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Interdisciplinary research in diabetology

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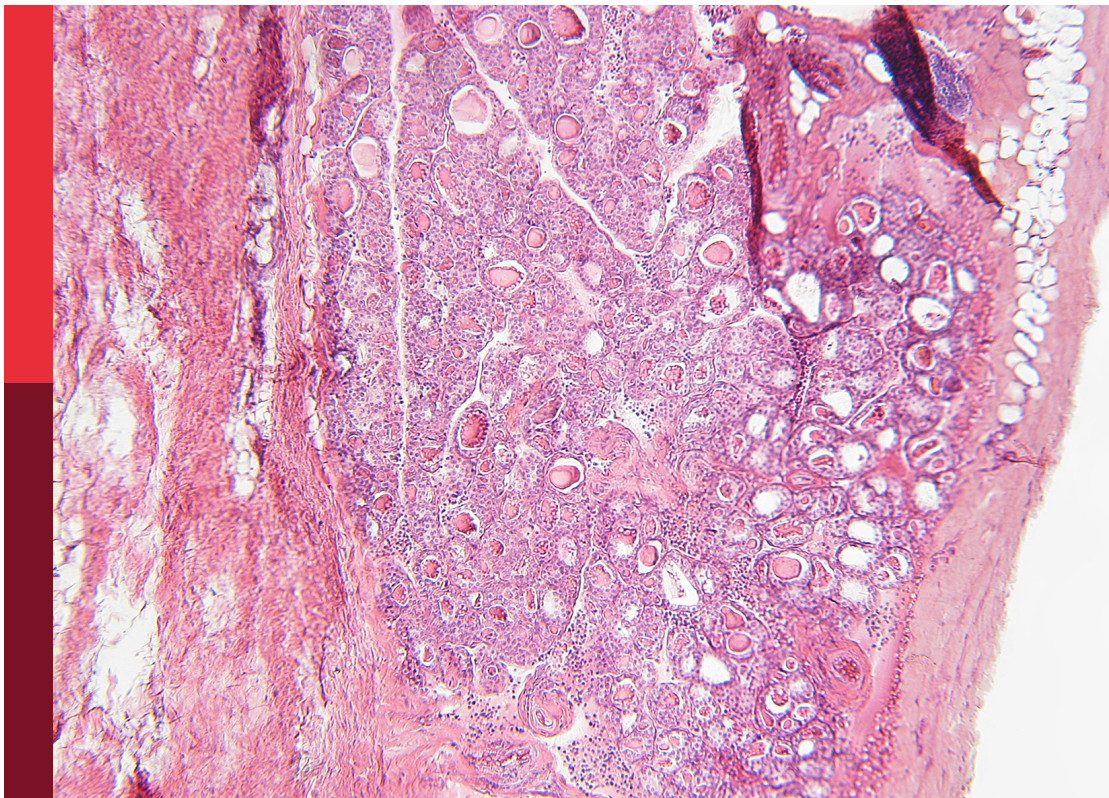

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Interdisciplinary research in diabetology

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Editorial: Interdisciplinary research in diabetology

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Editorial on the Research Topic
Interdisciplinary research in diabetology

Introduction

Interdisciplinary research is becoming increasingly important in endocrinology, especially in the management of diabetes. The multifaceted nature of diabetes, marked by its complex etiology and various comorbidities, requires a collaborative strategy that brings together insights from multiple fields, including basic science, epidemiology, technology, and beyond. This integration not only improves our understanding of the disease and fills the gaps in our knowledge but also fosters innovative solutions that can lead to improved patient outcomes. Studies have shown that interdisciplinary collaboration can significantly improve the quality of care for patients with diabetes by addressing the intricate interplay of biological, psychological, and social factors that influence disease progression and management (1, 2). Moreover, as diabetes care evolves, the incorporation of advanced technologies, such as continuous glucose monitoring and telemedicine, highlights the importance of cross-disciplinary expertise in developing and implementing effective management strategies. The ability to work collaboratively across specialties not only enriches the research landscape but also ensures that clinical practice is informed by the latest evidence and innovations, ultimately leading to a more holistic approach to patient care. The aim of this Research Topic is to underscore the vital role of multidisciplinary research in advancing our understanding of diabetes and to promote this point of view among researchers, ultimately leading to improved health outcomes for individuals affected by this pervasive condition.

This Research Topic showcases the latest multidisciplinary research in diabetology, featuring 13 cutting-edge articles covering a wide range of topics related to type 1 and type 2 diabetes. From systematic analyses of the global burden of diabetes to innovative diagnostic methods and personalized treatment strategies, these studies underscore the vital role of collaborative, cross-disciplinary research in improving our understanding and management of this intricate disease.

Discussion

Starting with epidemiology is crucial in a multidisciplinary approach to diabetes as it provides a foundational understanding of the disease's prevalence, risk factors, and trends across different populations. Epidemiological studies reveal critical insights into how social determinants, lifestyle choices, and genetic predisposition contribute to the development and progression of diabetes. By identifying at-risk populations and understanding the geographic and demographic variations in diabetes incidence, researchers can tailor interventions that are culturally and contextually relevant. The global burden of diabetes is a pressing public health challenge, with the International Diabetes Federation predicting that over 1.31 billion people will be living with diabetes by 2050, driven primarily by rising obesity rates and lifestyle factors across diverse populations (3). Two articles in this Research Topic tackle the immense global burden of diabetes from different angles. Ye et al. in a systematic analysis of the Global Burden of Disease Study, provided a comprehensive overview of the past, present, and future trends in type 2 diabetes mellitus at the global, regional, and national levels. These data are critical for informing public health policy and resource allocation to combat the growing diabetes epidemic. Liang et al. focused specifically on the burden of type 1 and type 2 diabetes and high fasting plasma glucose in Europe from 1990 to 2019. By examining trends over this three-decade period, the authors shed light on the evolving nature of the disease and the need for tailored, region-specific interventions.

The incorporation of new technologies into the prevention, diagnosis, and management of diabetes marks a significant breakthrough in interdisciplinary research. Innovations such as continuous glucose monitoring systems, telehealth platforms, and artificial intelligence-driven predictive analytics are enabling more personalized and proactive care, allowing healthcare providers to tailor interventions based on real-time data and individual patient needs. These technologies not only improve clinical decision-making but also empower patients to take an active role in managing their condition, ultimately leading to better health outcomes. By fostering collaboration between technology developers, clinicians, and researchers, interdisciplinary approaches can harness the full potential of these advancements to combat the diabetes epidemic effectively. Several articles in this Research Topic showcase the potential of emerging technologies to revolutionize diabetes diagnosis and management. Litvinova et al. explored the patent landscape of digital sensors for continuous glucose monitoring, highlighting the rapid advancements in this field and the promise of improved glycemic control for patients. An et al. took a deep dive into the use of MRI fat fraction mapping to assess the association between type 2 diabetes and body composition. This non-invasive imaging technique holds promise for early detection and risk stratification, potentially leading to more targeted interventions.

Personalized medicine tailors treatment strategies based on individual patient characteristics, including genetic makeup, lifestyle, and comorbidities, requiring input from various medical disciplines such as endocrinology, genetics, nutrition, and psychology. This collaborative effort enhances the ability to identify specific biomarkers and genetic variants that predict treatment response, allowing for more effective and individualized interventions. Personalized medicine has been shown to be highly effective in diabetes management, particularly when implemented through a multidisciplinary approach. Studies show that personalized interventions that leverage the expertise of different healthcare professionals, significantly improve clinical outcomes for patients with type 2 diabetes. One study examined the practice effects of personalized interventions with interdisciplinary teamwork in achieving type 2 diabetes remission (Tian et al.). By leveraging the expertise of a diverse team of healthcare professionals, this approach demonstrates the potential for tailored, patient-centered care to yield positive outcomes. Another article delved into the relationship between illness perception and medication adherence in patients with diabetes in North Shoa, Ethiopia (Eshete et al.). Understanding the factors that influence patient behavior is crucial for developing effective, patient-centered interventions to improve treatment outcomes.

The interplay between diabetes and other conditions underscores the importance of collaboration across disciplines to better understand the origins and causes of the disease. By integrating insights from fields such as nutrition, psychology, and endocrinology, researchers can uncover the complex mechanisms that contribute to the development of diabetes. Albeloushi et al. investigated the differential effects of fish-oil and cocoa-butter-based high-fat/high-sucrose diets on endocrine pancreas morphology and function in mice, shedding light on the potential mechanisms underlying the development of diabetes. Geng et al. examined the bidirectional relationship between type 2 diabetes and major depressive disorder in a Chinese population, highlighting the importance of screening for and treating comorbid mental health conditions in diabetes patients. Wang et al. employed Mendelian randomization to investigate the causal relationship between Chronic Obstructive Pulmonary Disease (COPD) and type 2 diabetes mellitus (T2DM), revealing that COPD may serve as a significant risk factor for T2DM. Marhefkova et al. examined circadian dysfunction and its association with cardio-metabolic disorders, emphasizing the role of biological rhythms in diabetes management. Yang et al. in a narrative review focused on the methods of measuring the biomechanical properties of plantar soft tissues in patients with diabetic foot, highlighting the importance of early detection and intervention. Additionally, research by Feng et al. on the elevated triglyceride-glucose (TyG) index highlighted its association with an increased prevalence of gallstones, further illustrating the interconnectedness of metabolic disorders. Finally, Breznoscakova et al., in a case report uncovered hidden glucose patterns in patients with bipolar disorder and comorbid type 1 diabetes, underscoring the necessity of personalized approaches to treatment. Collectively, these articles underscore the multifaceted nature of diabetes and the critical need for collaborative efforts across various disciplines to improve patient care and outcomes.

Conclusion

This Research Topic showcases the breadth and depth of multidisciplinary research in diabetology, from global epidemiology to personalized treatment approaches and the exploration of underlying mechanisms. By fostering collaboration across disciplines and borders, we can continue to advance our understanding of diabetes and develop more effective strategies for prevention and management. We hope that these articles will inspire further research and innovation in this critical field.

Author contributions

NT: Writing – original draft. BL: Writing – review & editing.

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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The global, regional and national burden of type 2 diabetes mellitus in the past, present and future: a systematic analysis of the Global Burden of Disease Study 2019

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Aim: To report the global, regional, and national burden of type 2 diabetes mellitus (T2DM) in 2019, assess its trends in the past, and forecast its trends in the future.

Methods: The main data source was the Global Burden of Disease 2019 database. We assessed the changes in T2DM burden from 1990 to 2019 with joinpoint regression analysis. Age-period-cohort analysis was used to forecast the T2DM incidence and mortality rate from 2020 to 2034.

Results: The burden of T2DM has increased from 1990 to 2019 generally. The low-middle socio-demographic index (SDI) region had the highest increase in age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), age-standardized mortality rate (ASMR), and age-standardized disability-adjusted life years (ASDR) due to T2DM. Nationally, the increase in ASIR (r=0.151, p=0.046) and the decrease in ASMR (r=0.355, p<0.001) were positively correlated with SDIs. In 2019, the global ASIR, ASPR, ASMR, ASDR due to T2DM were 259.9 (95% UI 240.3-281.4), 5282.9 (95% UI 4853.6-5752.1), 18.5 (95% UI 17.2-19.7), and 801.5 (95% UI 55477000-79005200) per 100,000 population, respectively. Additionally, the ASIR (r=0.153, p=0.030) and ASPR (r=0.159, p=0.024) of T2DM were positively correlated with SDIs, while ASMR (r=-0.226, p=0.001) and ASDR (r=-0.171, p=0.015) due to T2DM were negatively correlated with SDIs. The ASIR was estimated to increase to 284.42, and ASMR was estimated to increase to 19.1 from 2030 to 2034, per 100,000 population.

Conclusion: Globally, the burden of T2DM has increased in the past and was forecast to continue increasing. Greater investment in T2DM prevention is needed.

KEYWORDS

type 2 diabetes mellitus, epidemiology, global burden of disease, trend, forecast

1 Introduction

Type 2 diabetes mellitus (T2DM), which is characterized by hyperglycemia resulting from progressive loss of adequate insulin production in the setting of insulin resistance, has been identified as a serious global health threat by WHO (1, 2). The International Diabetes Federation estimated that the prevalence of diabetes which was 10.5% in 2021, would increase to 11.3% by 2030 and 12.2% by 2040 (3). T2DM patients have a higher risk of dysfunction and failure of various organs, especially the kidneys, eyes, and nerves, causing increased costs of medical care and decreased life quality (2, 4, 5). In addition, it was observed that T2DM patients had a 15% increased risk of premature death and an approximate 20-year reduced life expectancy (6). The improvement in prevention and prognosis of T2DM has become an urgent medical problem, and studying the epidemiological characteristics of T2DM will contribute to its mitigation.

