and get reimbursement for encouraging healthier eating, especially among underserved populations. For example, with a prescription, some regions are experimenting with providing low-income residents with food vouchers redeemable at neighborhood grocery stores, convenience stores, and farmers markets, resulting in increased intake of fresh fruits and vegetables (28). Digital health solutions have the potential to connect public health, primary care, specialty care, and community resources in order to speed and simplify those types of interventions, thus improving care and lowering costs for all.

It is recognized that physical activity, food tracking, patient distress level, and social determinants of health are also important drivers of both health and wellness. Digital solutions can bring together all of those types of data from multiple devices in order to significantly improve care. The anonymity of technology can encourage candor in the self-reporting of mental state and other factors, and the connection to a wealth of additional data can give clinicians more integrated and actionable information to enrich the healthcare interaction. That direct line of sight to the whole person is a crucial aspect to effective care.

6 What practical steps are needed to become a digital health-ready clinical practice?

Digital health tools will inherently affect the patient care process and will introduce some changes to clinician workflow. Burdensome and time-consuming changes will impede the use of the new technology. Based on the experience and knowledge of the authors, here are some suggestions:

6.1 Designate a digital champion or technology navigator in the practice or clinic

This individual may be a diabetes care and education specialist, a medical assistant, nurse, or other designated staff. This individual becomes the technology expert for the practice, developing efficient workflows for helping people with diabetes identify and get started on various diabetes technology tools (29). In addition, the role helps assure that the data generated from use of the technology is available for use at clinic visits. In a feasibility evaluation exploring the potential role of a technology navigator in an academic practice, a sample of visits pre- and post-technology navigator implementation (n = 173) showed a 22% (41% vs. 19%) increase in patients who successfully shared their data from home before their visit and a 52% (67% vs. 15%) increase in visits where data were available to the provider for review before the appointment, whereas billing claims for continuous glucose monitor interpretation increased by 86% during the same period. Incorporating a digital champion or navigator role may improve data availability, decrease time spent on non-billable activities, and support data interpretation and billing (30).

6.2 Define workflow and responsibilities for a data-informed practice model

As technology is integrated into clinical care, it will be important to determine and redesign workflows to optimize resources and integrate the data into decision-making. It will be important, for example, to define protocols for remote physiological monitoring and population health management. Determine who on the clinical team will receive, review, and respond to person and population level data. Work must be done to allow integration of the data from various connected technologies into the most commonly used electronic health records (EHR) to allow for proper documentation and quality management.

6.3 Integrate technology into the clinical workflow using the ADCES identify-configure-collaborate technology framework

This framework serves to expand technology access and adoption and enable data-informed care in a standardized way in clinical practice (31) (Figure 2).

6.3.1 Identify

Help every person with diabetes make informed choices regarding technology as a standard of care. Recognize that choices will evolve over time.

6.3.2 Configure

Provide onboarding and ongoing support and training to help individuals get off to a strong start with their technology choices, customizing the technology to match the individual's therapy and lifestyle. The digital champion or technology navigator can serve to show individuals how to check their email on their phone, how to connect to other connected devices, and preparing individuals ahead of time to come to their onboarding or clinical appointment with their sign-in credentials for the app store or other connected technologies such as their CGM system and/or with the desired application already downloaded on their phone. Developing practice protocols for the electronic health record for the configuration steps and data output for various technologies can help standardize best practices.

6.3.3 Collaborate

Develop a plan for ongoing use of both the person and population level data to assess and address barriers to following the care plan and incrementally adjusting the care plan as needed in a continuous feedback loop to disrupt therapeutic inertia.

7 Discussion

An increasingly supportive policy landscape, and a growing base of evidence are paving the way for digital health to become an

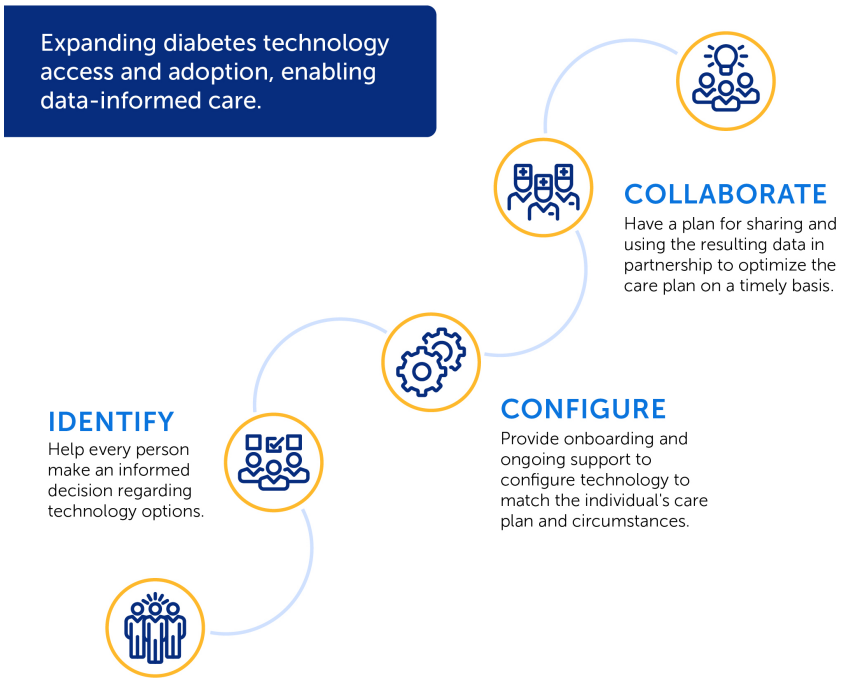

FIGURE 2
Digital Health Workflow.

integral part of care delivery. Nevertheless, successful integration of digital health into mainstream healthcare has been slow, complicated by a confusing landscape, worries about health data privacy, and questions about who pays for it. Evidence-based digital health solutions could spark a care delivery revolution that would dramatically improve the management of chronic illness, ease clinician burden, and lower costs. As disruptors to traditional care models, innovative healthcare organizations must meet infrastructure constraints head-on. Digital health solutions rely on powerful, reliable, and highly portable tablets, mobile devices, and laptops that give them the ability to deliver care not only inside hospital walls but also beyond including at a person's home, which is increasingly becoming a healthcare hub. Because of that, organizations must consider infrastructure and interoperability and the ways a person's data could move seamlessly and securely across the care continuum. Healthcare organizations will have to take the lead, but they won't be able to do it alone. Addressing infrastructure challenges on such a scale must be a collaborative effort that includes multiple parties and entities from regulators and policy makers to health technology vendors, EHR systems, and even entities that deliver broadband—so that the reach of digital health can be extended to rural communities.

Solutions should easily and seamlessly connect to data sources and devices without added burdens on care teams or consumers. Users should be able to pair any device, such as activity trackers, blood glucose meters, blood pressure monitors, and weight scales. Users should be able to connect to labs, pharmacies, and EHRs to ensure consistency of data as well as removal of the friction associated with manual data entry. Patient data should be encrypted securely and live in the cloud so it can be accessed easily and not be lost. And patients should have full control over who can access it. When providers do access such data, they should not need a separate portal. A preferred option is a HIPAA-compliant, fully agnostic application programming interface that can work with any EHR or technology. With such a flexible and reliable infrastructure in place, clinicians could more readily combine digital solutions and other aspects of digital health—including telehealth—to create highly effective, highly efficient virtual house calls for managing chronic illness. If, for example, a clinician is managing a patient with diabetes, the clinician should, prior to a telehealth visit, be able to receive information that combines data on such health variables as the patient's blood glucose levels, food tracking, weight, physical activity, and level of diabetes distress. That information could be paired with evidence-based, personalized clinical recommendations, thereby optimally preparing the clinician to observe self-care in the home environment before guiding a patient through next steps in their care plan.

Digital health can serve as a force multiplier to address healthcare challenges. Potential future areas of digital health advancement and research include highlighting the compelling possibilities and unresolved challenges for advancing trustworthy digital technology for the benefit of all people across society at every stage of their lives. We must identify the structural, technical, and policy preconditions for long-term progress as well as the critical priorities for cooperation and collaboration between policy makers, practitioners, and industry leaders to propel the development and application of best-in-class digital health tools. It will be important to prioritize ethical research addressing issues of user consent and addressing socioeconomic disparities in access and effectiveness. It

is also important to consider the impact of digital health on health outcomes and the cost-effectiveness of service delivery. Building evidence on engagement and outcomes through strategic prospective and retrospective studies is needed. It should be recognized that digital health requires a different approach to research with the intervention continuously changing.

It is an exciting yet stressful time for healthcare. Care models such as value-based care are coming and may eventually replace traditional fee-for-service models. Younger clinicians, often coming from the "iPhone generation," are entering the workforce and are more likely and willing to embrace technology solutions that help them and their patients. Technological solutions are improving and are incorporating more AI features. AI-powered health technologies enable true person-centered care for entire populations at scale, moving from mass generalization to mass customization. Fostering health technology literacy and confidence among those living with chronic conditions, as well as addressing the digital divide, will be essential to reach these goals. The time is ripe for implementing thoughtfully designed digital health tools that strengthen the connection between the individual and their care team and enable continuous, data-informed, on-demand diabetes care and education.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

MS: Conceptualization, Writing – original draft, Writing – review & editing, Formal analysis, Investigation, Methodology, Supervision, Validation. PM: Conceptualization, Writing – original draft, Writing – review & editing. GA: Writing – review & editing, Conceptualization. MP: Writing – review & editing, Conceptualization. AK: Visualization, Writing – review & editing. JM: Conceptualization, Visualization, Project administration, Writing – original draft, Writing – review & editing. AI: Conceptualization, Formal analysis, Investigation, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

MS, AK, and AI are employees of Welldoc, Inc. MP is an advisor for Welldoc, Inc. JM is a consultant for Welldoc, Inc.