Previous studies have directly reported the epidemiological data from the database named Global Burden of Disease (GBD) 2019, including the incidence, death rates and disability-adjusted years (DALYs) (7, 8). Additionally, the trends in incidence, death rates and DALYs due to T2DM over the past 30 years have been evaluated by estimated annual percentage changes (EAPCs) (7). However, EAPCs were calculated with the assumption that the trend is linear over the interval, which is contradictory when the data are sparse, giving unreliable results (9). Additionally, previous studies have not assessed the impact of interregional differences in socioeconomic development status on the burden of T2DM and its changes, nor have they forecasted the future trend of T2DM burden. Therefore, more in-depth studies are needed to systematically analysis the global, regional and national burden of T2DM in the past, present and future.

In this study, the burden of T2DM was mainly reflected by its age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), age-standardized mortality rate (ASMR), and age-standardized DALYs due to T2DM (ASDR). The socio-demographic Index (SDI) value was used to evaluate the socio-economic development status of a country or region. We aimed to evaluate the changes of global, regional, and national burden of T2DM from 1990 to 2019, systematically reported the latest epidemiology of T2DM, and assessed the association between them and SDIs. Moreover, the incidence and mortality rate of T2DM from 2020 to 2034 were forecast based on sex and age groups. These results contribute to evidence-based health-policy decision making in different countries and territories.

2 Methods

2.1 Data source

The GBD project is a comprehensive endeavor that evaluates epidemiological trends and levels related to illnesses and injuries worldwide. In the most recent version of this study, GBD 2019, 369 illnesses and injuries, together with 87 risk variables, were calculated in 21 GBD regions, and 204 countries and territories between 1990 and 2019 (10). In this research, data about the disease burden of T2DM was acquired from GBD 2019, including prevalence, incidence, deaths, and DALYs. In addition, the GBD 2019 global standard population was used to compute the age-standardized rates (ASR) to take into account population and age structure disparities, such as ASPR, ASIR, ASMR, and ASDR. Global population forecasts for 2017-2100 were used to forecast the T2DM disease burden trends.

The SDI value is a composite indicator of the socio-economic development status of a country or region, which is calculated from the overall fertility rate of female under 25-years, the average educational achievement among women at least 15-years of age, and per capita income with a lag in distribution (11). According to the SDI, 204 territories and countries are divided into high SDI regions (SDI>0.81), high-middle SDI regions (0.70≤SDI ≤ 0.81), middle SDI regions (0.61≤SDI ≤ 0.69), low-middle SDI regions (0.46≤SDI ≤ 0.60), and low SDI regions (SDI<0.46) (12). The data mentioned above was from the GBD database (GHDx), which is publicly accessible online at (https://vizhub.healthdata.org/gbd-results).

2.2 Statistical analysis

2.2.1 Descriptive analyses

We conducted the descriptive analyses on the global, regional and national burden of T2DM. Of note, the number of incidence cases, prevalence cases, mortality cases, and DALYs were too large in some regions or countries. To clearly presented those data, we only kept the value of one decimal place of the original data in all tables. When the data was too small in some age groups, it would be presented as "0". The origin data is publicly accessible at https://vizhub.healthdata.org/gbd-results). Additionally, we assessed the association between the ASIR, ASPR, ASMR, and ASDR due to T2DM and SDI to explore the factors that influence the national burden of T2DM.

2.2.2 Joinpoint regression analysis

The changes in T2DM disease burden were evaluated using the Joinpoint Regression Program (Version 4.9.1.0.). Joinpoint regression analysis recognizes the best match for inflection points, also known as "joinpoints," where there is significant change in trends by using a set of permutation tests and multiple comparisons with Bonferroni adjustment. Joinpoint analysis was applied in this study to recognize the independent variable (years) with significant changes in the dependent variable (ASIR, ASPR, ASMR, and ASDR) from 1990 to 2019, together with the size of these changes. We utilized the log-linear model to analyze constant percentage rate change. Up to 5 joinpoints were allowed by employing a Monte Carlo permutation procedure. Each joinpoint reflects a statistically significant (p-value < 0.05) change in trend, with each trend defined by the average annual percentage change (AAPC) and its associated 95% confidence intervals (95% CI). In addition, we assessed the association between the AAPCs of ASIR, ASPR, ASMR, and ASDR caused by T2DM and SDI to explore the factors that influence the changes in the burden of T2DM at the national level.

2.2.3 Age-period-cohort analysis

This study used the age-period-cohort model, a generalized linear model, to analyze the trends in burden of T2DM. The independent variables in the age-period-cohort model are age, period, and cohort, while the dependent variable is the appearance of a particular observable event or phenomenon in the population, which follows a specific probability distribution. Based on the past incidence, mortality rate and the population forecast in GBD 2019, we forecast the incidence and mortality rate of T2DM from 2020 to 2034 using the age-period-cohort model by running the Nordpred package in R. Moreover, to assess the association between incidence, mortality rate and age, we analyzed the trends of incidence rate and mortality rate in different age groups.

The R program was used to perform all statistics (Version 4.2.0). Statistical significance was defined as a p value less than 0.05.

The R program was used to perform all statistics (Version 4.2.0). Statistical significance was defined as a p value less than 0.05.

3 Results

3.1 Changes in the global, regional, and national burden of T2DM, from 1990 to 2019

Globally, the ASIR of T2DM increased from 184.6 (95% UI 170.9-199.7) per 100,000 population in 1990 to 259.9 (95% UI 240.3-281.4) per 100,000 population in 2019, corresponding to an AAPC of 1.176 (95% CI 1.129-1.224). Similarly, the AAPCs of ASPR, ASMR, ASDR of T2DM, shown in Table 1, suggested that ASPR, ASMR, and ASDR due to T2DM were increased around the world.

All five SDI regions had increased ASIR, among which the low-middle SDI region had the highest AAPC of ASIR, whereas the high-middle SDI region had the lowest. The ASPR, ASMR, ASDR also showed the largest increase in the low-middle SDI region. Of note, the ASMR of T2DM decreased in the high-middle SDI region and high SDI region.

At the regional level, the ASIRs and ASPRs in all GBD regions increased from 1990 to 2019 (Table 1). Central Asia had the largest increased burden of T2DM, including ASIR, ASPR, ASMR, and ASDR due to T2DM. Though the ASMRs and ASDRs were increased in most GBD regions, opposite results were observed in some GBD regions. Eight GBD regions had decreased ASMRs, among which Western Europe had the greatest decrease, with an AAPC of -1.494 (95% CI -1.589 to -1.399). Meanwhile, a decrease in ASMRs and ASDRs due to T2DM was found in three GBD regions, including Eastern Sub-Saharan Africa, the High-income Asia Pacific, and Tropical Latin America.

Changes in the burden of T2DM by country and territory from 1990 to 2019 are presented in Supplementary Table S1; Figure 1. As shown in Figure 1A, in almost all countries and territories, the ASIRs of T2DM were increased from 1990 to 2019. The highest increase of ASIR was observed in Luxembourg (AAPC= 4.2 [95% CI 4.153- 4.246]), followed by Ireland. Only Ethiopia and Singapore showed a decreased ASIR, in which AAPC of ASIR was -0.536 (95% CI -0.677 to -0.396) and -0.171 (95%CI -0.374 to 0.033), respectively. Except for Ethiopia, all countries and territories had increased ASPR of T2DM, among which Luxembourg (AAPC= 4.373 [95% CI 4.304- 4.441) was the largest, as shown in Figure 1B. Similar to ASIR and ASPR, ASMR (Figure 1C) and ASDR (Figure 1D) due to T2DM increased from 1990 to 2019 in most of the countries and territories. The largest increase in ASMR and ASDR due to T2DM were in Uzbekistan. Fortunately, in more than 1/3 (84/204) of the countries and territories, the ASMR was decreased, among which Singapore (AAPC= -6.916 [95% CI -7.776 to -6.048]) showed the largest reduction. Additionally, nearly 1/5 (35/204) of the countries and territories had decreased ASDRs due to T2DM, among which Ethiopia (AAPC= -1.836 [95% CI -2 to -1.671]) had the largest decrease, followed by Singapore (AAPC= -1.781 [95% CI -2.375 to -1.184]). Moreover, the correlation between the AAPCs of ASIR, ASPR, ASMR, and ASDR and SDIs was analyzed in this study, and the results are shown in Figure 2. The AAPCs of ASIR were positively associated with SDIs (r=0.15, p=0.045, Figure 2A). On the contrary, a negative correlation was observed between the AAPCs of ASMR and SDIs (r=-0.35, p<0.01, Figure 2C). However, no correlation was found between AAPCs of ASPR and SDIs (r=0.07, p=0.36, Figure 2B), nor between AAPCs of ASDR and SDIs (r=-0.08, p=0.29, Figure 2D).

3.2 The global, regional, and national burden of T2DM in 2019

Globally, as shown in Table 2, there were 21,669.9 (95% UI 20,020.9-23,513.5) thousand new cases and a total of 437,906.6 (95% UI 402,043.3-477,018.2) thousand cases of T2DM in 2019. Per 100,000 population, the ASIR was 259.9 (95% UI 240.3-281.4), the ASPR was 5282.9 (95% UI 4853.6-5752.1), and the ASMR was 18.5 (95% UI 17.2-19.7). 66,299.8 (95% UI 55477.0-79005.2) thousand DALYs were caused by T2DM, with an ASDR of 801.5 (95% UI 670.6-954.4) per 100,000 population.

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TABLE 1 The global and regional AAPCs of T2DM ASIR, ASPR, ASMR, and ASDR from 1990 to 2019.

Characteristics	AAPCs			
	ASIR (95% CI)	ASPR (95% CI)	ASMR (95% CI)	ASDR (95% CI)
Global	1.176(1.129-1.224)	1.374 (1.319 1.429)	0.365 (0.319 - 0.412)	0.817 (0.738 0.896)
Sociodemographic index				
Low SDI	1.128 (1.066 - 1.191)	1.478 (1.403 - 1.553)	0.178 (0.024 - 0.333)	0.496 (0.444 0.549)
Low-middle SDI	1.433 (1.35 - 1.516)	1.657 (1.446 - 1.868)	0.852 (0.543 - 1.162)	1.116 (0.869 - 1.364)
Middle SDI	1.024 (0.9 1.149)	1.2 (1.143 - 1.258)	0.597 (0.457 - 0.737)	0.815 (0.682 - 0.948)
High-middle SDI	0.938 (0.81 - 1.067)	1.175 (1.144 - 1.207)	-0.142 (-0.233 -0.051)	0.455 (0.381 - 0.528)
High SDI	1.402 (1.263 - 1.54)	1.563 (1.43 - 1.697)	-0.883 (-1.07 -0.694)	0.665 (0.573 - 0.758)
Region				
Andean Latin America	1.532 (1.472 - 1.593)	1.826 (1.801 - 1.85)	0.748 (0.425 - 1.073)	1.016 (0.742 - 1.291)
Australasia	1.458 (1.351 - 1.565)	1.936 (1.8 - 2.072)	-0.754 (-0.977 -0.53)	0.555 (0.415 - 0.696)
Caribbean	0.96 (0.917 - 1.003)	1.215 (1.198 - 1.233)	-0.45 (-0.708 - -0.191)	0.202 (0.066 - 0.338)
Central Asia	2.333 (2.246 - 2.419)	2.328 (2.242 - 2.414)	3,418 (2.866 - 3.972)	2.753 (2.597 - 2.909)
Central Europe	1.348 (1.145 - 1.55)	1,463 (1.36 - 1.567)	0.076 (-0.074 0.225)	0.766 (0.675 0.858)
Central Latin America	0.588 (0.298 - 0.88)	0.98 (0.809 - 1.15)	0.131 (-0.258 - 0.521)	0.399 (0.255 - 0.544)
Central Sub-Saharan Africa	0.892 (0.855 0.93)	1.225 (1.19 - 1.26)	-0.408 (-0.602 - -0.213)	0.042 (-0.105 - 0.189)
East Asia	0.457 (0.159 - 0.756)	0.697 (0.604 - 0.79)	0.183 (0.032 - 0.335)	0.259 (0.042 0.477)
Eastem Europe	1.068 (0.939 - 1.197)	0.971 (0.929 - 1.013)	1.491 (0.606-2.383) -	1.042 (0.821 - 1.263)
Eastern Sub-Saharan Africa	0.465 (0.438 - 0.493)	0.878 (0.846 0.91)	-0.403 (-0.488 - -0.318)	-0.303 (-0.365 -0.241)
High-income Asia Pacific	0.552 (0.413 - 0.691)	0.776 (0.717 - 0.836)	-2.111 (-2.352 -1.868)	-0.006 (-0.071 - 0.06)
High-income North America	1.365 (1.02 - 1.711)	1.456 (1.084 - 1.83)	-0.234 (-0.502 - 0.034)	0.821 (0.596 1.046)
North Africa and Middle East	2.05 (2.015 - 2.085)	2.178 (2.118 - 2.239)	0.074 (-0.088 - 0.237)	0.964 (0.836 - 1.092)
Oceania	1.327 (1.306 - 1.349)	1.792 (1.779 - 1.805)	1.105 (0.984-1.226) -	1.216 (1.138 - 1.293)
South Asia	1.57 (1.49 1.649)	1.769 (1.593 - 1.946)	0.89 (0.277 - 1.507)	1.233 (0.783 - 1.686)
Southeast Asia	1.373 (1.323 - 1.424)	1.624 (1.593 - 1.655)	0.567 (0.486 - 0.648)	0.837 (0.752 - 0.922)
Southern Latin America	1.66 (1.613 - 1.708)	2.06 (1.996 - 2.125)	-0.394 (-0.706 - -0.082)	0.614 (0.478 - 0.75)
Southern Sub-Saharan Africa	1.387 (1.341 - 1.434)	1.65 (1.595 - 1.704)	1.697 (1.161 - 2.235)	1.497 (1.109 - 1.887)
Tropical Latin America	0.364 (0.327 - 0.4)	0.484 (0.44 - 0.527)	-0.419 (-0.64 -0.197)	-0.165 (-0.289 -0.04)
Western Europe	1.326 (1.238 - 1.414)	1.635 (1.582 - 1.689)	-1.494 (-1.589 -1.399)	0.392 (0.281 - 0.504)
Western Sub-Saharan Africa	1.076 (1.058 - 1.095)	1.448 (1.42 1.477)	0.656 (0.558 0.756)	0.779 (0.736 0.821)

Among the five SDI regions, the middle SDI region had the most significant number of new cases (Table 2) and deaths of T2DM. The highest ASIR was in high SDI region, while the highest ASMR and ASDR due to T2DM were in low SDI region. The low-middle SDI region had the highest ASPR and the largest number of DALYs.