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

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Whole body vibration therapy and diabetes type 2: a systematic review and meta-analysis

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Background: Vibration platforms have demonstrated systemic effects generated by the use of mechanical vibrations, which are similar to those of any physical activity. The effect that whole body vibration (WBV) generates on the organism could be recommended in Diabetes Mellitus 2 (DM 2) patients.

Objective: To systematically review and meta-analyze the available evidence on the effects of WBV on glycemic control in patients with DM 2

Material and methods: Exhaustive bibliographic searches were carried out until October 2023 in different biomedical portals and databases: Public Medline (PubMed), Scientific Electronic Library Online (SciELO), VHL Regional Portal, Cochrane Central and Latin American and Caribbean Literature in Health Sciences (LILACS). Randomized clinical trials based on the effects of Whole Body Vibration on glycosylated hemoglobin levels, with control group and participants were non-insulin dependent were the inclusion criteria. Two reviewers extracted data independently. A third reviewer was available for discrepancies.

Results: Six articles with 223 participants met the criteria and were included in the systematic review; only four of them met the criteria to be part of the meta-analysis. This meta-analysis reveals a positive and significant effect size (μ ê=0.5731), indicating a substantial difference between the groups studied. Although there is some variability between studies (heterogeneity of 30.05%), the overall direction of the effects is consistent. These findings conclusively suggest the presence of a significant influence of the variable evaluated, underscoring the robustness and consistency of the relationship observed in the literature reviewed.

Conclusion: There are no conclusive results due to the lack of data for some variables, which prevents comparison; but WBV may be an effective therapy to improve glycemic control in DM 2 patients. More studies with more patients and longer follow-up are needed.

KEYWORDS

whole body vibration, vibration platform, diabetes mellitus type 2, physical exercise, fasting blood glucose, glycosylated hemoglobin

1 Introduction

Worldwide, 537 million people suffer from diabetes and this data will be increased up to 643 million by 2030 and 783 by 2045; in our country (Spain) the incidence of Diabetes Mellitus type 2 (DM 2) is estimated at 1 in 7 people, equivalent to 10.3% of the population (around 5.1 million adults). This situation generates a great impact on society, as well as concern among health professionals due to its high and ever-increasing prevalence, not to mention the high cost to the health system which could reach USD 966 billion dollars, which represents an increase of 316% over the last 15 years; raising awareness among these people is the key to combating this problem (1).

Several disciplines have made contributions to the current knowledge about DM 2; however, despite the passage of time, the fundamental pillars in the treatment of a diabetic person are based on diet and exercise, especially in DM 2. In addition, the physical disabilities and comorbidity present in most people with DM 2 are challenges to adherence to physical activity (2).

Due to the research during the last decades, the etiology, pathophysiological mechanisms, diagnosis and treatment of DM 2 are better understood. Traditionally, vibration exposure has been considered detrimental for causing harm in humans. However, several studies have shown beneficial effects of the application of whole-body vibration (WBV) with low frequencies, low amplitudes and short exposure times (3, 4) as a novel treatment for DM 2 patients (5).

The application of WBV has been associated with favorable changes in hormone levels, strength, power, muscle mass, muscle electrical activity, jumping ability, balance, psycho-physical health and activation at the cortical level, among others (6). Nevertheless, the effects of WBV on DM 2 are less well known.

Various systematic reviews have evaluated the impact of WBV on glycemic control in patients with DM 2. The results obtained are contradictory. While some studies, conducted in 2016 (7) and 2019 (8), suggest a slight improvement in glucose and HbA1c levels, another systematic review published in 2018 (9) questions the strength of this evidence, pointing out a low methodological quality in the included studies.

Nowadays most WBV studies published are focused on the level of neuromuscular dysfunction (10) and the muscular system. Muscles are known to react to vibration by contracting and stretching automatically. Vibration produces a muscle contraction reflex, called the tonic vibratory reflex (11–13). This reflex has been related to decreased pain threshold, increased blood circulation (14) increased hormone secretion, activation of the Golgi tendon organ and inhibition of antagonist muscles (4, 15–17).

The physiological modifications observed with WBV are analogous to those of any physical activity, having been described in addition to acute changes, chronic adaptations. Adaptation to physical exercise is what determines the positive changes that appear in our organism when performing any sport. The WBV effectiveness could be explained by the fact that, while with training work is performed on a certain number of tissues, with the use of mechanical vibrations the whole body is subjected to vibration, obtaining beneficial effects at a systemic level (16-118-19).

To summarize the current evidence, our objective was to perform a systematic review and meta-analysis of the effects of WBV intervention on blood glucose levels and glycosylated hemoglobin (HbA1c) levels in people with DM 2.

2 Materials and methods

2.1 Systematic literature research

An exhaustive literature search including randomized and controlled clinical trials obtained from the different biomedical portals and existing databases, from January 2019 to October 2023: Public Medline (PubMed), Scientific Electronic Library Online (SciELO), VHL Regional Portal, Cochrane Central Register of Controlled Trials (Cochrane CENTRAL) and Latin American and Caribbean Literature in Health Sciences (LILACS) has been conducted. Search terms included were *Type 2 Diabetes Mellitus*, *physical exercise*, *whole body vibration* and *glycosylated hemoglobin or HbA1c*.

The databases were searched using Boolean operators such as: "AND" and "OR". Keywords have been combined with connectors in order to find valid articles for the aim of the present work. The "OR" connector has been used by joining the words that mean almost the same thing "exercise" and "Exercise on vibrating platforms", and the "AND" connector has been used in order to

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give greater sensitivity and specificity to the search. No filters have been used and searches were made in "all fields" and "all index" (Table 1).

2.2 Selection criteria

Randomized controlled trials were considered eligible if they met inclusion criteria such as addressing the effects of WBV on glycosylated hemoglobin levels, the WBV intervention had to be at least 8 weeks, at least one control group did not perform WBV, and participants were non-insulin dependent. Exclusion criteria were studies in which individuals had a reported diabetic complication (neuropathy, retinopathy or diabetic peripheral nephropathy), animal studies and studies with insufficient description of WBV. Besides, a manual search was carried out based on the references of the selected articles as well as the references of other articles not included because they are a different type of study than the one selected in the present review.

2.3 Screening, selection and data extraction

Two independent reviewers in a first step carried out the bibliographic research and after that, examined the titles and abstracts of all studies identified through the search strategies. Studies that did not meet the inclusion criteria, based on titles or abstracts, were discarded. The two reviewers analyzed the full text of the remaining studies in a second review independently. If there is any disagreement a third reviewer was available to solve it.

Reviewers independently extracted data from the studies that met the inclusion criteria using a standardized data extraction form. Data extracted were: authors; year of publication; type of platform used; number of individuals forming the study sample; WBV parameters and intervention outcomes; mean and standard deviation of results.

2.4 Assessment of methodological quality and risk of bias

The physiotherapy evidence database (PEDro) scale was used to evaluate the methodological quality and the risk of bias of the randomized clinical trials included. This is a useful tool for assessing trial quality and the total score of this scale is 10 points. Punctuation more than 6 points is considered as a high-quality clinical trial. Sample selection, randomization, blinding (both participants and therapists), initial homogeneity and statistical analysis (intention to treat and comparisons) are included in this scale (20).

The quality of the included studies was scored by 2 investigators using the PEDro scale. The investigators rated the studies independently scoring from 0 to 10. If there is any disagreement a third reviewer was available to solve it.

Besides, the Van Heuvelen et al. (21) guidelines has been followed to report the quality of WBV studies. These guidelines encourage the authors to provide a detailed description of the WBV protocol applied (type of platform, frequency and amplitude of vibration, acceleration), the exposure parameters such as the duration and number of sessions as well as the total duration of the training program and the mode of application. In addition, the characteristics of the participants (demographic data, inclusion and exclusion criteria) should be presented. randomization and the

TABLE 1 Search strategy.

DATABASE	SEARCH STRATEGY
PUBMED	**(((((Type 2 Diabetes Mellitus) AND (physical exercise)) OR (exercise on vibrating platforms)) AND (whole body vibration)) AND (glycosylated hemoglobin)) OR (HbA1c)** ((((“diabetes mellitus, type 2”[MeSH Terms] OR “type 2 diabetes mellitus”[All Fields]) AND (“exercise”[MeSH Terms] OR “exercise”[All Fields] OR (“physical”[All Fields] AND “exercise”[All Fields]) OR “physical exercise”[All Fields])) OR ((“exercise”[MeSH Terms] OR “exercise”[All Fields] OR “exercises”[All Fields] OR “exercise therapy”[MeSH Terms] OR (“exercise”[All Fields] AND “therapy”[All Fields]) OR “exercise therapy”[All Fields] OR “exercising”[All Fields] OR “exercise s”[All Fields] OR “exercised”[All Fields] OR “exerciser”[All Fields] OR “exercisers”[All Fields]) AND (“vibrate”[All Fields] OR “vibrated”[All Fields] OR “vibrates”[All Fields] OR “vibrating”[All Fields] OR “vibration”[MeSH Terms] OR “vibration”[All Fields] OR “vibrations”[All Fields] OR “vibrational”[All Fields] OR “vibrator”[All Fields] OR “vibrators”[All Fields]) AND (“platform”[All Fields] OR “platform s”[All Fields] OR “platforms”[All Fields]))) AND ((“whole”[All Fields] OR “wholeness”[All Fields] OR “wholes”[All Fields]) AND (“human body”[MeSH Terms] OR (“human”[All Fields] AND “body”[All Fields]) OR “human body”[All Fields] OR “body”[All Fields]) AND (“vibrate”[All Fields] OR “vibrated”[All Fields] OR “vibrates”[All Fields] OR “vibrating”[All Fields] OR “vibration”[MeSH Terms] OR “vibration”[All Fields] OR “vibrations”[All Fields] OR “vibrational”[All Fields] OR “vibrator”[All Fields] OR “vibrators”[All Fields])) AND (“glycosylated haemoglobin”[All Fields] OR “glycated hemoglobin”[MeSH Terms] OR (“glycated”[All Fields] AND “hemoglobin”[All Fields]) OR “glycated hemoglobin”[All Fields] OR (“glycosylated”[All Fields] AND “hemoglobin”[All Fields]) OR “glycosylated hemoglobin”[All Fields])) OR (“glycated hemoglobin”[MeSH Terms] OR (“glycated”[All Fields] AND “hemoglobin”[All Fields]) OR “glycated hemoglobin”[All Fields] OR “hba1c”[All Fields] OR “hba1cs”[All Fields])
SciELO	(Type 2 Diabetes Mellitus) AND (physical exercise) OR (whole body vibration)
VHL Regional Portal	(Type 2 Diabetes Mellitus) AND (whole body vibration) (Type 2 Diabetes Mellitus) AND (physical exercise OR whole body vibration)
Cochrane CENTRAL	(Type 2 Diabetes Mellitus) AND (physical exercise OR exercise on vibrating platforms) AND (whole body vibration) AND (glycosylated hemoglobin OR HbA1c)
LILACS	(Type 2 Diabetes Mellitus) AND (whole body vibration) (Type 2 Diabetes Mellitus) AND (physical exercise OR whole body vibration) (whole body vibration) AND (glycosylated hemoglobin OR HbA1c)

PICO strategy has been followed as follows:
- POPULATIONS: diabetes type 2 patients
- INTERVENTIONS: whole body vibration therapy
- COMPARISONS: control groups
- OUTCOMES: fasting blood glucose, glycosylated hemoglobin

existence of control groups should also be controlled, together with a presentation of the results and analysis of the data with statistical methods. finally, the existence of adverse effects and the existence or not of adherence, the interpretation of the results and the recommendations for clinical practice should be presented.

Besides, to test the quality of the meta-analysis the analysis implemented Random Effect Model using Jamovi software (22).

The *Random-Effect Model*: The analysis was carried out using the standardized mean difference as the outcome measure. A random-effects model was fitted to the data. The amount of heterogeneity (i.e., tau^2), was estimated using the restricted maximum-likelihood estimator (23). In addition to the estimate of tau^2, the Q-test for heterogeneity (24) and the I^2 statistic are reported. In case any amount of heterogeneity is detected (i.e., $tau^2 > 0$, regardless of the results of the Q-test), a prediction interval for the true outcomes is also provided. Studentized residuals and Cook's distances are used to examine whether studies may be outliers and/or influential in the context of the model. Studies with a studentized residual larger than the 100 x (1 - 0.05/(2 X k))th percentile of a standard normal distribution are considered potential outliers (i.e., using a Bonferroni correction with two-sided alpha = 0.05 for k studies included in the meta-analysis). Studies with a Cook's distance larger than the median plus six times the interquartile range of the Cook's distances are considered to be influential. The rank correlation test and the regression test, using the standard error of the observed outcomes as predictor, are used to check for funnel plot asymmetry.

3 Results

3.1 Study selection

After the initial search, 735 potential studies were found to evaluate its possible inclusion in the systematic review. 131 manuscripts were removed as duplicates. The first screening by title and abstract reduced the sample to 174. A carefully full- text read of these files was made by reviewers and finally 6 records were included in the systematic review and 4 in the meta-analysis due the lack of some values in the two studies removed, which avoid comparisons. Figure 1 shows the Prisma flowchart of the study selection.

3.2 Study characteristics

The sample analyzed in the articles reviewed ranged from 24 to 50 subjects, the mean of the sample being 37.1 patients. The selected

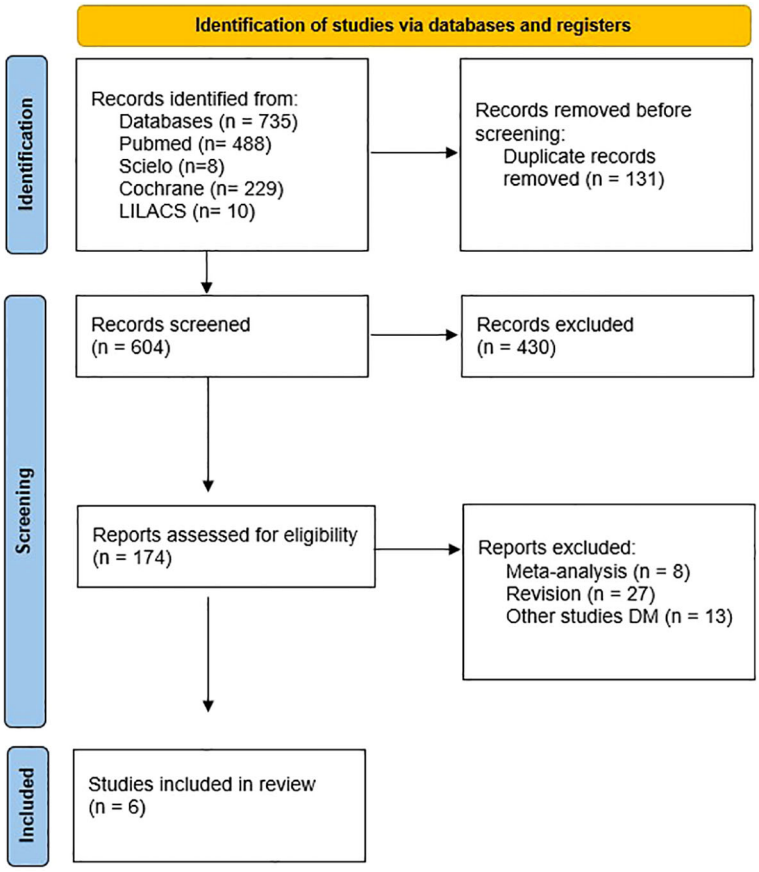

FIGURE 1
Study selection.

articles show that 33.33% of the reviewed studies show the existence of a statistically significant decrease in glycosylated haemoglobin (HbA1c) after exposure to vibratory exercise (25–27). While for the remaining 66.66% (28, 29) there is no statistically significant decrease in HbA1c. Fasting blood glucose (FBG), however, decreased in 66.66% of the studies analyzed (25–27, 29), after the use of WBV, while for 33.33% (25, 30) there was no significant decrease.

There are basically 2 types of vibration platforms: vertical platforms or oscillating platforms. Vertical platforms vibrate in a predominantly vertical direction, moving vertically under both feet at the same time. Oscillating platforms vibrate around a horizontal axis, resulting in a simultaneous and symmetrical movement of both sides of the body during exposure (31, 32). The most commonly used platform in several studies (25, 26, 28), was the oscillating platform, obtaining positive results with respect to HbA1c and white blood cells (WBC). However, the use of the vertical platform (27), also concluded with positive effects on HbA1c and WBC results.

The duration of the intervention in the studies analyzed was between 8 (29) and 12 weeks (25–28, 30), with a mean of 11.33 weeks. Regarding the rest time between exercises applied in the interventions, it is located in an average of 34 seconds for those that reflect rest time between exercises (25–27). The other authors do not reflect rest time between exercises (28, 30). Most researchers propose an exercise frequency of 3 times per week, except Michels et al. (30) who carried out the intervention with 7 days of vibratory exercises. No study reports on possible adverse effects during the period of vibration work.

In Table 2, the main results of these articles were showed.

Manimmanakorn (25) implemented a research with 36 patients with DM 2 divided into two groups. The WBV group performed for 3 times per week, 2 sets of 6 one-minute vibrating squats for 12 weeks and the control group performed their usual physical activity. These six positions were "(a) a deep squat position (knee angle 90o), (b) high squat position (knee angle 125o), (c) high squat position (with raised heels), (d) slight knee flexion 1 (holding hand straps with shoulder flexion), (e) slight knee flexion 2 (holding hand straps with shoulder abduction) and (f) slight knee flexion 3 (holding hand straps with elbow flexion)". It was established a progression to 40 Hz and 4mm. They found no significant differences in HbA1c or FBG, concluding that WBV did not improve glycemic indices.

Alfonso-Rosa (26) published an article with 19 subjects with DM 2 exposed to a training based on 8 static and dynamic exercises with an elastic band (warm-up exercise: squat, up and down once with each foot, lunge, heel lift, squat, squat with weight changes, squats held with elastic bands, squat with elastic bands and side with elastic bands) on a vibrating platform at different frequencies (12, 14 and 16 Hz) while the control group continued with their usual activity. After 12 weeks it can be concluded that WBV produces an acute decrease in plasma levels, and the application of WBV at low frequencies is shown to be an effective and safe technique for the co-treatment and management of DM 2.

In this line, Del Pozo Cruz et al. (27) carried out a study with 50 subjects diagnosed with DM 2 were studied to test the feasibility, safety and efficacy of a whole body vibration intervention for 12 weeks in a primary health care setting performing 8 exercises in Physio Wave 700 oscillating platform (lunge, step up and down, squat, calf raises, left and right pivot, shoulder abduction with elastic bands, shoulder abduction with elastic bands while squatting, arm swinging with elastic bands) and the control group followed standard care. They establish a progression from 30 seconds for exercises and 30 seconds rest during the first month, while during the second and third months the exercise duration increased to 45-60 seconds and 30 seconds of rest and 2 more Hz each 4 weeks. They found a reduction in HbA1c and FGB compared to the control group concluding that the application of WBV in primary care is feasible, safe and effective in improving the glycemic profile.

Besides, Baum et al. (28) conducted another investigation with 40 non-insulin-dependent adult patients divided into 3 groups analyzed during 12 weeks of training with 3 training sessions per week. One group followed the WVB training with 30 Hz and 2mm from 1 to 9 week and 35 Hz the last weeks, the second, the strength group did the leg extension, seated leg flexion, leg press, seated calf raise, lat pulley, horizontal chest press, butterfly, and rowing exercises (1 set the first 6 weeks and 2 sets the last weeks) and the third group, flexibility group (control group) implemented 8 static exercises (the same progression was done increasing from 1 to 2 sets the last weeks). The main findings were that FBG remained unchanged after training and HbA1c tended to decrease below baseline in the vibration training group, while they increased in the other two intervention groups. Besides, the glucose tolerance improvement in WBV and strength groups. The authors concluded that these results suggest that vibration exercise may be an effective and low time-consuming tool to control glycemic control in patients with DM 2.