At the GBD regional level, the largest number of new cases of T2DM was in South Asia (Table 2). The highest ASIR in 2019 was in Oceania, with the lowest number of cases. Similarly, South Asia had the highest T2DM prevalence, mortality, and DALYs. The highest ASPR, ASMR, and ASDR due to T2DM were also in Oceania.

The national burden of T2DM in 2019 is presented in Figure 3 and Supplementary Table S2. Among 204 countries, India had the greatest number of incidence (4,206,580 [95% UI 3821838.07 – 4647331.08]), following by China and United States of America (Figure 3A). The highest ASIRs were in American Samoa (819 [95% UI 763-882] per 100,000 population), Qatar (818 [95% UI 774-869] per 100,000 population), and Fiji (797 [95% UI 764-836] per 100,000 population). In 2019, the highest ASIR (819 per 100,000 population in American Samoa) was 7.8 times higher than the lowest (105 per 100,000 population in Mongolia).

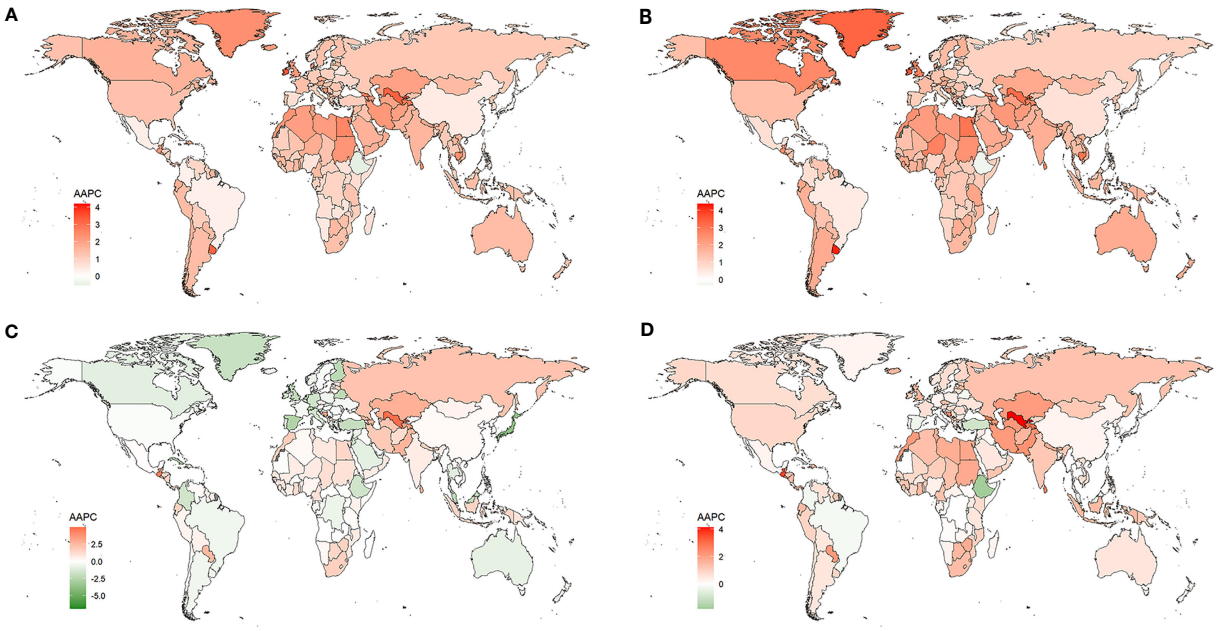

FIGURE 1
Changes in the ASIR **(A)**, ASPR **(B)**, ASMR **(C)**, ASDR **(D)** of T2DM by countries and territories from 1990 to 2019.

Similarly, China and India have the greatest number of prevalence, mortality and DALYs. American Samoa had the highest ASPR in 2019. The highest ASMR and ASDR were seen in Fiji. Moreover, we analyzed the association between the national burden of T2DM and SDI which presented the results in Figure 4. The ASIRs were significantly positively associated with SDIs (r=0.15, p=0.03, Figure 4A). Similarly, a significant positive association between the ASPRs and SDIs (r=0.16, p=0.02, Figure 4B) was observed. On the contrary, a significant negative correlation was observed between the ASMRs (r=-0.23, p<0. 01; Figure 4C) and ASDRs (r=-0.17, p=0.02; Figure 4D) of T2DM and SDIs in 2019. Notably, in high SDI regions (SDI>0.81), high-middle SDI regions (SDI 0.70-0.81), ASIR, ASPR, ASMR, and ASDR due to T2DM all decreased with the increase of SDIs.

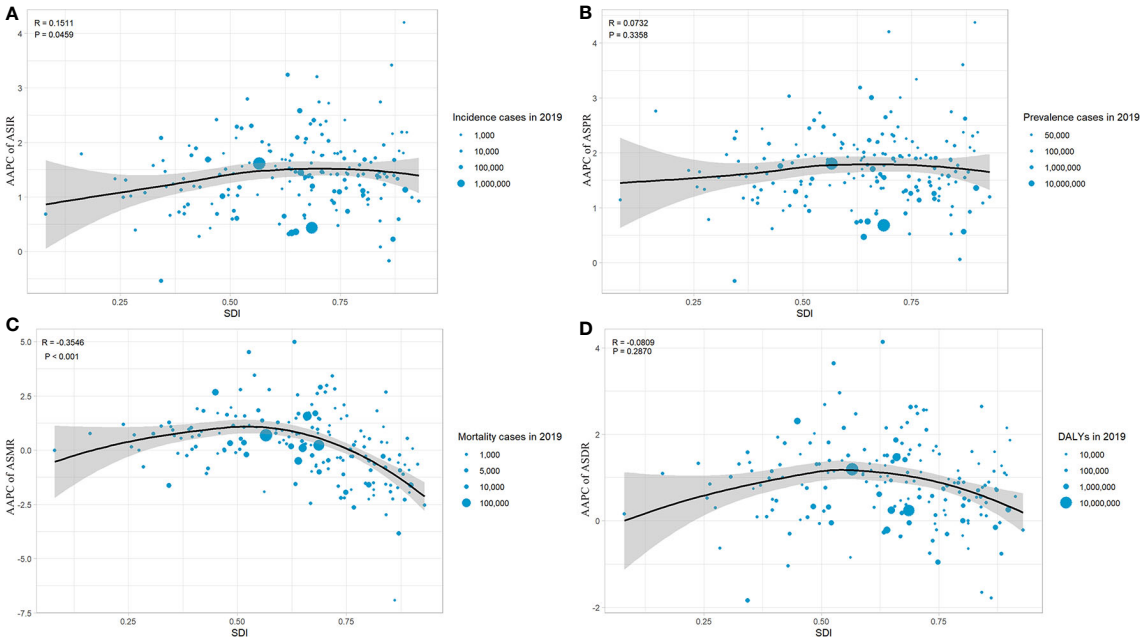

FIGURE 2
The correlation between the AAPC of ASIR **(A)**, ASPR **(B)**, ASMR **(C)**, ASDR **(D)** of T2DM by countries and territories from 1990 to 2019.

TABLE 2 The global and national incidence cases, ASIR, prevalence cases, ASPR, mortality cases, ASMR, DALYs and ASDR of T2DM in 2019.

Characteristics	Incidence_cases No.×10^3 (95% UI)	ASIR per 100000 NO.(95% UI)	Prevalence_cases No.×10^3 (95% UI)	ASPR per 100000 NO.(95% UI)	Mortality_cases No.×10^3 (95% UI)	ASMR per 100000 NO.(95% UI)	DALYs per 100000 NO.(95% UI)	ASDR per 100000 NO.(95% UI)
Global	1669.9 (20020.9-23513.5)	259.9 (240.3-281.4)	437906.6 (402043.3-477018.2)	5282.9 (4853.6-5752.1)	472.9 (1371.9-1565.9)	18.5 (17.2-19.7)	66299.8 (55477-79005.2)	801.5 (670.6-954.4)
Sociodemographic index								
Low SDI	1737 (1581.8-1907.1)	237.2 (217.3-260.6)	28649.2 (25687.8-31899.3)	4690.7 (4226.1-5191.6)	140.3 (127.2-154.7)	31.9 (29-35)	5822.7 (4934-6778.3)	1064.4 (915-1236.7)
Low-middle SDI	4531.3 (4152.5-4954.4)	277.8 (255.3-302.4)	85125.8 (77155.1-93944.5)	5746.9 (5235.1-6306.3)	350.5 (320.2-380.7)	29.1 (26.5-31.5)	14715.5 (12376.8-17318.7)	1049.8 (891.2-1231.4)
Middle SDI	7104.8 (6574.2-7710.3)	261.7 (243.1-283.2)	139200 (127781.1-151612.8)	5330.4 (4909.8-5785.9)	541.5 (503.9-579.6)	23.7 (22-25.5)	23402.7 (19913.2-27520.9)	915.1 (780.4-1075.8)
High-middle SDI	4322.4 (3984.4-4695.9)	232.1 (214.5-251.6)	93989.8 (85771.9-102490.2)	4753.7 (4343-5193.2)	253.1 (232.2-270.7)	12.6 (11.6-13.5)	12282.1 (9912.7-14945.6)	610.2 (492.1-743.7)
High SDI	3959 (3649.7-4283.6)	287.9 (265.5-310.5)	90647.4 (83461.5-97916.7)	5553 (5088-6008.2)	186.1 (167.7-197)	9.1 (8.3-9.5)	10016.1 (7870.4-12530.8)	584.7 (454.6-735)
Region								
Andean Latin America	141.6 (130.7-153.4)	236.3 (218-255.9)	2443.5 (2239.8-2652.1)	4250.7 (3898.4-4602.7)	13.1 (10.9-15.4)	24 (20.1-28.3)	493.6 (408.1-592.3)	873.5 (722.3-1045.3)
Australasia	76.2 (68.5-83.6)	190.5 (172.4-209.3)	1520.3 (1362.2-1688.6)	3368.8 (3006.6-3764.6)	4.8 (4.2-5.2)	8.7 (7.8-9.5)	198.5 (153-250.2)	419.6 (320.7-531.7)
Caribbean	187.5 (173.9-201.6)	366.6 (340.5-393.8)	3848.8 (3562.1-4157.7)	7479.2 (6913.6-8083.3)	18.4 (15.5-21.8)	35.5 (29.9-42.1)	766.9 (633.8-930.7)	1483.1 (1226-1800.5)
Central Asia	243.3 (225.7-262.4)	255.4 (237.9-274.4)	4444.2 (4078-4824.8)	5343 (4931.1-5771.4)	16.6 (14.9-18.5)	23.6 (21.4-26.1)	809.2 (665.8-976.7)	1013.8 (841.9-1219.1)
Central Europe	459.5 (421.8-499.4)	286 (263.2-309.9)	10798 (9798.1-11706.2)	5619.9 (5099.5-6110.2)	26.8 (23.3-30.6)	11.9 (10.4-13.6)	1479.3 (1147-1854.6)	730.2 (559-923.1)
Central Latin America	1072.2 (995.2-1149.3)	418.9 (388.6-448.7)	20824.3 (19192.7-22360)	8505.6 (7837.2-9133.4)	102.7 (90.5-115.6)	44.6 (39.3-50.2)	4206.5 (3578.3-4997.8)	1746.5 (1485.3-2073.9)
Central Sub-Saharan Africa	210 (190.7-230.8)	258 (236-282.2)	3289.3 (2945.4-3654.6)	4955.9 (4481.2-5480.5)	16.9 (13.9-20.7)	38.3 (32.1-46.2)	732.6 (597.4-901.7)	1265.1 (1049.1-1533.2)
East Asia	3894.3 (3585.4-4259.6)	202.1 (186.9-220)	93251.5 (85377.5-101871.9)	4502.3 (4110.8-4930)	182.9 (157.8-208.4)	9.6 (8.3-11)	10164.5 (8071.1-12540.9)	487.6 (387.8-602.7)
Eastern Europe	403.3 (369.2-443.5)	142.6 (131-156)	9148.1 (8294.6-10074.4)	2856.6 (2582.5-3157)	21.6 (19-24.1)	6.1 (5.4-6.8)	1254 (989.7-1562.2)	376 (295.1-468.2)