Behboudi et al. (29) selected a sample, 30 diabetic males, who followed a vibration exercise during 8–12-minute sessions of standing and semi-sitting positions at a frequency of 30 Hz and an amplitude of 2 mm, for 8 weeks three times a week. The aerobic exercise implemented 3 walking sessions a week and control group continued their routine activities. They detected no significant differences in HbA1c concentrations or fasting WBC between the conventional aerobic exercise groups and those subjected to vibration.

Finally, Michels et al. (30) investigated 22 adults with DM 2 who were taking oral antidiabetic agents were divided into 2 groups to submit one of them to 12-weeks intervention of WBV and control group received tips on how to change their lifestyle. After 12 weeks of intervention, they found a significant reduction in HbA1c in the WBV group, but no significant differences in FGB between groups.

3.3 Methodological quality and risk of bias

PEDro scale shows the quality of the randomized clinical trials. In this review, three articles showed high quality with 6, 7 and 9 points. Nevertheless, low methodological quality was shown in the other three articles with scores of 4, 5 and 5 points. In Table 3, the PEDro Scale assessment of the six selected articles is presented. Given the variability of the data presented in each manuscript and the lack of data for comparison with the other articles in the review, two manuscripts were removed from the meta-analysis.

TABLE 2 Study characteristic of the selected articles.

AUTHOR	OBJECTIVE	PLATFORM	SAMPLE	INTERVENTION	RESULTS	CONCLUSIONS
Manimmanakorn et al. (2017) (25)	To identify beneficial changes for the health of people with DM 2 at WBV.	Fitvibe Excel (Vertical)	n = 36 WBVG (n=17) CG (usual physical activity) (n=19)	f 30Hz-2mm: 1 Wk. f 40Hz-4mm: 5-12 Wk. 3 x/Wk; 12 Wk 60sec VE/20 sec rest 12 min/session	↓ (p > 0,05) in FBG, HbA1c, insulin level and insulin sensitivity in both groups.	WBV may be an effective method to control some of the deleterious outcomes of DM 2 only in the most severe cases. No adverse effects.
Alfonso-Rosa (2016) (26)	To determine the applicability and effectiveness of WBV to improve functional capacity and quality of life in subjects with DM 2.	Physio Wave 700 (Oscillating)	n = 39 WBVG (n=19) CG (n=20)	f 12, 14 and 16Hz-4mm 3 x/Wk; 12Wk. 30-45-60 sec VE (↑ progressive)/30 sec rest 8-16 min/session	↓ (p < 0,05) HbA1c and FBG WBVG CG ↓ HbA1C and FBG	↓ Glycaemia level in a VE session. No adverse effects.
Del Pozo-Cruz et al. (2013) (27)	To test the feasibility, safety and effectiveness of a 12-wk WBV intervention on glycemic control, lipid-related cardiovascular risk factors and functional capacity among DM 2 patients in a primary care context.	Physio Wave 700 (Oscillating)	n = 50 WBVG (n= 25) CG (n=25)	f 12, 14 and 16 Hz - 4mm 3 x/Wk; 12Wk. 30-45-60 sec VE (↑ progressive)/30 sec rest 10 min/session	↓ (p < 0,05) HbA1c and FBG WBVG and CG	VE is feasible, safe and effective in improving glycemic profile. No adverse effects.
Baum et al. (2007) (28)	Influence of AE and vibration on glucose metabolism parameters in people with DM 2.	Vibrogym Professional © (Oscillating)	n = 40 WBVG (n=14) Flexibility training group (8 static exercises) (n=13) Strength training group (8 stations in weight machines) (n=13)	f 30Hz-2mm: de la 1-9 Wk. f 35Hz-2mm: 10-12 Wk 3 x/Wk; 12Wk 30 sec EV/no rest 20 min/session	↓ (p < 0,05) in FBG for all groups. HbA1c ↓ (p > 0,05) in WBVG. ↑ HbA1c for other groups.	VE can be an effective and time-efficient tool for improving glycemic control in people with DM 2, although no significant data were obtained. No adverse effects.
Behboudi et al. (2011) (29)	Comparing how AE and WBV affect glycemic control in DM 2.	Star Sport-Taiwan (Oscillant)	n 30 AEG (n=10) WBVG (n=10) CG (n=10)	f= 30Hz-2 mm 3 x/Wk; 8 Wk 60 sec EV/60 sec rest 16 min/session (1-3 week) 20 min/session (4-6 week) 24min/session (7-8 week)	No effect for FBG for HbA1c. ↓ higher for AE and WBV than CG	Insignificant results due the sample size. WBV could be an option for DM 2 patients with obesity or those who cannot implement active physical activity No adverse effects.
Michels et al. (2021) (30)	To evaluate the effect of whole-body vibration at 28 Hz on glycemic control and other metabolic parameters in adults with DM 2.	SmartWalk (Vertical)	n = 22 WBVG (n= 11) CG (n=12)	f 28 Hz mm (no data) 7 x/Wk; 12Wk. 20-30 min/session No rest	HbA1c ↓ (p < 0,05) in WBVG FBG increase in both groups but there are no significant changes	Daily use of the vibration platform for 12 weeks improved HbA1c in adults with DM 2.

n, Sample size; WBV, whole body vibration; WBVG, whole body vibration group; CG, Control Group; DM 2, Diabetes mellitus type 2; FBG, fasting blood glucose; AEG, aerobic exercise group; Wk, week; Hz, Hertz; VE, vibration exercise; HbA1c, Glycosylated Hemoglobin; f, Frequency; AE, aerobic exercise; mm, millimeters; min, minutes.

3.3.1 Quality of studies

Considering Van Heuvelen guidelines most of the articles have not adhered to these lines, so the results should be interpreted with caution (Table 4).

3.3.2 Random-effect model

A total of k=4 studies were included in the analysis. The observed standardized mean differences ranged from 0.2582 to 1.3338, with most estimates being positive (100%). The estimated average standardized mean difference based on the random-effects model was \hat{\mu} = 0.5895 (95% CI: 0.1782 to 1.0008). Therefore, the average outcome differed significantly from zero (z= 2.8088, p = 0.0050). According to the Q-test, there was no significant amount of heterogeneity in the true outcomes (Q (3) = 4.2890, p = 0.2319, tau^2 = 0.0436, I^2 = 24.6411%). A 95% prediction interval for the true outcomes is given by 0.0092 to 1.1698. Hence,

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TABLE 3 PEDro score of the randomized clinical trials selected.

AUTHOR	1	2	3	4	5	6	7	8	9	10	SCORE
Manimmanakorn (2012) (15)	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	9/10
Alfonso-Rosa (2016) (16)	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5/10
Del Pozo-Cruz et al. (2014) (17)	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5/10
Baum et al. (2007) (18)	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	7/10
Behboudi et al. (2011) (19)	Yes	No	Yes	No	No	No	Yes	No	Yes	No	4/10
Michels et al. (2021) (20)	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/10

even though there may be some heterogeneity, the true outcomes of the studies are generally in the same direction as the estimated average outcome. An examination of the studentized residuals revealed that none of the studies had a value larger than ± 2.4977 and hence there was no indication of outliers in the context of this model. According to the Cook's distances, none of the studies could be considered to be overly influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (p =

TABLE 4 Van Heuvelen et al. guidelines.

	ITEM	Manimmanakorn et al. (25)	Alfonso-Rosa et al. (26)	Del Pozo-Cruz et al. (27)	Baum et al. (28)	Behboudi et al. (29)	Michels et al. (30)
Device	Device specifications	Yes	Yes	Yes	Yes	Yes	Yes
	Platform constructions	No	No	No	No	No	No
Vibration	Type of vibration	Yes	Yes	Yes	Yes	No	No
	Vibration parameters	Yes	Yes	Yes	Yes	Yes	Yes
	Parameters verification	No	No	No	No	No	No
	Side-alternating vibrations: accelerometer location	No	No	No	No	No	No
	Frequency and magnitude: constant or modulated	Modulated	Modulated	Modulated	Constant	Modulated	Constant
Administration	Posture/ body position	Yes	Yes	No	Yes	Yes	Yes
	Feet position	Partly	Yes	No	Yes	No	Yes
	Feet skidding prevention	No	No	No	No	No	No
	Head vibration transmission prevention	No	No	No	No	No	No
	Handrail	No	No	No	No	No	No
	Hands position	Partly	Partly	No	Partly	No	No

(Continued)

TABLE 4 Continued

	ITEM	Manimmanakorn et al. (25)	Alfonso-Rosa et al. (26)	Del Pozo-Cruz et al. (27)	Baum et al. (28)	Behboudi et al. (29)	Michels et al. (30)
	Body parts subjected to vibration	Yes	Yes	Yes	Yes	Yes	Yes
	General exercise parameters	Yes	Yes	Yes	Yes	No	Yes
Protocol	Setting of sessions	Yes	Yes	No	No	No	No
	Trainer	No	No	No	Yes	No	No
	Previous instructions	Yes	Yes	Yes	No	No	No
	Preparatory exercises	No	No	Yes	No	Yes	No
	Subjects' footwear	No	No	No	No	No	No
	Control intervention	Yes	Yes	Yes	Yes	Yes	Yes
	Time of outcome measurement	Yes	Yes	Yes	Yes	Yes	Yes
Subjects	General characteristics	Yes	Yes	Yes	Yes	Yes	Yes
	Previous experience	No	No	No	No	No	No
	Acute, short-term or long-term effects	Acute	Acute	Acute	Acute	Yes	Acute

0.3333 and p = 0.1512, respectively). The funnel plot asymmetry was not assessed because there are less than 10 articles (Tables 5, 6, Figure 2).

4 Discussion

Whole body vibration is a simple, safe and effective non-pharmacological measure to reduce HbA1c and plasma glucose levels in patients with DM 2 whose physical condition prevents conventional aerobic exercise (33).