(Continued)

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TABLE 2 Continued

Characteristics	Incidence_cases No.×10^3 (95% UI)	ASIR per 100000 NO.(95% UI)	Prevalence_cases No.×10^3 (95% UI)	ASPR per 100000 NO.(95% UI)	Mortality_cases No.×10^3 (95% UI)	ASMR per 100000 NO.(95% UI)	DALYs per 100000 NO.(95% UI)	ASDR per 100000 NO.(95% UI)
Eastern Sub-Saharan Africa	412 (376.1-451.7)	176.1 (162.3-191.4)	6067.7 (5427-6771.4)	3052.3 (2760.6-3377.6)	49.1 (43.6-55.7)	36.5 (32.5-40.9)	1748.9 (1499.6-2025.2)	1026.8 (889.8-1182.4)
High-income Asia Pacific	527.5 (481.3-579.1)	194.9 (178.6-212.9)	13222.2 (12034.5-14509.7)	3744.9 (3383.3-4140.2)	21.5 (18.5-23.6)	4.2 (3.7-4.6)	1439.3 (1080.4-1851.5)	383.2 (285.3-495.5)
High-income North America	1665.3 (1542.9-1803.9)	342.3 (317.8-368.3)	38227.8 (35420.2-41150.2)	6725.2 (6220.5-7224.4)	80.3 (73.8-84.1)	12.3 (11.4-12.9)	4392.4 (3527.8-5435)	748.2 (596-931.1)
North Africa and Middle East	2007.3 (1842.5-2191.9)	353.2 (326.1-383.4)	32927.7 (29948-36228)	6753.3 (6170.2-7394.2)	95.4 (84.9-107.4)	25.2 (22.4-28.2)	4806.9 (3927.1-5857.2)	1060.8 (872.1-1279.1)
Oceania	57.2 (53.1-61.8)	506.1 (472.9-542.4)	1021.9 (935.5-1121.7)	11086.1 (10196.7-12087.4)	7.8 (6.3-9.6)	121 (100.2-146.5)	298.1 (244-357)	3703.4 (3060-4399.3)
South Asia	5108.1 (4649.8-5628.1)	299.7 (273.8-329.2)	98137 (88391.9-108844)	6375.2 (5752.2-7067.8)	337.9 (301-379.8)	28.1 (25-31.6)	15119.4 (12449.1-17998.4)	1049.7 (869.3-1244.9)
Southeast Asia	1900.9 (1761.1-2053.7)	273.3 (254-295.6)	31222 (28746.8-33964.8)	4875.1 (4493.5-5285.6)	214.8 (193-236.3)	38.1 (34.1-41.7)	8080 (7008.9-9255.2)	1273.4 (1103.9-1452.4)
Southern Latin America	210.2 (191.7-228.6)	274.6 (249.9-298.4)	4069.9 (3674.7-4445.7)	5031 (4528.4-5494.2)	14.8 (13.7-15.7)	17.4 (16.1-18.5)	593.9 (484.5-720.8)	722.4 (588.2-878.5)
Southern Sub-Saharan Africa	217.9 (202.8-233.7)	326.1 (304.7-349.2)	3389.9 (3098.5-3696.2)	5605.7 (5133.9-6083)	33.9 (31.4-36.6)	68.5 (63.2-73.8)	1063.4 (946.9-1191.2)	1878 (1679.9-2098.8)
Tropical Latin America	677.7 (623.1-740)	268.6 (247.3-292.8)	12302.1 (11179-13438.1)	4979.1 (4525.8-5443.8)	65.3 (59.2-68.9)	28 (25.3-29.6)	2492.5 (2113.1-2920.3)	1020.4 (868-1194.5)
Western Europe	1703.8 (1555.4-1855.1)	276.4 (252.2-301.2)	40769.8 (37016.4-44749.5)	5360.8 (4812.9-5915.5)	93.4 (82.5-99.8)	8.5 (7.6-9.1)	4248.6 (3267.6-5403.5)	515.8 (389.5-663.9)
Western Sub-Saharan Africa	494.2 (451.1-540.4)	197.6 (181.7-214.6)	6980.6 (6275.4-7737.5)	3279.9 (2962.2-3612.2)	55.1 (47.2-63.3)	35.6 (30.8-40.2)	1911.2 (1614-2238.7)	994.8 (851-1148.4)

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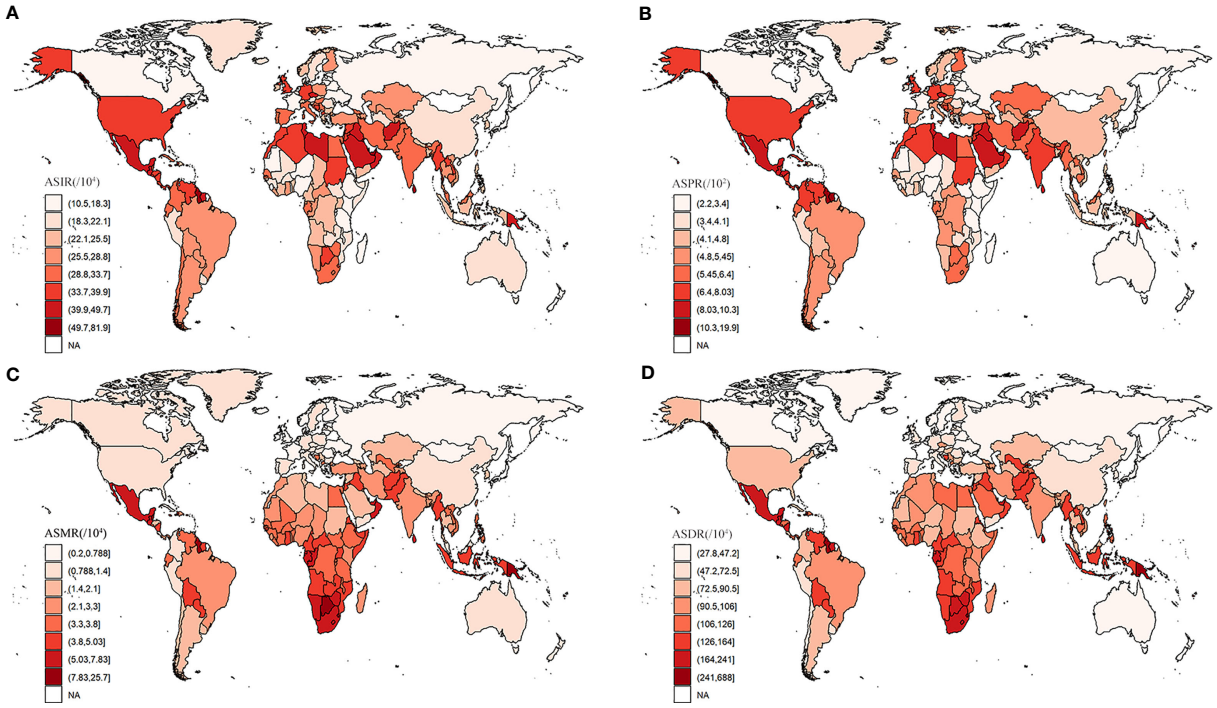

FIGURE 3
The national burden of T2DM in 2019. **(A)** ASIR, **(B)** ASPR, **(C)** ASMR, **(D)** ASDR.

3.3 Forecast of global burden of T2DM

Based on the past incidence, mortality rate and the population forecast in GBD 2019, we forecasted the incidence and mortality rate from 2020 to 2034. As shown in Figure 5, the ASIR and ASMR of T2DM will still continue to increase in the future. Globally, the ASIR is estimated to increase to, 263.53 per 100,000 population in 2020 to 2024, 274.25 per 100,000 population in 2025 to 2029, and 284.42 per 100,000 population in 2030 to 2034 (Figure 5A). The ASMR is estimated to increase to 18.66 per 100,000 population in

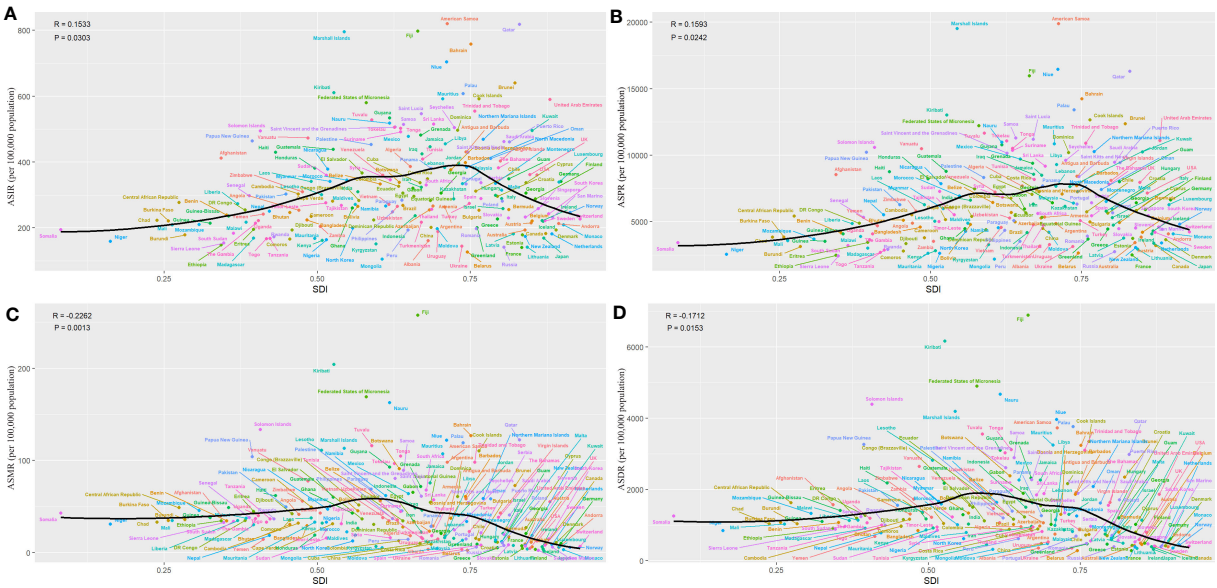

FIGURE 4
Global T2DM burden of T2DM across 204 countries by SDIs in 2019. **(A)** ASIR, **(B)** ASPR, **(C)** ASMR, **(D)** ASDR.

2020 to 2024, 18.9 per 100,000 population in 2025 to 2029, and 19.1 per 100,000 population in 2030 to 2034 (Figure 5C). Of note, incidence and mortality rates for male have been higher than for female in the past and will remain so in the future.

Moreover, we analyzed the trends in incidence rates (Figure 5B) and mortality rates (Figure 5D) in different age groups. It was estimated that the incidence rate in most age groups would continue to increase in the future. In 2030-2034, the age group 55-59 will have the highest incidence rate (813.5 per 100,000 population), followed by the age group 60-64 (783.56 per 100,000 population) and age group 50-54 (747.55 per 100,000 population). Different from the incidence rate, the mortality rate of T2DM will remain relatively stable in the future, with the highest mortality rate (345.27 per 100,000 population in 2030-2034) in the 85+age group. Notably, as shown in Figure 5D, the mortality rate increased with age.

4 Discussion

In this study, we presented a comprehensive picture of the burden and its trends in T2DM in 21 GBD regions and 204 countries and territories from 1990 to 2019, including ASIR, ASPR, ASMR, ASDR. The change trends in T2DM burden were evaluated by AAPCs that were calculated by joinpoint regression analysis. Moreover, we assessed the influence of socio-economic development status on the burden of T2DM and its changes over the past 30 years. Additionally, the incidence and mortality rates of T2DM from 2020 to 2034 were forecast by sex and age groups. All these results help make evidence-based decisions regarding improvements in T2DM prevention and prognosis.

From 1990 to 2019, the global burden of T2DM generally increased. Previous studies have tried to explore the trends in T2DM with percentage change and the EAPCs (7, 8). EAPCs were calculated assuming the trend is linear over the interval, which is concerning when the data are sparse, causing inconsistent results. In this study, we used AAPCs, which considered all inflection points from 1990 to 2019, to assess the trends in T2DM burden from 1990 to 2019. When the data are sparse, AAPC is especially reliable for characterizing small segments based on joinpoint models fitted over considerably longer periods (9). Therefore, compared to the previous studies, this study found a more accurate result which suggested worsening changes in T2DM burden. For example, the ASIR and ASDR were decreased while evaluating by EAPC in previous study, but opposite results was found in this study. The largest increased burden of T2DM from 1990 to 2019, including ASIR, ASPR, ASMR, and ASDR, was found in the low-middle SDI region. Fortunately, the high-middle and high SDI regions had a decreased ASMR. Similarly, at the national level, though the T2DM burden generally increased in most countries and territories, an opposite result was shown in some countries and territories. The ASMR decreased in over 1/3 of countries and territories, and the ASDR decreased in nearly 1/5 of countries and territories. Further analysis suggested that the ASIR of T2DM was positively corrected with SDIs, while the ASMR of T2DM was negatively associated with SDIs, but no association was observed between both ASPR or ASDR and SDIs. However, possibly due to the difference in database or observation periods, a multi-country analysis found that the rate of diagnosis of diabetes was stabilizing or declining from 1995 to 2018 in many high-income countries (13).