Regarding the pharmacological drugs for the treatment of DM 2, they do not inherently exhibit the ability to maintain sustained glycemic control over a prolonged period (34). In addition, adverse effects such as gastroenteritis, hypoglycemia and weight gain, among others, are undesirable manifestations associated with the use of orally administered pharmacological agents in patients with DM 2. These side effects lead to a decrease in adherence to pharmacological treatment by patients diagnosed with DM2 (35, 36). For that reason, moderate-intensity aerobic physical exercise is recognized as an effective non-pharmacological approach to reducing blood glucose levels for people whose physical condition allows it to be performed. However, WBV could be a physical exercise option to reduce blood glucose and HbA1c levels for those who cannot perform aerobic exercise (26–29).

Regular physical exercise increases glucose uptake in activated muscle, which induces increased insulin sensitivity in diabetics. Regular WBV training has been shown to generate muscle adaptation similar to resistance exercise training (37). Thus, regular WBV training may help diabetic patients to control glucose metabolism (25).

WBV does not require a specific physical condition, nor prior supervision and may help in physical exercise adherence for patients with DM 2. Moreover, it has demonstrated its efficacy in animal (38–40) and human (16, 41, 42) studies. Some of the

TABLE 5 Random-effects model.

Random-Effects Model (k = 4)						
	Estimate	se	Z	p	CI Lower Bound	CI Upper Bound
Intercept	0.589	0.210	2.81	0.005	0.178	1.001

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TABLE 6 Heterogeneity statistics.

Heterogeneity Statistics							
Tau	Tau^2	I^2	H^2	R^2	df	Q	p
0.209	0.0436 M (SE = 0.1438)	24.64%	1.327		3.000	4.289	0.232

participants who underwent the WBV intervention showed a statistically significant reduction in HbA1c levels compared to those who did not receive the intervention.

Some studies (26, 27, 30) point out, it seems that 12 weeks of WBV intervention is sufficient for a statistically significant improvement in both WBC and HbA1c in people with DM 2 compared to those who did not undergo any intervention. This data is similar to those found in another meta-analysis (7) in which the sample was subjected to aerobic training for 12 weeks, achieving a reduction in HbA1c. On the other hand, authors stated that there is no significant differences in HbA1c concentrations or fasting WBC between the conventional aerobic exercise groups and those subjected to vibration (29).

However, there is no clear consensus on what the most beneficial parameters for these patients should be. Studies with longer duration and parameters of frequency, intensity and duration should be investigated in the future in order to adapt this therapy to patients with type 2 diabetes.

In this period, Baum et al. (28) and Manimmanakorn (25), using a step-up frequency of 30-40Hz, did not show a significant reduction in HbA1c which was only revealed after *post-hoc* dichotomization. However, Alfonso-Rosa (26) and Del Pozo-Cruz et al. (27), using a lower frequency, also of progressive increase (12-16Hz), did show a significant reduction in both HbA1c and WBC. These data coincide with another study (31), where an increase in the effects was demonstrated in relation to the progressive increase in frequency. The gradual increase in frequency may be the reason for the difference in the results. Therefore, it seems that a low frequency with progressive increase and the number of weeks of intervention play a determining role in obtaining a beneficial effect. On the other hand, Michels et al. (30), using a constant frequency of 28 Hz, showed a reduction in HbA1c and WBC. Behboudi et al. (29) using a constant high frequency of 30 Hz for a shorter number of weeks showed no significant differences in HbA1c or fasting glucose, but concentration was higher in the control group.

During exposure, the vibration of the vertical platform moves vertically under both feet at the same time, producing a simultaneous symmetrical movement of both sides of the body, whereas the oscillating platform generates an asymmetrical perturbation of the legs. Vertical platforms work at higher frequencies (between 30 and 50 Hz) than oscillating platforms (between 5 and 30 Hz). In addition, vertical platforms have shown greater chronic effects on strength training and oscillating platforms greater acute effects (31). However, the limited scientific literature on the use of these platforms in diabetes makes it difficult to determine which is the best choice. Regarding the type of platform used, different studies (26, 28) have carried out an intervention using an oscillating type of platform, obtaining positive results with respect to HbA1c and WBC, as in the study by Lythgo et al. (43). However, in one of the studies (25), using the same type of platform, they did not obtain positive results for HbA1c, but did obtain positive results for WBC.

On the other hand, two of the studies (27, 30) used a vertical type of vibrating platform and found positive effects on HbA1c and WBC results. These data agree with what was announced by another study (32) where they determined that vibration transmission was higher during vertical vibration compared to oscillating vibration. This could indicate that the type of platform alone is not determinant to assess its effectiveness, more conclusive studies are needed to evaluate the different vibratory devices in people with DM 2.

HbA1C is one of the most determinant parameters in the diagnosis and long-term control of DM. According to the American Diabetes Association (ADA) (44), an HbA1c > 6.5% is considered a diagnostic criterion for DM, while values < 7.0% HbA1c determine good blood glucose control in the last four months (45, 46). Unfortunately, most of the studies using the HbA1chave performed short-term follow-ups, which prevents us from knowing the physiological effects in the long term,

Based on the information offered by the ADA (44), which considers that maintaining HbA1c levels below 7% acts as a

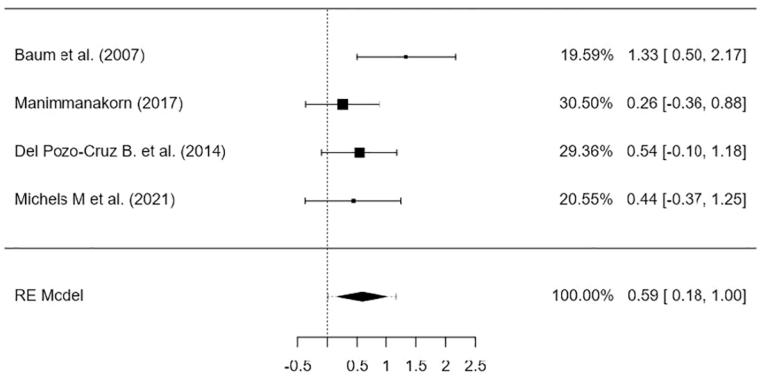

FIGURE 2
Forest plot.

protective factor, helping to manage glycemic imbalance and evaluate the risk of developing, Manimmanakorn (25) found a slight reduction in HbA1c, after 12 weeks of intervention in subjects with values above 8% using a *post hoc* dichotomization; in contrast, in a previous study, in which intervention exercises were applied for 8 weeks, no significant improvement in HbA1c was observed (47).

In relation to the control group, no significant changes in HbA1c levels were observed, according to the data provided by Manimmanakorn (25). On the other hand, Baum et al. compared the WBV group with a strength and flexibility group. After the vibration intervention, a reduction in HbA1c levels was found in both groups, although not reaching statistical significance (28). However, other authors, such as Alfonso-Rosa (16), Del Pozo-Cruz et al. (27) and Behboudi et al. (29) indicated that a conventional exercise program resulted in a decrease in HbA1c levels after the intervention period.

These data are in line with those provided by other studies (48), which show how a conventional training program reduces HbA1c levels.

The WBV guidelines reported by Van Heuvelen et al. (21) are essential to improve reproducibility and transparency in WBV studies, and their adherence allows for proper assessment of the efficacy and safety of WBV interventions. Follow them ensures that the necessary criteria for robust and replicable research are met. In this sense, all the authors of the selected articles (25–30) have reported the frequency of the intervention, as well as the amplitude, except for Michels et al. (30), the duration and frequency of the sessions and the total duration of the program, which was established at 12 weeks, except for Behboudi et al. (29) who applied 8 weeks. The application of the therapy, the results, the statistical analysis and the absence of adverse effects in all the selected articles were described. However, adherence has been variable, with 4 losses reported by Manimmanakorn et al. (25), 11 by Alonso-Rosa et al. (26) and del Pozo-Cruz et al. (27), and 2 by Michels et al. (30); only Baum et al. (28) and Behboudi et al. (29) did not report any losses. The recommendations for clinical practice and future lines of research recommend stratifying patients in the sampling according to the degree of severity of diabetes based on HbA1c or the duration of the disease (25) and analyzing cost effectiveness (27) as well as including more patients and longer follow-up (30) and optimizing frequency, amplitude, and duration of vibration exercises (28).

Finally, there is no consensus with the conclusions: WBV is applicable, safe and effective in reducing HbA1C and basal blood glucose level (26–28, 30), while for others (25) there was no change in FBS or HbA1c, nor for Behboudi et al. (29) who proposed that insignificant results of the present study can be attributed to the small number of samples and improper time and intensity of exercise. However, whole body vibration can be considered as a better way to exercise in a shorter time for majority of diabetic patients who suffer from obesity and unwillingness to join active physical activities. Because of these results, the effect size of these interventions is small and the clinical implications, although they appear to be promising, should be interpreted with caution.

The review has several limitations. the review was not registered; however, all steps were taken to ensure the reliability, transparency and thoroughness of the process and data. Only full-text registries have been considered; the number of experimental clinical trials using WBV in these pathologies is small and some of the studies do not provide all the data on the variables used like disease duration or some outcomes which prevent the effect comparisons. One of the selected articles has not been submitted a per-review process, therefore, the results obtained in this manuscript should be treated with caution and most of them did not follow the quality guidelines and recommendations exposed by Van Heuvelen (21). In addition, the sample size has been very diverse and small; there is not a standard protocol or parameters to achieve the best effectiveness of this therapy although most of them agree with a frequency of three times a week for 12 weeks, and the follow-up of the studies has been only focused on the short-term effects of WBV. In addition, it should be noted that the treatments received by the patients of the selected studies were not composed only of WBV treatment, so that the sum of the effects of the prescribed pharmacological treatment and lifestyle may have contributed to the positive effects obtained.

Nevertheless, the clinical implications are promising, being a safe therapy with no adverse effects that can be used in this population as a complement to other therapies or as an alternative for patients who are unable to perform physical activity. In future lines of research larger samples should be recruited as well as similar measurements, platforms and long term follow up to be able to better determine the clinical effects of the use of WBV.