In the past 30 years, the global economy has flourished, especially in developing countries, and significant changes in food, life, and work patterns have accompanied this change. Lightly processed foods have been replaced by heavily processed

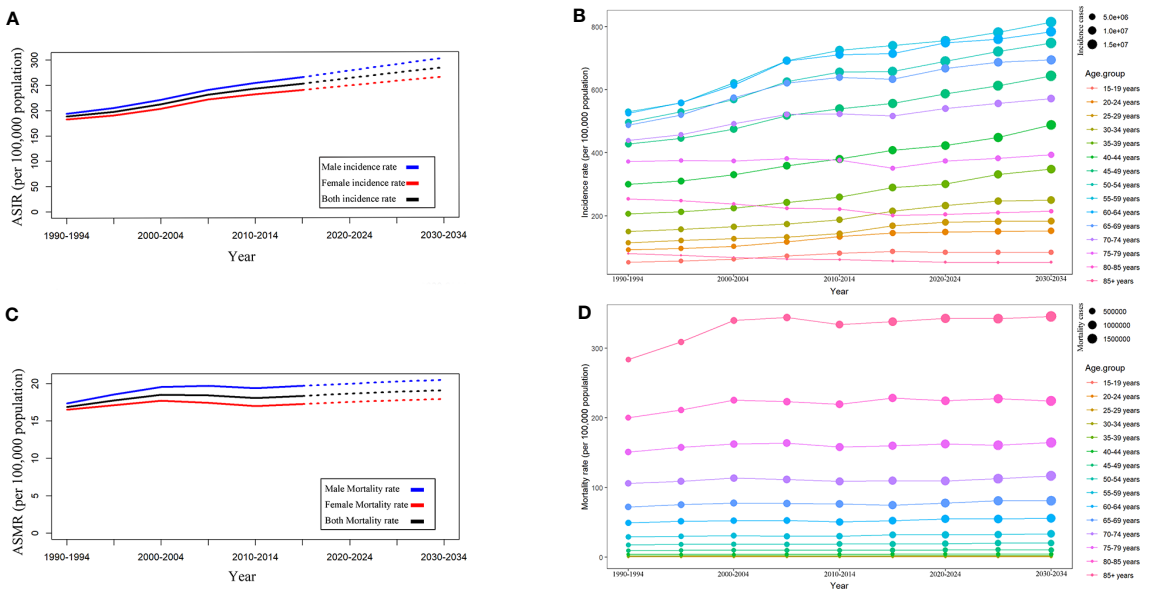

FIGURE 5
Trends in T2DM incidence and mortality rates by sex and age groups. **(A)** ASIR by sex. **(B)** ASIR by age group. **(C)** ASMR by age groups. **(D)** Mortality by age groups.

foods high in calories, saturated fatty acids, sugar, and salt (14–16). Rapid urbanization and industrialization have caused enormous environmental pollution, especially in the air (17). Additionally, the work pattern has become more sedentary, causing reduced activity levels (17, 18). These factors are considered to play important roles in the development of T2DM. Therefore, it was unsurprising that the ASIR and ASPR increased in most countries, especially in low-middle SDI countries. Unfortunately, it seems that healthcare systems in low-SDI countries have not kept pace with their economic development, causing more disease burden from chronic diseases, including T2DM (19–21). In addition, existing medications are not effective enough to control blood glucose, and adherence in patients with T2DM is inadequate (22, 23). The prognosis for T2DM remains poor due to these factors. Therefore, there is an urgent need to improve the medical systems to reduce the burden of T2DM globally, especially in low-income countries (24).

The burden of T2DM varies between countries and territories. In 2019, the highest ASIR was in the high SDI region. Further analysis also suggested that the ASIR of T2DM was positively associated with SDIs value. The highest ASPR was observed in the low-middle SDI region, but a positive correlation was observed between ASPR and SDIs upon further analysis. For reasons, obesity rates are generally high in high SDI countries, which is closely related to the development of T2DM (25, 26). Additionally, premium medical and health resources were more readily available in high SDI countries, causing a higher early diagnosis rate of T2DM (27, 28). Therefore, though low SDI countries had a lower T2DM incidence rate compared to high SDI countries, they should pay more attention to the early diagnosis of T2DM that may lead to a better prognosis (29, 30). From the perspective of the prognosis of T2DM, the low-middle SDI region has the highest ASMR and ASDR due to T2DM. It was not surprising that further analysis suggested negative associations between both ASMR and ASDR and SDIs. The prognosis of T2DM tended to be worse in low SDI countries, possibly due to limited medical resources and technology (28). In addition, there were also significant differences between and within low-income and high-income countries in terms of diagnosis and treatment of diabetes (31, 32). Approximately 53% of global healthcare spending on diabetes was in the United States. In comparison, less than 1% of that was spent in India, which has one of the highest numbers of diabetes patients, and only 0.3% of that was spent in an African region consisting of 18 countries (33). Moreover, a previous multicenter study on T2DM patients found that only 20-30% of T2DM patients can control their HbAlc level within the recommended limits (22). Therefore, improving the prognosis of T2DM is still an essential task in all countries.

In this study, the incidence rates and mortality rates of T2DM from 1990 to 2019 were analyzed by gender and age group, and those from 2020 to 2034 were forecast with the Nordpred package in R. Worryingly, the incidence rate was forecast to keep increasing from 2019 to 2034. Previous studies only forecasted the incidence rate of all types of diabetes, so the results of previous studies and this study cannot be compared directly (15). However, all results show that the incidence rate will keep increasing. Overall, T2DM incidence and mortality rates for men have been higher than for women and will remain so. The sex distribution of T2DM is strongly associated with the difference in physiology and metabolism, lifestyle, education attainment, cultural factors and socioeconomic status between the genders (34, 35). Previous studies have discovered that different countries have varying burden disparities between genders (36–38). Overall, females are more concerned about the treatment of T2DM and have higher treatment compliance, which may contribute to a better prognosis of T2DM (39). Moreover, differences in incidence and mortality rate by age group also play important roles in decision-making for prevention and prognosis improvement policies for T2DM. According to our forecast, the five age groups of 55-59, 60-64, 50-54, 45-49, and 40-44 years will have the highest incidence rates in that order. Fortunately, the mortality rate of T2DM will remain relatively stable as forecasted. The mortality rate of T2DM increased with age in the past and will remain so in the future, possibly due to old adults having more underlying diseases and polypharmacy. A systematic review suggested a positive correlation between polypharmacy in old adults and the risk of hypoglycemia, poor glycemic control, incident falls, hospitalization, syncope, and death (40). Of note, Covid-19 (SARS-CoV-2) has significantly impacted the health of all humans since 2019. The human pancreas is one of the target organs of covid-19, and covid-19 may damage beta cells by triggering pro-inflammatory cytokines, which may cause hyperglycemia and insulin resistance (41–43). Moreover, a retrospective cohort analysis estimated that covid-19 patients presented an increased T2DM incidence compared to other acute upper respiratory tract virus infections (44). Therefore, the future morbidity and mortality of T2DM may be even higher than our estimates suggest.

In summary, the burden of T2DM increased globally from 1990 to 2019. The low-middle SDI region had the highest increased T2DM burden. In 2019, the highest ASIR of T2DM was observed in the high SDI regions, whereas the highest ASPR, ASMR, and ASDR due to T2DM were observed in the low-middle regions. As forecast, the global incidence rates and mortality rates of T2DM will keep increasing. The 40-70 age group will have the highest incidence rate, while the 60-85+ age group will have the highest mortality rate of T2DM from 2020 to 2034. Therefore, a more robust investment in T2DM prevention is needed in high SDI regions and in the 40-70 age group, while prognosis improvement of T2DM is needed more in low SDI regions and in the 60-85+ age group to prevent an increased burden of T2DM. However, there were some limitations in this study. Due to differences in the speed of economic development and the foundation of health systems in different countries, GBD database was difficult to adopt a unified standard to accurately determine the burden of disease. Stronger leadership and political support are needed for continuous monitoring and evaluation of prevention programs. The establishment of national or subnational diabetes registries can provide comprehensive data on the epidemiology, risk factors, and outcomes of diabetes at both individual and population levels. Moreover, the registry can facilitate the integration of diabetes care across healthcare sectors and enhance collaboration between researchers, clinicians, policymakers, and patients.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://vizhub.healthdata.org/gbd-results.

Author contributions

JJY and YXW are responsible for the design and manuscript writing. JJY, YXW, SHY, DZ, JXC, and XXJ are responsible for editing the structure of the article, obtaining the documents, and further arranging the manuscripts. KJH is responsible for the supervision, review, and final editing of the manuscript.

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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.2023.1192629/full#supplementary-material

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Patent analysis of digital sensors for continuous glucose monitoring

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The high need for optimal diabetes management among an ever-increasing number of patients dictates the development and implementation of new digital sensors for continuous glucose monitoring. The purpose of this work is to systematize the global patenting trends of digital sensors for continuous glucose monitoring and analyze their effectiveness in controlling the treatment of diabetes patients of different ages and risk groups. The Lens database was used to build the patent landscape of sensors for continuous glucose monitoring. Retrospective analysis showed that the patenting of sensors for continuous glucose monitoring had positive trend over the analyzed period (2000–2022). Leading development companies are Dexcom Inc., Abbott Diabetes Care Inc., Medtronic Minimed Inc., Roche Diabetes Care Inc., Roche Diagnostics Operations Inc., Roche Diabetes Care Gmbh, and Ascensia Diabetes Care Holdings Ag, among others. Since 2006, a new approach has emerged where digital sensors are used for continuous glucose monitoring, and smartphones act as receivers for the data. Additionally, telemedicine communication is employed to facilitate this process. This opens up new opportunities for assessing the glycemic profile (glycemic curve information, quantitative assessment of the duration and amplitude of glucose fluctuations, and so on), which may contribute to improved diabetes management. A number of digital sensors for minimally invasive glucose monitoring are patented, have received FDA approval, and have been on the market for over 10 years. Their effectiveness in the clinic has been proven, and advantages and disadvantages have been clarified. Digital sensors offer a *non-invasive* option for monitoring blood glucose levels, providing an alternative to traditional invasive methods. This is particularly useful for patients with diabetes who require frequent monitoring, including before and after meals, during and after exercise, and in other scenarios where glucose levels can fluctuate. However, non-invasive glucose measurements can also benefit patients without diabetes, such as those following a dietary treatment plan, pregnant women, and individuals during fasting periods like Ramadan. The availability of non-invasive monitoring is especially valuable for patients in high-risk groups and across different age ranges. New world trends have been identified in the patenting of digital sensors for non-invasive glucose monitoring in interstitial skin fluid, saliva, sweat, tear fluid, and exhaled air. A number of non-invasive devices have received the CE

mark approval, which confirms that the items meet European health, safety, and environmental protection standards (TensorTip Combo-Glucometer, Cnoga Medical Ltd.; SugarBEAT, Nemaura Medical; GlucoTrack, GlucoTrack Inc.), but are not FDA-approved yet. The above-mentioned sensors have characteristics that make them popular in the treatment of diabetes: they do not require implantation, do not cause an organism reaction to a foreign body, and are convenient to use. In the EU, in order to increase clinical safety and the level of transparency about medical devices, manufacturers must obtain certificates in accordance with Regulation (EU) 2017/745, taking into account the transition period. The development of systems, which include digital sensors for continuous glucose monitoring, mobile applications, and web platforms for professional analysis of glycemic control and implementation of unified glycemic assessment principles in mobile healthcare, represent promising approaches for controlling glycaemia in patients.

KEYWORDS

continuous glucose monitoring, minimally invasive sensors, non-invasive sensors, digital sensors, diabetes

1. Introduction

According to statistics from the International Diabetic Federation, as of 2021, diabetes mellitus (DM) has higher prevalence in developed countries due to technical progress, urbanization and changes in the life style and diet, that lead to obesity and high blood pressure. The prevalence of Type 1 diabetes mellitus (DM1) varies across different regions and populations. The most prevalent form of diabetes, type 2 (DM2), affects more than 90% of diabetic people globally. The increasing life expectancy has led to a rise in the incidence of DM. If such trends persist, then by 2045 this figure will grow to 783 million adults aged 20–79 years (1).

According to the World Health Organization (WHO), diabetes mellitus is among the top 10 leading causes of death worldwide. The prevalence of the disease is rising, with a notable trend of affecting individuals at younger ages.