5 Conclusion

The habitual use of vibration platforms with a frequency of 14-16 Hz for 12 weeks is reflected in the literature. These results are encouraging and suggest that WBV may be an effective therapy to improve glycemic control in patients with DM 2. The addition of Whole Body Vibration therapy as a complement for exercise programs could be effective in sedentary people and could be a useful tool for clinicians. However, further studies with more patients and longer follow-up are needed to confirm these findings.

Data availability statement

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

Author contributions

JF-F: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. VR-P: Conceptualization, Funding acquisition, Methodology, Project administration, Writing – original draft, Writing – review & editing. RL-R: Conceptualization, Funding acquisition, Methodology, Project administration, Writing – original draft, Writing – review & editing. AL-R: Investigation, Methodology, Writing – review & editing. MC-R: Data curation, Formal analysis,

Writing – review & editing. IL-R: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing, Project administration.

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Conflict of interest

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

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Clinical perspective on innovative insulin delivery technologies in diabetes management

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Introduction: The primary objective of this study is to report the results of an online questionnaire and the in-person discussion sessions of physicians specializing in diabetes care in which their opinions about current diabetes management was obtained.

Methods: The Diabetes Innovation Summit 2023 drew attendance from a diverse group of specialized physicians from multiple countries. A comprehensive literature review was conducted to examine the technologies and medical needs associated with diabetes management. Using the results of the review, a questionnaire was developed by three experts from the steering committee to solicit feedback from specialized physicians. The online survey was made accessible between 10th December 2022 and 10th January 2023. Following the online survey, six structured in-person discussion sessions were conducted with specialized physicians from the Middle East, Central-Eastern Europe, and North Africa regions.

Results: The study revealed that about 59% of survey requests were answered, with many participants being pediatric endocrinologists from North Africa. Around 60% of diabetes patients followed Multiple Daily Injections (MDI) according to specialized physicians. Among MDI users, 62% employed Blood Glucose Monitors (BGM), 31% used intermittent-scanning Continuous Glucose Monitors (isCGM), and 23% used CGM. In North Africa, nearly 90% of patients used MDI due to financial constraints. While physicians focused on both Time in Range (TIR) and HbA1c for MDI-treated patients, satisfaction with TIR achieved was expressed by 31%, while 74·1% believed Real-Time CGM (rtCGM) was effective. Concerns arose about potentially misleading HbA1c results and the relatively low patient achievement of target TIR despite CGM usage. The Smart

MDI System was seen favorably compared to other applications. The system's affordability was a significant barrier, particularly in the Middle East and Africa.

Conclusion: The present study highlights that physicians are generally supportive of utilizing new technology. The questionnaires and the open discussion revealed the expectation that the Smart MDI technology provides better control, primarily by identifying missed boluses, while expressing concerns on the use of the technology by teenagers and children, who might forget the device and be reluctant to use in public, and by the older population, who might be challenged by the technology.

KEYWORDS

diabetes mellitus, diabetes management, multiple daily injections (MDI), continuous glucose monitor (CGM), smart insulin pens, new technologies

Introduction

Diabetes mellitus is a chronic condition caused by either a lack of insulin production (T1D) or insulin resistance (T2D), leading to elevated blood glucose levels. This results in complications like blindness, renal failure, dementia, amputations, and cardiovascular events, ultimately causing premature death. In 2021, 537 million adults globally had diabetes, with an additional 240 million undiagnosed cases. Three-quarters of these individuals live in low- and middle-income countries (1). In 2021, there were approximately 8·4 million individuals with T1D worldwide: 1·5 million (18%) of them aged below 20 years, 5·4 million (64%) were 20-59 years and 1·6 million (19%) were 60 years or older (2). Epidemiologic studies show that there is a 3% increase in age-standardized death rate from diabetes during the period 2000 and 2019. The death rate was even greater (13%) in low-to-middle income countries (3). Not only is it associated with increased mortality and complications, but it also consumes a large percentage of health care expenditures. Overall, 9% of total health expenditures (USD 966 billion) were related to diabetes (1).

The main goals of diabetes treatment are to provide tight glycemic control, relieve symptoms, reduce diabetes-related mortality and prevent the development of acute complications (severe hypoglycemia and diabetic ketoacidosis) and long-term complications noted above as well as increasing the quality of life of the individuals living with diabetes (4). Overall, there is inadequate glycemic control in diabetic patients especially those who require insulin for their treatment (5). Aids to diabetes management include frequent blood glucose monitoring (BGM) by fingerstick or by continuous glucose monitoring (CGM) as well as access to a well-functioning healthcare infrastructure (6). Diabetes patients can choose between BGM systems, which measure glucose in capillary blood, and CGM systems, which measure glucose in interstitial fluid. While BGM is the traditional method, CGM use has rapidly increased. CGM systems are either real-time (rtCGM), providing updates every 5 minutes if within range, or intermittently scanned (isCGM/flash), requiring users to scan the sensor for current glucose values on a reader or smartphone (7).

Glycemic control has traditionally been assessed by measurement of glycated hemoglobin (HbA1c). However, over the last 10 years, the use of CGM and the glucose metrics derived from these devices has become the favored method of assessing glycemic control by many if not most healthcare providers working with diabetes. CGM allows the healthcare professionals (HCPs) and diabetic patients to assess the percent of time spent in the target range (TIR=70-180 mg/dL), time below target range (TBR <70 mg/dL and <54 mg/dL) and time above target range (TAR >180 mg/dL and >250 mg/dL), and act upon predictive glucose information (8). It has been shown that starting CGM early after being diagnosed with T1D reduces HbA1c level for young people (9).

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have published guidelines which set out the goals for times-in-ranges (10). The goals for most diabetic patients are: TIR 70-180 mg/dL >70% of the readings; TBR of <70 mg/dL of <4% of the readings and TBR of <54 mg/dL of <1% of the readings; and TAR >180 mg/dL <25% of the readings and TAR >250 mg/dL <5% of the readings (11).

There are several methods of insulin delivery available to diabetic patients. These include the traditional insulin syringe, insulin pens, smart insulin pens (SIPs) and insulin pumps [with or without concomitant CGM and with or without automated insulin delivery (AID)]. While AID systems provide the best glycemic control compared with the other methods, there are many reasons why diabetic patients may not have access to or want such a system. For those diabetic patients, SIPs when combined with CGM and an insulin dosing calculator represent a new category of diabetes management – the smart insulin pen system – for those managing their insulin with multiple daily injections (MDI) and can provide many of the benefits of an AID

system. A SIP records the time and amount of the dose of short-acting insulin and transmits this data to an app on a smartphone and thereby providing the dose calculator essential information that takes insulin-on-board into account. This can reduce the risk of insulin stacking and provides a more accurate meal and correction insulin dose. The report that the system generates is invaluable to the HCPs, the diabetic patients and their caregiver because it can show the consequences of behaviors such as missing or late insulin doses and inaccurate carbohydrate counting thus providing an opportunity for targeted diabetes education (12, 13).

Recently developed, the Smart MDI system, which combines a CGM with a SIP, offers a comprehensive solution for individuals managing diabetes through insulin injections. This system aims to reduce the physical and mental burden of diabetes management by integrating smart-enabled technological devices. The Smart MDI includes a CGM, an injection port, and a smart insulin pen, providing advanced tools for individuals with type 1 or type 2 diabetes to better manage their condition.

Adolfsson et al. reported that there was a 43% reduction in missed bolus doses of the participants in the ≥180-day follow-up from the initiation of use of the smart pens in their study. They also found a significant increase in TIR of 1·9 hr./day with reduced time spent for hyperglycemia (>180 mg/dL) and hypoglycemia (<54 mg/dL) (14). Increasing concordance with insulin therapy not only has a positive effect on glycemic control but also potentially reduces healthcare costs and utilization (12). Use of the bolus calculator in the SIP system has been associated with a 0·7-1% reduction in HbA1c level and a reduced fear of hypoglycemia. A SIP system can help patients achieve better glycemic results by reminding the user to take their insulin.

With regard to the published literature, the aim of this study is to capture the opinion of diabetes specialists from several regions to better understand how they currently use and how they may use diabetes technologies in the management of diabetic patients using MDI.

Methods

Steering committee

The nominal group technique (NGT) is a widely used method for developing consensus on a given topic. Through NGT, experts provide their input and group consensus is reached through in-person meetings. Within the focus group setting, NGT provides a rigorous approach for acquiring trustworthy and pertinent qualitative information from a group of experts. Through its structured questioning approach, NGT encourages participation from all members, enabling the synthesis of divergent viewpoints on a shared area of interest and identification of consensus areas and priorities for change (15).

Using the nominal group technique (NGT), the steering committee assembled a group of diabetes experts from academia, industry, and consulting backgrounds. The steering committee consists of diabetes clinicians and health economics experts from different countries. The committee developed a structured questionnaire and further led face-to-face discussions to elicit expert opinions.

Survey design

A comprehensive literature review was conducted to examine the technologies and medical needs associated with diabetes management. Using the results of the review, a questionnaire was developed by three experts from the steering committee to solicit feedback from specialized physicians. The remaining six members of steering committee reviewed the questionnaire. The survey was finalized after the review of other clinicians in the steering committee. The pilot test of the questionnaire was conducted with a randomly selected group of 10 specialized physicians. The specialized physicians randomly selected for the pilot test were experts in the relevant field, ensuring that the feedback received was both informed and constructive. Their responses and feedback were utilized to assess the format, language, and clarity of the specified items. Based on the feedback provided by the specialized physicians, several modifications were made to the questionnaire, including rephrasing ambiguous questions, adding more response options to certain items, and restructuring the survey to improve its logical flow (Figure 1).

The questionnaire consisted of five sections and 40 questions in total. The sections were Demographics, General Insights, Expectations, Barriers & Drivers, and New Therapeutic Options. The questionnaire was transferred to an online survey tool and was sent via e-mail to 100 specialized physicians working in Middle East, Eastern Europe, and Africa in order to obtain expert opinions from different geographical regions. Efforts were made to follow up with non-responders to ensure that the invitation to participate was received and understood. The online survey was made accessible between 10th December 2022 and 10th January 2023. The online questionnaire was filled in completely anonymously. Descriptive analyses were conducted using Microsoft Office Excel 360.

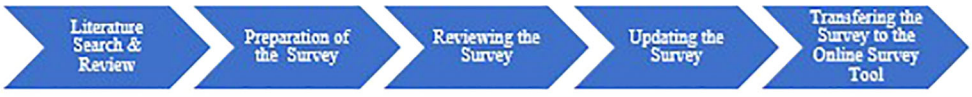

FIGURE 1
Steps of Questionnaire Preparation.

Demographics of the specialized physicians participating in the study

The selection of participants for the study involved identifying specialized physicians across different countries to ensure a diverse and representative sample. In order to avoid any selection bias and increase the generalizability of the findings, all physicians who attended The Diabetes Innovation Summit 2023 event constituted the participants. Volunteers from among the physicians who attended the event participated in the survey. The participants represented a broad demographic, including various age groups, genders, and medical specialties. This diversity was crucial to ensure that the topic was evaluated across different demographic locations.

The Diabetes Innovation Summit 2023 event was held in Istanbul on 13th and 14th of January 2023. The Diabetes Innovation Summit 2023 drew attendance from a diverse group of specialized physicians, including pediatric endocrinologists, adult endocrinologists, diabetologists, internal medicine specialists, and general pediatricians from multiple countries, including Bosnia and Herzegovina, Croatia, Czech Republic, Egypt, Finland, Hungary, Iraq, Latvia, Lebanon, Libya, North Macedonia, Poland, Qatar, Saudi Arabia, Serbia, Slovenia, The United Arab Emirates, The United Kingdom and Türkiye. As part of the study, these experts were divided into small groups based on geographic distribution and engaged in an in-person post-survey discussion session at the Istanbul meeting.

The study adhered to the ethical guidelines set forth by the Declaration of Helsinki. All participating physicians were informed about the study's objectives, procedures, and their rights as participants. Written informed consent was obtained from each participant, ensuring that they were fully aware of the voluntary nature of their involvement and their right to withdraw from the study at any point without any consequences. The confidentiality and anonymity of the participants were strictly maintained throughout the study, and all collected data were securely stored and accessed only by authorized personnel.

Discussion session design

Following the online survey, six structured discussion sessions were conducted in person with specialized physicians from the Middle East, Central-Eastern Europe, and North Africa regions. Physicians were organized into distinct groups based on their respective regions and encouraged to provide feedback on the survey results as well as their clinical practices. The sessions were moderated by members of the steering committee.

Evaluation and reporting

The steering committee members moderated, evaluated, and reported on the discussion sessions. Moderation was tailored to the specific questionnaire results, with each question discussed among specialized physicians from the corresponding region under the guidance of steering committee members. The steering committee members who did not participate in the discussions were responsible for reporting on the sessions.

Results

Demographics

We obtained a responses from 59% of requests to complete the survey. The non-participation of the remaining 41% was primarily due to personal preferences and scheduling conflicts, rather than any inherent issues with the survey itself. A significant number of participants work in North Africa, with more than half of the participants being pediatric endocrinologists. A similar number of physicians from the Eastern Europe and Middle East regions participated in the study (Table 1).

60% of diabetic patients were using MDI according to the clinical practice of specialized physicians. Specialized physicians stated that among diabetic patients who employ MDI, 62% use BGM, 31% isCGM and 23% CGM (Figure 2).

Physicians from North Africa stated that almost 90% of their diabetic patients use MDI because they must pay out of pocket for other treatments and devices which include medication pens, blood glucose meters, strips, injection needles and ketone monitors. In addition, they stated that, their patients used BGM more than CGM. Physicians from Central-Eastern Europe have stated that the usage ratio of MDI in adults is 20 to 30%. For example, MDI is only reimbursed for T1D patients, but not for T2D patients in Czech Republic. This leads to less MDI use.

TABLE 1 Distribution of physicians.

Region	n (%)
North Africa	26 (44·0%)
Central-Eastern Europe	17 (28·8%)
Middle East	13 (22·0%)
Other	3 (5·0%)
Specialty	
Pediatric Endocrinologist	33 (55·9%)
Adult Endocrinologist	13 (22·0%)
Diabetologist	9 (15·2%)
General Paediatrician	2 (3·3%)
Internal Medicine Specialist	1 (1·6%)
Other	1 (1·6%)

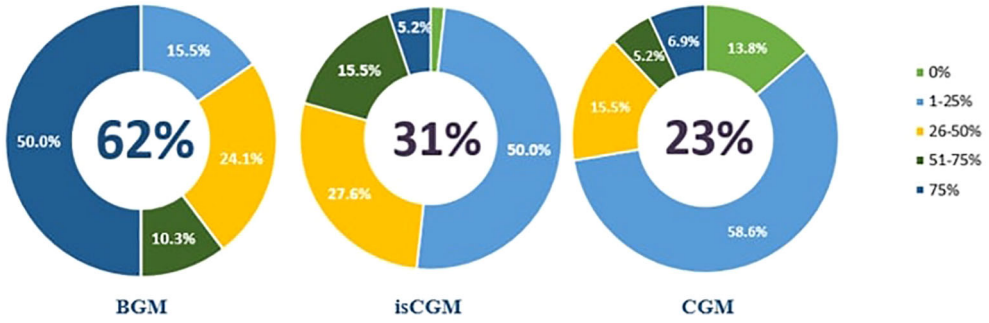

FIGURE 2
BGM, isCGM and CGM Usage Rates of Diabetic Patients Using MDI.

The nominal group technique results

The following will describe and compare the results of the debated topics of questionnaire with the outcome of face-to-face discussion followed by the shared conclusions

Questionnaire: Attitudes and concepts about the use of the glucose metrics HbA1c measurements, TIR and the ability to achieve glycemic goals

While 86·2% of the physicians stated that they place emphasis on both TIR and lab HbA1c parameters for glycemic control of diabetic patients using MDI, 5·2% and 1·7% mentioned only TIR and only HbA1c results, respectively. Additionally, a minority of participants (1·7%) expressed the importance of considering TIR, TAR, and TBR (Figure 3).

Satisfaction with TIR that was achieved in diabetic patients treated with MDI+BGM was expressed by 31% of physicians, while 27·5% remained neutral and 41·3% were dissatisfied. The majority of participants (77·5% and 82·7%) reported satisfaction with the achieved TIR in MDI+isCGM and MDI+CGM treatments, respectively. Participants reported satisfaction with HbA1c results in the following proportions: 32·7% with MDI+BGM treatment, 63·7% with MDI+isCGM treatment, and 68·9% with MDI +CGM treatment.

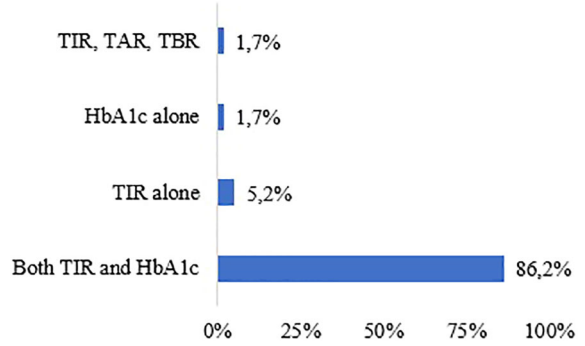

FIGURE 3
Preferred Parameters to Measure Glycemic Control.

According to the study findings, 74·1% of physicians believed that Real-Time CGM (rtCGM) treatment was satisfactory for achieving TIR targets in diabetic patients. A smaller proportion (10·3%) considered the treatment to be insufficient, while 15·5% remained uncertain. The majority of physicians (79·3%) believed that rtCGM treatment was adequate for achieving their HbA1c goals, with 15·5% remaining neutral and 5·1% considering the treatment to be insufficient (Table 2).

Open discussion

During the discussion sessions, physicians from the Middle East region raised concerns about the potential for misleading results with HbA1c, particularly among pregnant women or patients with Down syndrome or hemoglobinopathies. As such, they suggested that TIR and HbA1c be assessed in conjunction. Physicians from Eastern Europe, on the other hand, expressed less satisfaction with HbA1c results when using MDI+isCGM and MDI+CGM treatments. Furthermore, some physicians noted that HbA1c might not be necessary if CGM was utilized.

According to the physicians in the Middle East region, the proportion of patients achieving the target TIR was relatively low (20-30%) despite the analysis results indicating that patients treated with CGM were able to achieve their TIR targets. Similarly, physicians from Eastern Europe reported that the rate of patients using isCGM who achieved the TIR target was approximately 30%. They also noted that while HbA1c results in patients using isCGM were promising during the first two weeks, there were some misleading results in the subsequent period.

Questionnaire: Attitudes and concepts about barriers & drivers to achieve glycemic targets

According to the responses, it is perceived that an average of 44% of diabetic patients using MDI adhered to carbohydrate counting. This rate was higher in the pediatric population than in adults (51% vs 36%). Among diabetic patients using MDI, the frequency of using the sensor per month is 52% and it is similar in in both pediatric & adult populations (54% vs 52%). The study findings revealed that 24% of physicians reported that diabetic patients using MDI could potentially miss two or more doses per week. According to the results, the rate of missed doses among

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TABLE 2 Use of TIR or HbA1c satisfaction rate by type of treatment.