Achieving optimal and sustained glycemic control is one of the most effective approaches to prevent complications and reduce mortality in patients with DM. Glycemic variability is a key therapeutic focus in the treatment of diabetic patients (2–5).

Continuous glucose monitoring (CGM) is crucial in achieving glycemic control for most patients with DM1 and DM2 in accordance with the American Diabetes Association's Standards of medical care in diabetes (6).

CGM is strongly recommended by the International Society for Pediatric and Adolescent Diabetes Guidelines for all children, adolescents, and young adults with DM1 (7).

The market of innovative medical products for the treatment of DM1 is constantly expanding, namely with the development of insulin pumps, closed-loop systems. The first model of a hybrid closed loop system (the MiniMed 770G System) for patients aged 2 to 6 with DM1 was approved by the FDA in 2020 (8).

The clinical accuracy of continuous glucose monitoring in patients with DM1 is shown in systematic reviews of randomized trials and meta-analyses by Teo et al., Moser et al., and Elbalshy et al. (9–11). It is emphasized that future research should assess the precision and efficiency of CGM for various age groups and insulin therapy regimens. Abrupt changes in glucose levels were associated with lower measurement accuracy. Wang et al. and Daskalaki et al. also noted that CGM may benefit diabetic patients (12, 13).

Mihaya et al. and Fedorova et al. compared the different methods of CGM and readers are referred to these previous works for more detailed comparative overview. The authors also reviewed different classifications of sensors for continuous glucose measurement, including by analytical methods (14, 15).

In reviews by Lin and Gonzales et al., much attention is paid to the technical characteristics of sensors for CGM (16, 17). Data on the applied technologies and measurement accuracy parameters are presented. Unfortunately, no validation in patients or volunteers is described. Shang et al. have characterized products for continuous monitoring of glucose levels based on their consumer, technological, and regulatory features (18).

Underscoring the economic side of the treatment of diabetes mellitus, researchers draw attention to the fact that, at present, direct costs for the treatment of diabetes are high and reach about 1 trillion US dollars; by 2030, they are predicted to double. At the same time, there is evidence that continuous glucose monitoring has both positive clinical and economic effects in patients with diabetes (19).

While the necessary methodological basis exists, at the same time, many aspects of the application of continuous glucose monitoring by digital sensors need additional research and clarification.

It has to be mentioned that the measurement of glucose by non-invasive methods has several limitations. CGM is dependent on skin properties, changes in the blood supply of tissue, concomitant therapy affecting the distribution of fluid in tissues, concomitant diseases, skin edema, hypotension, etc. (20–24). Additionally, the requirement for capability to detect slight variations in glucose levels during continuous monitoring needs to be taken into consideration.

Thus, at the moment, scientific research covers a wide range of aspects with relevance for CGM. However, there are still insufficiently explored issues related to minimally invasive and non-invasive continuous glucose monitoring in people of different ages and risk groups, respective patent protections, and implemented digital technologies. The increase in the requirements for modern medical digital systems contributes to the active search for medical sensor technologies for continuous glucose monitoring, combining simultaneously informational, analytical, predictive, and control functions.

Digital technologies for people with diabetes are becoming an increasingly common aspect of monitoring the effectiveness of diabetes care (25, 26). Further development and implementation of mobile applications and web platforms for continuous glucose monitoring devices is a promising approach.

Patent information concerning innovative technologies appears in patent databases earlier than in scientometric databases the market introduction. Using an analysis of the global patent landscape, researchers can identify the most active and promising areas of research and direct their resources accordingly.

The purpose of this work is to systematize the global patenting trends of digital sensors for continuous glucose monitoring and gain insights on their effectiveness in controlling the treatment of diabetes patients of different ages and risk groups.

2. Materials and methods

The information base for building the patent landscape was compiled by the Lens database as of *December 31, 2022*. During the study, we used the following methods: system and logical analysis, synthesis, methods of comparison, graphic representation methods, patent research, content analysis, and others.

The strategy of the conducted patent and literature studies is shown in Figure 1.

Key words selected as search queries are "continuous glucose monitoring," "continuous glucose sensor," "continuous non-invasive glucose monitoring," "continuous non-invasive glucose sensor," "non-invasive glucose," "non-invasive sensor," "digital system," and their combinations. A search by keywords was carried out in the title, abstract, and claim of patent documents.

Patent classification codes were also used in the search. It should be noted that the classification of inventions, including in the field of continuous glucose monitoring, is carried out by specific experts of the patent office, i.e., it is largely subjective, which explains the wide spread of patents by class in the International Patent Classification and the Cooperative Patent Classification. In addition, various analytical methods are used for continuous glucose monitoring, which also leads to the use of a wide range of patent classification codes. The study used the code of the Cooperative Patent Classification "A61B5/14532," which is the most widely used by leading manufacturers and also covers various analytical approaches. We also used codes from the Cooperative Patent Classification, which are connected with invasive, minimally invasive, and non-invasive sensors (A61B5/14546, A61B5/1473, A61B5/14865, A61B5/14503, and A61B5/6848) (27). For example, the code of the Cooperative Patent Classification "A61B5/14865" is related to the measurement of glucose using implanted sensors.

The search was limited to inventions submitted or prioritized since the year 2000. Using the in-build Lens database's functionality, a numerical analysis of the found documents was done.

As a rule, the presence of patent protection for a technology in the territory of a country indicates the presence of potential demand for it. An analysis of inventive activity regarding geography for patent coverage and the patent offices was carried out.

In the Web of Science database, clinical studies of sensors for minimally and non-invasive continuous glucose monitoring were analyzed using their trademarks and commercial names of manufacturers as keywords.

Exclusion criteria were used to narrow the search results. Irrelevant patents were excluded using the Cooperative Patent Classification codes. The excluded manuscripts were reviews of previous literature and manuscripts related to invasive glucose monitoring technologies.

The FDA medical device database (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm) and the European database on medical devices "Eudamed" (https://ec.europa.eu/tools/eudamed/#/screen/home) were used to examine the registration and certification of patented sensors for minimally and non-invasive continuous glucose monitoring in accordance with ISO standards.

3. Results

3.1. Current trends in patenting within the segment of continuous glucose monitoring

Patent analysis has identified 6.181 patents and 2.207 simple families in the area of continuous glucose monitoring filed between 2000 and 2022 (*accessed on December 31, 2022*; Figure 2).

A stable increase in the number of patents over the period 2000–2022 was identified, which is associated with the development of new sensors for CGM (Figure 2). At the same time, the largest number of patents were published in 2018 and 2020, covering 7.6 and 8.4% of all publications, respectively, for 2000–2022. The number of patents in 2015, 2016, and 2017 compared to 2005 increased by 2.48, 2.97, and 2.73 times, respectively. Retrospective analysis showed that the advancement of technologies for sensors for continuous glucose monitoring had a positive trend during the analyzed period. At the same time, the largest (516) number of applications was submitted in 2020.

An analysis of the patenting of sensors for continuous glucose monitoring by the patent offices was also carried out. Figure 3 depicts the dynamics of their patenting in five leading patent offices.

The largest number of patents was registered in the United States (3.482), which amounted to about 56% of the total data set. A significant (19%) share of patents related to continuous glucose monitoring are international documents filed under the PCT procedure. Advantages of this procedure are that: by filing at the initial stage of the application in one language, according to the results of an international search, researchers can choose a circle of patenting countries, obtaining a strong patent that is difficult to dispute. Under the PCT (patent cooperation

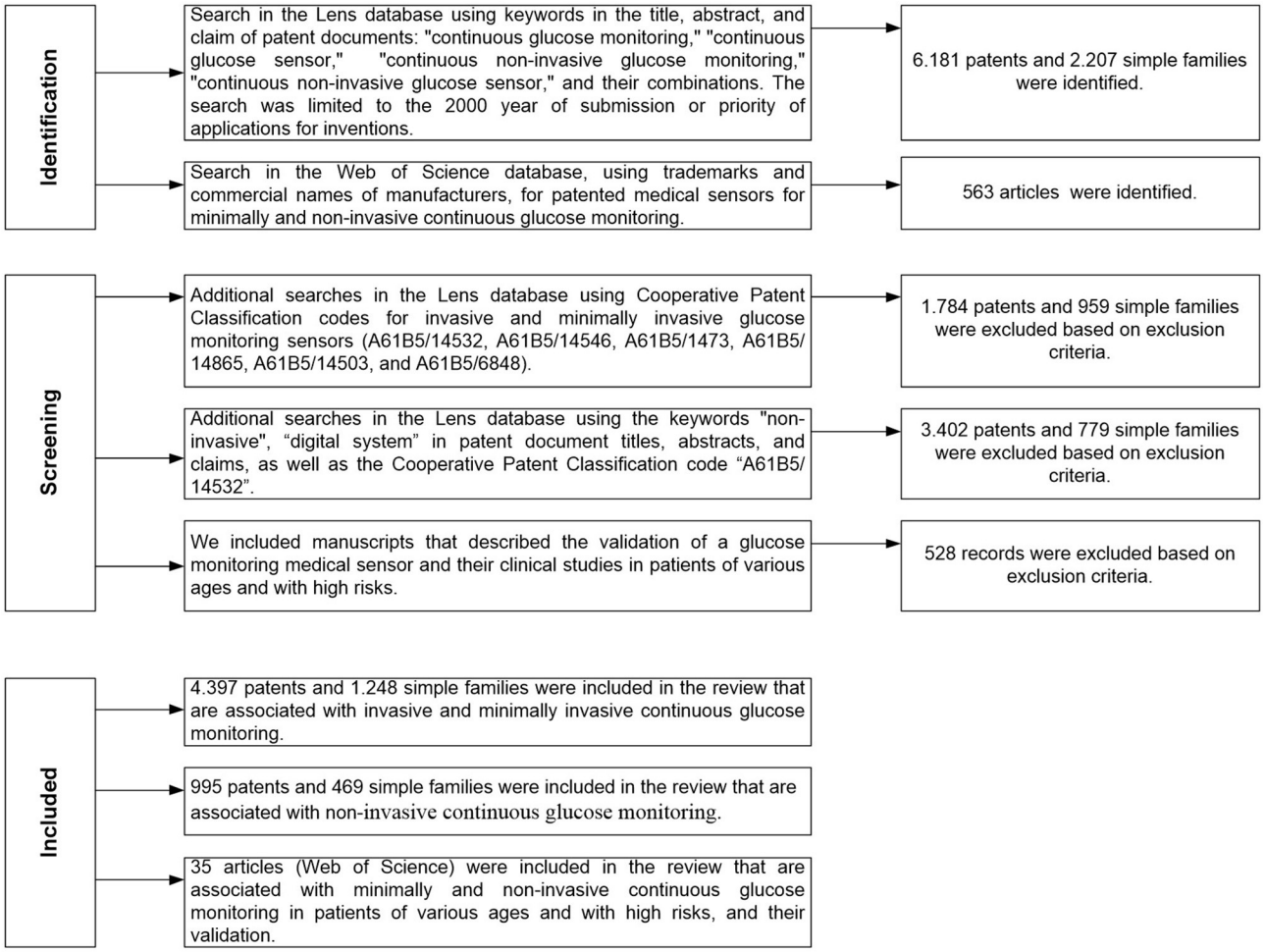

FIGURE 1
The strategy of patent and literature studies.

treaty) system, it is economically feasible to patent the invention in more than five countries. The number of patents (602), conducted through the European Patent Office, is 9.7% of the total number.

The leaders in the patenting field of devices for continuous glucose monitoring are Dexcom Inc., Abbott Diabetes Care Inc., Medtronic Minimed Inc., Roche Diabetes Care Inc., Roche Diagnostics Operations Inc., Roche Diabetes Care Gmbh, Ascensia Diabetes Care Holdings Ag, etc. (Figure 4). Their patented inventions are covering invasive, minimally invasive, and non-invasive devices.

It should also be noted that start-up companies are also creating innovative technologies for glucose monitoring. For example, the GWave sensor is a device about a third the size of a standard smartphone, inserted into a ceramic bracelet. It uses Bluetooth to transmit its glucose readings to an accompanying mobile app that tracks readings and alerts users to fluctuations in their blood sugar levels (28).

The inventions in the field of continuous glucose monitoring devices are most related to the Cooperative Patent Classification codes, which are shown in Figure 5.

Currently, on the background of recent ubiquitous technological developments penetrating the society, using of digital technologies to control the treatment of patients, including those with diabetes, and enhance their quality of life is becoming more relevant.

A patent analysis using the additional keyword "digital system" revealed that since 2006, the number of claimed and issued patents associated with the digitalization of constant glucose monitoring has been increasing (Figure 6).

In the past 2 years (2021 and 2022), the number of filed patent applications has dropped significantly. On the one hand, this may be due to the increased efforts of inventors in the fields of prevention and treatment of COVID-19, development of insulin pumps and closed-loop systems, etc. On the other hand, it could be related to the bringing of previously patented technologies to market.