	Satisfaction by use of TIR			Satisfaction by use of HbA1c		
	MDI+BGM	MDI+isCGM	MDI+CGM	MDI+BGM	MDI+isCGM	MDI+CGM
Satisfaction Level	31·3%	77·6%	82·8%	32·8%	63·8%	82·8%
Additional glucose data beyond BGM alone	22·4%	16·6%	–	29·8%	33·3%	–
Data on missed/late insulin doses	24·1%	25·0%	25·0%	22·8%	20·0%	28·5%
Prevention of Insulin stacking	17·2%	25·0%	25·0%	19·3%	13·3%	28·5%
More frequent blood glucose testing per day	18·9%	–	–	–	–	–
Data on miscalculated insulin doses	15·5%	33·3%	25·0%	26·3%	33·3%	42·8%
Not using additional features of CGM	–	–	25·0%	–	–	–

patients using MDI was found to be 22% for adults and 26% for pediatric patients. Furthermore, the study revealed that 32% of patients with diabetes using MDI were at risk of miscalculating their insulin dose. Consequently, the proportion of patients using MDI who may experience level 2 and level 3 hypoglycemia due to insulin accumulation was estimated to be 22% (Table 3).

Open discussion

In the discussion session, physicians from the Middle East region stated that they found these rates to be accurate and that their patients missed doses and calculated the dosage wrongfully almost every day. It was conceded that patients, pay little attention to what they eat in a day, and they believed that missed doses are the major problem according to their clinical practice. In addition, all physicians agree that carb counting is more prevalent in the pediatric population with T1D. During the discussion sessions, physicians from the Eastern Europe region noted that the use of sensors appeared to be more prevalent, possibly due to geographical and financial factors.

Questionnaire: Attitudes and concepts with regard to the value and importance of Smart MDI System

It was found that a significant majority (93%) of participants agreed that patients with diabetes using MDI would appreciate the additional clinical benefits of the Smart MDI System. Additionally, participants believed that the Smart MDI System would offer greater clinical advantages than MDI+BGM (93%), MDI+isCGM (86%), and MDI+CGM (81%) applications (Table 4). Participants evaluated clinical benefits of Smart MDI System provided by the system on a 5-point Likert scale. Depending on the evaluation, the pre-elimination of errors in insulin dose according to Likert scale was rated as 4·28/5, the complete picture of diabetes management as 4·18/5, the elimination of missed doses as 4·09/5, insulin stacking as 4·05/5 and the simplification of meal management (carb count) as 3·93/5 (Table 5).

The importance of a Smart MDI System for diabetic patients using MDI has been also evaluated on a 5-point Likert scale based on the categories. According to the analysis results, Smart MDI System has the highest level of importance for diabetic patients who are suitable for Advanced Hybrid Closed Loop System (AHCL) but cannot access it due to affordability (4·34/5). Other diabetic patients categories where a Smart MDI System is important were mentioned as: a) bolus on either BGM, CGM or isCGM with unsatisfactory clinical outcomes (4·00/5); b) unfavored by the user (3·84/5); c) bolus initiation irrespective of glucose monitoring technology (3·80/5) (Table 5).

During the study, the possible acceptance and usage of a Smart MDI System among diabetic patients using MDI were assessed. Results showed that 49% of the participants thought that diabetic

TABLE 3 Problems experienced in diabetic patients using MDI.

	Pediatric	Adult	Overall
Concordance with carb counting	51%	36%	44%
Sensor utilization	54%	52%	52%
Missing ≥2 Bolus doses per week	26%	22%	24%
Miscalculating the insulin dosage	34%	30%	32%
Level 2 and level 3 hypoglycemia (<54 mg/dl)	22%	22%	22%

TABLE 4 Additional clinical benefit of the smart MDI system for diabetic patients using MDI.

	Agree & Strongly Agree	Neutral	Disagree & Strongly Disagree
General additional clinical benefits of Smart MDI System	92·9%	5·2%	1·7%
Smart MDI System vs MDI+BGM	92·9%	5·2%	1·7%
Smart MDI System vs MDI+isCGM	85·9%	10·5%	3·5%
Smart MDI System vs MDI+CGM	80·7%	15·7%	3·5%

TABLE 5 Evaluation of clinical benefits and importance of the smart MDI system: results from a 5-point likert scale.

	1	2	3	4	5	Mean
Clinical Benefits						
Elimination of insulin dosage mistakes	1 (1·75%)	1 (1·75%)	4 (7·02%)	26 (45·61%)	25 (43·86%)	4·28
Full picture of diabetes management	1 (1·75%)	1 (1·75%)	9 (16·36%)	20 (36·36%)	24 (43·64%)	4·18
Eliminating missed doses	3 (5·26%)	0 (0·00%)	11 (19·30%)	18 (31·58%)	25 (43·86%)	4·09
Insulin stacking	1 (1·75%)	3 (5·26%)	10 (17·54%)	21 (36·84%)	22 (38·60%)	4·05
Simplifying meal management	2 (3·51%)	3 (5·26%)	11 (19·30%)	22 (38·60%)	19 (33·33%)	3·93
Important Patient Groups						
Diabetic patients who are suitable for AHCL but cannot access it due to affordability	0 (0·00%)	1 (1·79%)	10 (17·86%)	14 (25·00%)	31 (55·36%)	4·34
Diabetic patients already on Basal: Bolus on either BGM, CGM or isCGM with unsatisfactory clinical outcomes	0 (0·00%)	3 (5·36%)	12 (21·43%)	24 (42·86%)	17 (30·36%)	4·00
Diabetic patients who are suitable for AHCL but unfavored by the user	2 (3·57%)	4 (7·14%)	13 (23·21%)	19 (33·93%)	18 (32·14%)	3·84
Diabetic patients with Basal: Bolus initiation irrespective of glucose monitoring technology	2 (3·57%)	4 (7·14%)	12 (21·43%)	23 (41·07%)	15 (26·79%)	3·80

patients using MDI would be willing to use a Smart MDI System. Majority of physicians (96%) believed that diabetic patients who start the Smart MDI System would continue using it for more than 6 months. The study examined physicians' views on the appropriate pricing for a Smart MDI System compared to the current CGM prices in their respective countries. Results indicated that 50% of the physicians thought that the Smart MDI System should be priced 10 to 30% higher than the current CGM prices, while 27·5% believed that the price should be 31 to 50% higher and 22·5% believed that the pricing should be similar.

Open discussion

During the discussion session, physicians, particularly from the Eastern Europe region, emphasized that the use of a Smart MDI System is contingent on patient preference and cost. The anticipated level of adoption by patients was set to exceed 49%. In contrast, physicians from the Middle East expressed their view that patients aged 50-60 may not be inclined to use the new technology.

Discussions

The present study highlights that physicians are generally supportive of utilizing new technology. However, during open discussions, concerns were raised due to their limited practical experience with Smart MDI Systems. Additionally, there are concerns about accessing diabetic patients' phone, which could hinder optimal use of the technology. The questionnaires and the open discussion revealed the expectation that the Smart MDI technology provides better control, primarily by identifying missed boluses, while expressing concerns on the use of the technology by teenagers and children, who might forget the device and be reluctant to use in public, and by the older population, who might be challenged by the technology.

This study revealed gaps in the knowledge and experience of CGM in clinical use by physicians from the Middle East region. This gap may translate into a lower rate of use by patients. Physicians mentioned that online training should be given to patients and healthcare professionals about how to use the device, settings, and solutions to possible problems.

Another important barrier expressed, notably by Middle East and African region physicians, is the affordability. In contrast to the views of physicians from the Middle East, physicians from the Central-Eastern Europe region pointed out that the insurance systems in their countries cover the cost of new technologies, including Smart MDI System, subject to meeting certain conditions, and that reimbursement is available.

Based on the results and discussions, it is clear that the main hurdles to overcome are the access of the new technologies and the lack of experience of HCPs. Physicians should raise awareness and seek to negotiate with policy makers to include new technology in reimbursement, taking into account the perceived clinical utility of the new technology and the improved quality of life for patients.

Limitations

This study is based on a technique to assess attitudes and perception therefore cannot be used for quantitative statistical analysis. Since the participants were predominantly specialized physicians attending The Diabetes Innovation Summit 2023, primary care physicians, who are also integral to diabetes management, were not included in the sample. Additionally, the survey did not collect supplementary data beyond the questions presented in the questionnaire, as outlined in the Supplementary Materials. Therefore, further studies are needed to address these limitations and provide a more comprehensive understanding.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

GK: Writing – original draft. TB: Writing – review & editing. GP: Writing – review & editing. JJ: Writing – review & editing. BS: Writing – review & editing. NE: Writing – review & editing. DG: Writing – review & editing. MA: Writing – review & editing. BT: Writing – review & editing. AS: Writing – review & editing. SÖ: Writing – original draft. FÖ: Writing – original draft. MK: Writing – original draft.

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Conflict of interest

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

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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.2024.1308319/full#supplementary-material

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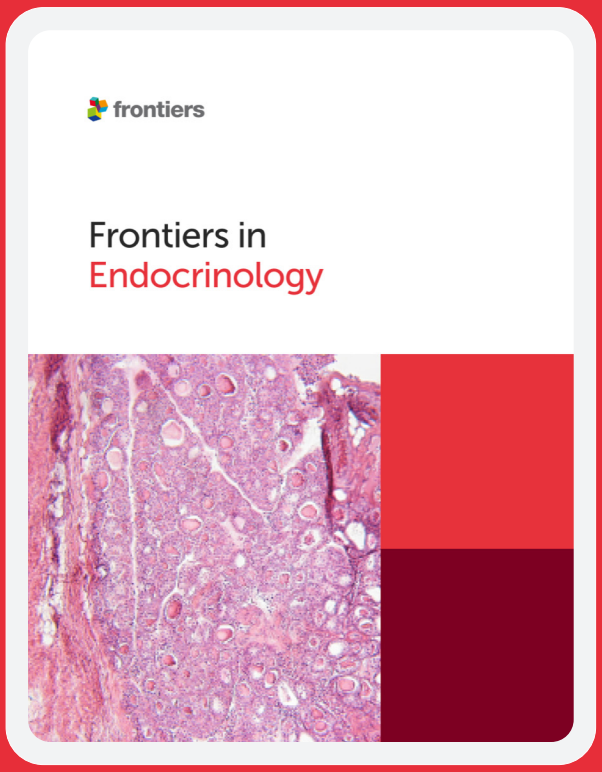

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