The implementation of digital technologies for continuous glucose monitoring increases its usability and provides new options for assessing the glycemic profile, such as information on the trend

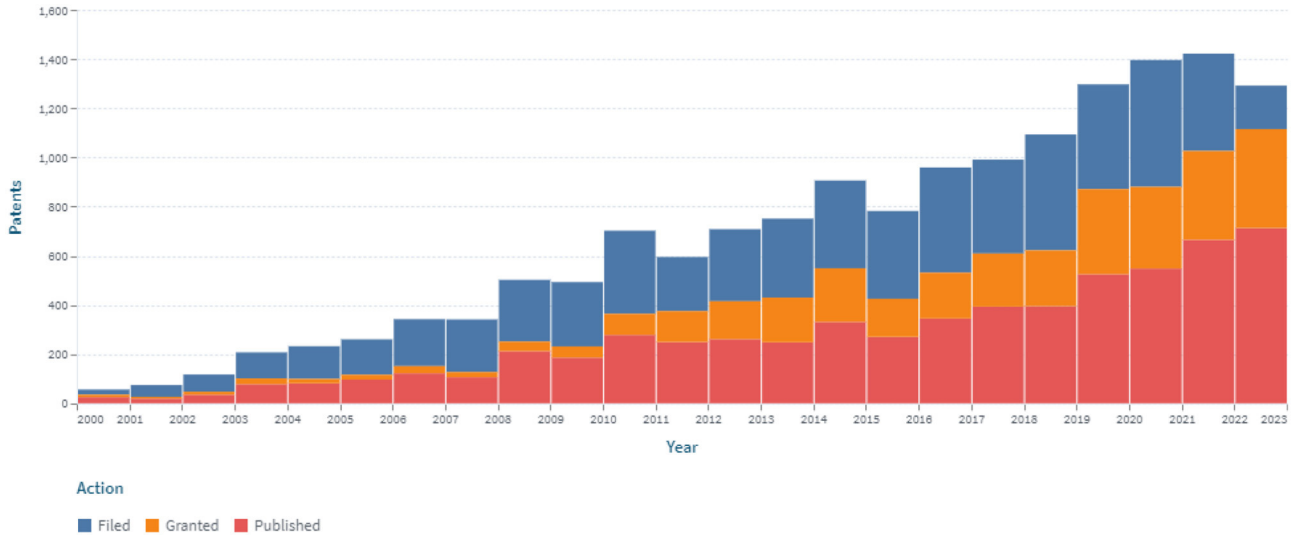

FIGURE 2
The dynamics of the patent landscape within the segment of continuous glucose monitoring in the period 2000–2022.

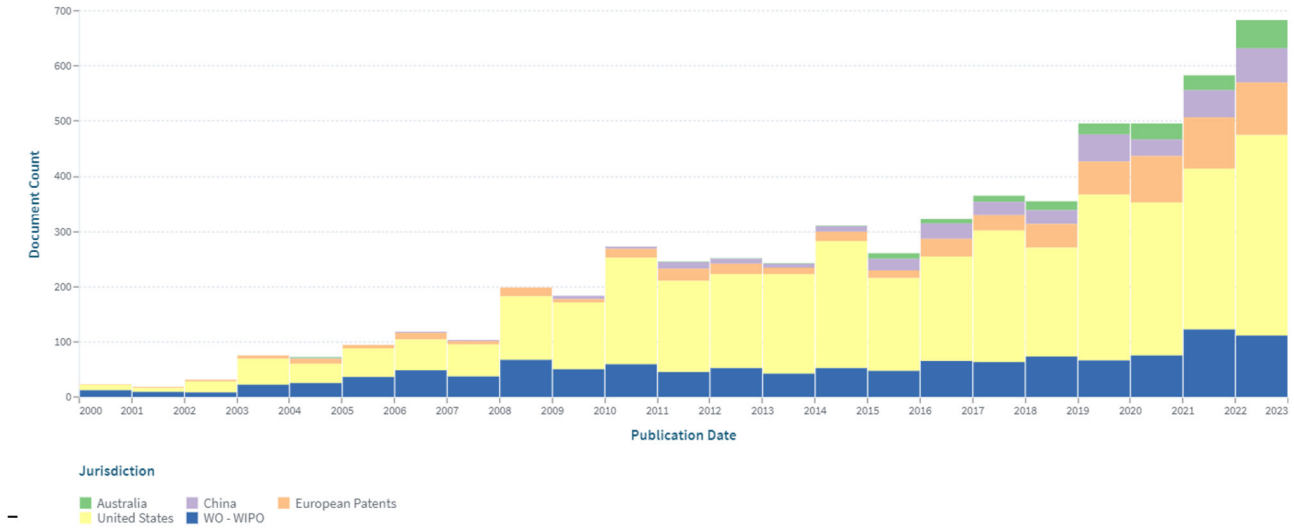

FIGURE 3
The dynamics of patenting in five leading patent offices within the segment of continuous glucose monitoring in the period 2000–2022.

of the glycemic curve, quantification of the duration and amplitude of glucose fluctuations.

The devices for CGM are also divided into the following types: continuous glucose monitoring in the "blind" regime, real-time continuous glucose monitoring, as well as scanning continuous glucose monitoring (flush glucose monitoring) (29).

The sensor is placed for several days for continuous glucose monitoring in the "blind" regime. Following that, the obtained outcomes are retrospectively evaluated. The goal of monitoring is to detect changes in glycemia in the subject's everyday life settings. The sensor does not send any indications indicating a fall or increase in glycemia, allowing researchers to rule out as much "increased motivation" and "false compensation" of carbohydrate metabolism throughout the study time as is feasible. Real-time continuous glucose monitoring shows a detailed graph of glycemia variations over time and alerts when glycemia levels exceed individual objectives. Flash glucose monitoring is a technology in which patients scan information from a sensor that continuously monitors and stores glucose data for the last few hours, with the ability to view previously stored values.

Modern developments for continuous glucose monitoring are aimed at improving the accuracy and usability of sensors. Thus, it should be noted that innovative devices for constant glucose monitoring not only display a graph of the change in the amount of glucose in the blood but

FIGURE 4
Top companies (by number of patents, reflecting the presented letter size) in the patenting field of devices for continuous glucose monitoring in the period 2000–2022.

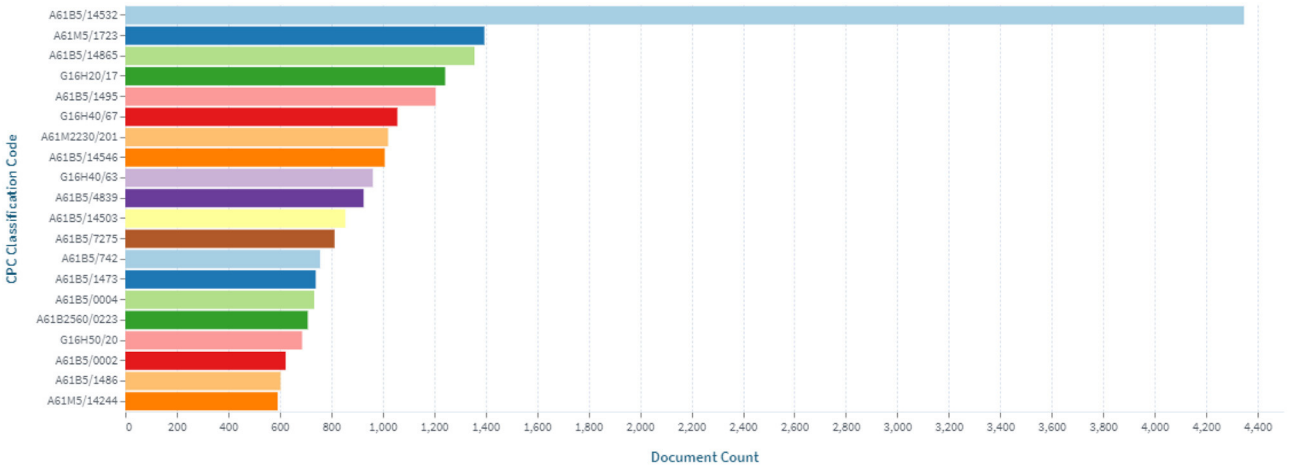

FIGURE 5
Distribution of inventions in the field of continuous glucose monitoring by Cooperative Patent Classification codes.

also warn the patient when this indicator is out of normal range and are also synchronized with the mobile application for smartphones.

According to ISO 15197:2015, the sensor is considered accurate if 95% of the test results are within ±0.83 mmol/L (±15 mg/dL) at glucose concentrations of <5.55 mmol/L (<100 mg/dL). At higher glucose concentrations, 95% of test results should be within ±15%. But this standard applies to glucometers. Most CGM accuracy assessment methods are based on comparing the CGM tool with the corresponding reference values.

The Clarke error grid analysis can be used to evaluate the clinical precision of a medical sensor for continuous glucose monitoring (30) as follows:

Zone A: Clinical decisions based on these indicators will result in identical results to those based on values obtained by the reference method.

Zone B: The indicators will not lead to an error in the prescription of treatment, or the error will be insignificant and will not affect the patient's condition.

Zone C: The use of the obtained indicator will lead to a serious error, which will most likely worsen the patient's condition.

Zone D: The score will lead to a very serious error, which will greatly worsen the patient's condition.

Zone E: The use of such an indicator will result in a fatal error that may be life-threatening to the patient.

The mean absolute relative difference (MARD) between devices is another measure for evaluating the accuracy of CGM systems. Valid MARD values require a significant number of paired measurements and are also related to the precision of the reference tool.

The clinical accuracy of continuous glucose monitoring is also assessed using Parkes nomograms (31). Zone A in the Parkes nomogram indicates no effect on clinical action. Zone B means changes in clinical action that have no or little effect on clinical outcome. Results in zones C, D, or E mean changes in clinical action that have a major impact on clinical outcome.

We systematized data on the world patent protection of invasive, minimally invasive, and non-invasive sensors. Minimally and non-invasive sensors for continuous glucose monitoring are of particular interest. Analysis was performed for clinical studies in patients of various ages and with high risks, and their implemented digital technologies, and data on their validation and registration by legislative bodies were summarized.

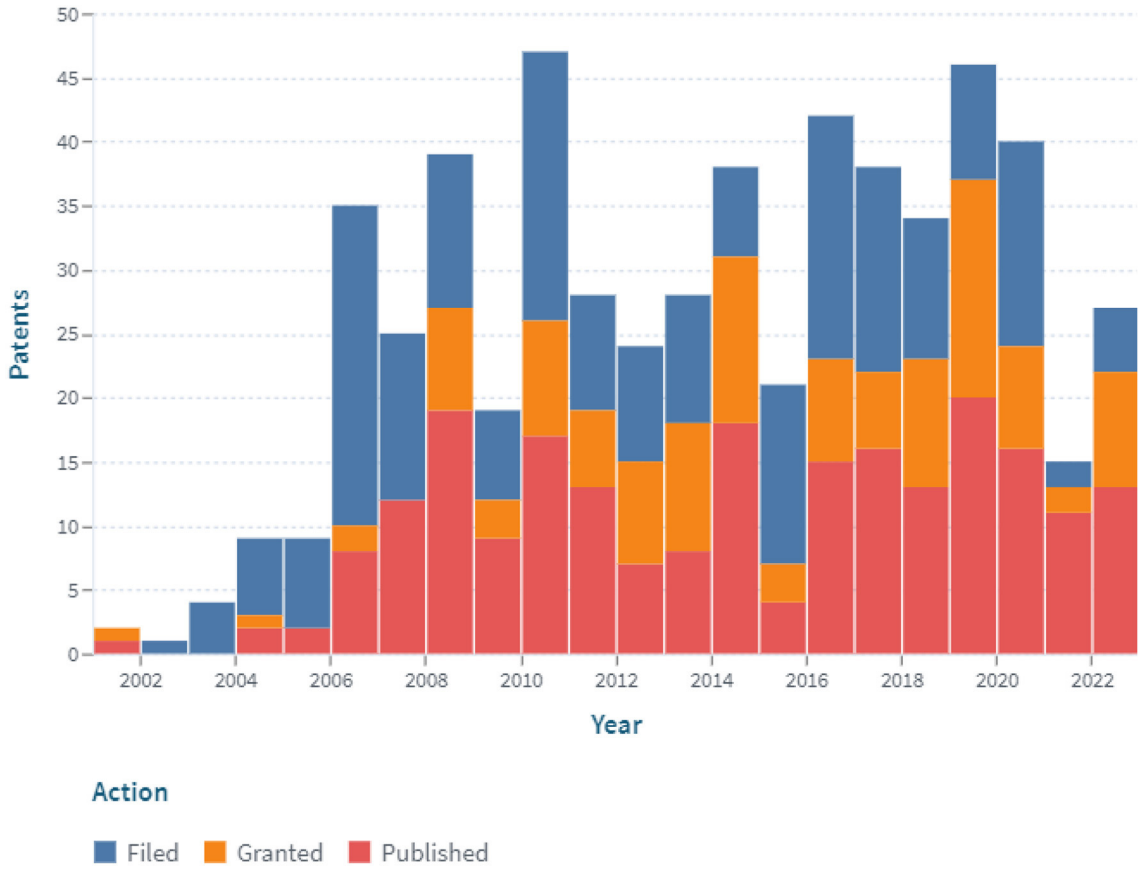

FIGURE 6
The dynamics of the patent landscape within the segment of digital continuous glucose monitoring in the period 2000–2022 (with the application of the additional keyword "digital system").

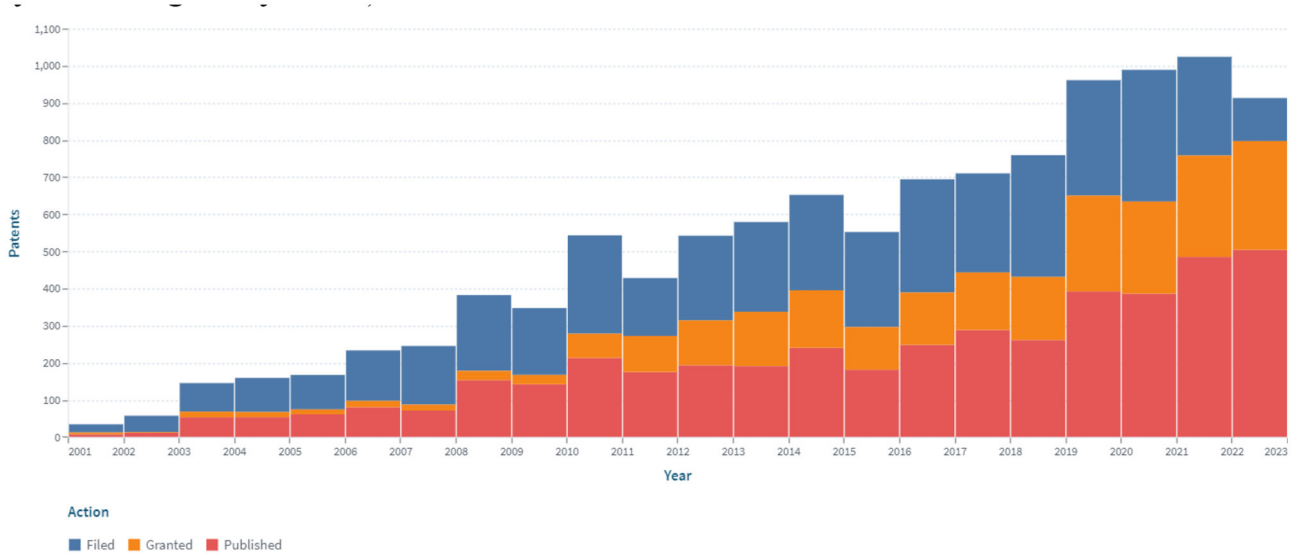

FIGURE 7
The dynamics of the patent landscape within the segment of invasive and minimally invasive continuous glucose monitoring in the period 2000–2022.

3.2. Invasive and minimally invasive continuous glucose monitoring

An additional filter with codes from the Cooperative Patent Classification was added to analyze the technological solutions associated with invasive and minimally invasive sensors for glucose monitoring (A61B5/14532, A61B5/14546, A61B5/1473, A61B5/14865, A61B5/14503, and A61B5/6848). The obtained data are shown in Figure 7. According to the conducted research, there are 4.397 patents and 1.248 simple families. The linear increasing of the patenting process has been revealed. These developments may also be presented with other patent classification codes and keywords.

The most patent publications concern obtaining patent protection in the United States (2.559; 58%), under the PCT procedure (711; 16%), and through the European Patent Office (473; 10.7%).

The first developments for continuous minimally invasive glucose monitoring in the "blind" regime include the 1999 invention by Medtronic MiniMed, USA. This device was able to measure the concentration of glucose in the interstitial fluid of subcutaneous fat every 5 min for 3 days in a row, after which the data was transferred to a computer and analyzed.

Of note is the Guardian Real-Time (Medtronic MiniMed, US) continuous minimally invasive monitoring device, which has been used for more than 15 years in clinical practice since 2004. It is capable of displaying the level of glucose in the blood in real time. The device is protected by numerous patents (US6809653, AU5623100, CA2666429, etc.) and measures glucose levels in interstitial fluid (32–34). It is necessary to calibrate the glucose concentration in the blood when using the device. The sensor is replaced after a few days (72 h). Medtronic has created a pediatric version of the Guardian Real-Time system specifically for young diabetics, which is quite remarkable.

There is evidence from a study on the effectiveness of implementing the Guardian Real-Time system in a clinical setting. This system is effective in children and adults against the background of insulin injections and insulin pump therapy for DM1 and DM2, as well as for heart surgery in children (35–39). Researchers noted a greater decline in HbA1c when using Guardian Real-Time monitoring. The Guardian real-time device's inaccuracies have been linked to abrupt changes in glucose levels in athletes (40). In addition, 56% measurement accuracy was observed in the hypoglycemic state.

It should be noted that Medtronic MiniMed develops new generations of devices and improves sensors for continuous glucose monitoring. An important fact is that Medtronic has gotten a CE mark for its Guardian Connect mobile continuous glucose monitor and app. Data can be transferred from a mobile phone to the Medtronic CareLink web platform. Modern systems, which include digital sensors for CGM, mobile applications, and web platforms, are opening up new opportunities in the management of diabetes mellitus.

Also, the real-time continuous glucose monitoring systems of Dexcom, Inc., and Abbott Diabetes Care are widely used. The Dexcom G4 Platinum system is disclosed in numerous patents (including CA2664528, US7935057, AU8088601, US8073519, US8858434, US7771352, US8682408, and US9750460) (41–45).

But in 2023, Dexcom G4 is no longer available on the market.

Dexcom Inc. is constantly expanding its portfolio of solutions regarding continuous glucose monitoring, which includes the Dexcom G6, Dexcom G7, and Dexcom ONE systems, among others. A crucial area for the advancement of medical devices for continuous glucose monitoring is related to their compatibility with mobile devices, cellphones. For example, the Dexcom G5 mobile system is disclosed in US Patent 9020572 (46). Also, data can be transferred from a mobile phone to the Dexcom Clarity web platform. As noted, systems, which include digital sensors for CGM, mobile applications, and web platforms, are playing an increasing role in the management of patients with diabetes mellitus.

The Dexcom G7 provides accurate, single-digit MARD glucose readings clinically proven when placed on the arm or abdomen in adults with diabetes (47). The accuracy of the Dexcom G7 sensors placed on the arm or abdomen is similar to the accuracy of the Dexcom G5 and Dexcom G6 sensors placed on the abdomen (48). Task analysis required for successful insertion of sensors favors Dexcom G7 over earlier systems. The G7 CGM placed on the arm or abdomen was accurate in children and adolescents with DM1 (49). However, accuracy measurements in the younger cohort (2–6 years old) were relatively few (50). The G7 CGM system has a lower cognitive burden than earlier CGM systems for older people utilizing it and for trained diabetes care and education specialists (51).

In 2018, the FDA approved the first CGM system, Eversense (Senseonics, Inc.), with a fully implantable sensor to measure glucose for up to 90 days. The measured glucose levels are sent to a device-specific mobile app every 5 min (52). The CGM system Eversense is disclosed in patent US9901293 (53). Inventors use the fluorescence method for glucose monitoring.

In 2014, the Flash monitoring device, FreeStyle Libre (Abbott Diabetes Care, USA), was launched on the European market. The system uses an electrochemical sensor that fits on the back of the shoulder for up to 14 days and a FreeStyle Libre scanner. The system estimates the concentration of glucose in the intercellular fluid every minute. Glycemia data is displayed as the scanner reaches the implantable sensor. The device displays the history of values over the past 8 h as well as trends in glucose levels. The device can be used to retrospectively assess glucose levels. The device also has powerful patent protection (for example, EP1466156, US7620438, US7920907, EP1942801, AU2012271333, etc.) (54–58). FreeStyle Libre also performs calibration using the built-in glucometer. It is recommended to replace the sensor after 120 h.

The results of the studies confirm that the use of the FreeStyle Libre Flash device contributed to a decrease in the level of HbA1 in diabetic patients (59–61). FreeStyle Libre was more accurate in patients with moderate to rapid glucose changes compared to Dexcom G4 Platinum (62). However, real-time continuous glucose monitoring (rtCGM) was more effective than intermittently scanned continuous glucose monitoring for a number of parameters in patients with DM1 and very high risk (63). The use of FreeStyle Libre Flash device had some limitations. In

children without diabetes who are overweight or obese, FreeStyle Libre Flash did not accurately assess glucose levels (64). Although the accuracy of the FreeStyle Libre was clinically acceptable during post-prandial rest and walking in overweight or obese young adults (65). The possibility of using FreeStyle Libre Flash during dietary treatment of patients without diabetes, during Ramadan in patients with DM1, and in pregnant women with DM1 and DM2 is shown (66–68). In addition, the successful use of FreeStyle Libre Flash by children with DM1 during summer camp is reported (69). Since 2017, the FreeStyle Libre system has a CE designation for use in diabetic pregnant women. Abbott has also launched new, improved systems for continuous glucose monitoring, FreeStyle Libre 2, FreeStyle Libre 3.

In addition to the continuous glucose monitoring system, Abbott has also created a single digital ecosystem that includes the FreeStyle LibreLink and LibreLinkUp smartphone apps as well as the LibreView cloud platform. The FreeStyle LibreLink application (patents US7826382, US 10820842, etc.) allows patients to measure their glucose level, evaluate the data obtained, and share it with specialists (70, 71). In addition, the LibreLinkUp application (patent US11147479) enables patients to share their glucose data with relatives and friends for their peace of mind (72). LibreView (patents US10872696 and US10923218) is a free and secure cloud system with a web interface through which health workers and patients can create and share a set of structured, understandable reports (73, 74). The doctor installs LibreView on his computer. The patient transfers data from the FreeStyle LibreLink mobile app to the LibreView patient account. With the consent of the examined, physicians can view remotely downloaded patient glucose scores on their professional LibreView account. The doctor works with patient data, compiling reports at anytime and anywhere remotely where there is access to the Internet. The report is generated for any period of interest, and if necessary, the data is evaluated over time.

Abbott's digital ecosystem, like other CGM systems available on the market, provides doctors and patients with continuous online access to glycemic profile data, as well as the ability for additional patient support from their relatives or patient caregivers. It is able to analyze results over time, adjust therapy, and eliminate errors made by patients.

3.3. Non-invasive continuous glucose monitoring

For characterization of the patent landscape, not only widespread technologies are of importance, but also narrow segments that have evolved in recent years. Such important recently evolved segment is the one encompassing non-invasive continuous glucose monitoring technologies.

Many methods from various branches of biophysics have been proposed for assessing the level of glucose with non-invasive sensors: optical, ultrasonic, electromagnetic, thermal, and others (15–17).

An additional filter with code from the Cooperative Patent Classification (A61B5/14532) and the keyword "non-invasive" was added to analyze the technological solutions associated with non-invasive sensors for glucose monitoring.

The dynamics of the patent landscape in the segment of continuous non-invasive glucose monitoring are shown in Figure 8.

The dynamics of patent publications in the area of non-invasive continuous glucose monitoring have a positive trend. Nine hundred and ninety-five patents were issued, and 469 simple families are represented. In the area of non-invasive continuous glucose monitoring, the largest number of patents have been published in the United States (500; 50%), according to the PCT system (225; 23%), through the European Patent Office (91; 9%), and in China (69; 7%).

It should be noted that not all patented developments for non-invasive continuous glucose monitoring are available for purchase. GlucoWatch Automatic Glucose Biographer (Cygnus, Inc., USA), used reverse iontophoresis (patent WO9600110) and obtained FDA approval (75). However, the developers recalled the device from the market due to failures in measurement accuracy and reliability, as well as discomfort and skin irritations in users.

Near infrared spectroscopy is used in patented devices: the TensorTip Combo-Glucometer (CNOGA Medical), the Helo Extense (World Global Network), and the Wizmi (WEAR2B LTD).

The TensorTip Combo-Glucometer is disclosed in US Patent No. 10687739 (76). The device was developed by Cnoga Medical and approved by the CE (certified in Europe). The TensorTip Combo-Glucometer is pending FDA approval. The measurement method used in the TensorTip Combo-Glucometer is based on the method of photoplethysmography, which assesses changes in the state of the vessels inside the user's finger when illuminated with light of different wavelengths. The device is hybrid because it is calibrated to take into account the individual characteristics (skin color, skin thickness, etc.) of each person when measuring the blood sugar level by a traditionally invasive method using test strips. The TensorTip Combo-Glucometer requires constant recalibration.

There is evidence from clinical studies supporting the concept that the TensorTip Combo-Glucometer may be an effective additional alternative for glucose monitoring.

The TensorTip Combo-Glucometer was investigated in 76 patients with diabetes mellitus; 77 patients after heart surgery; 19 participants at home; and two post-marketing users (77). More than 98% of measurements in each study were reported to be in zones A (over 81%) and B (over 11%). The results demonstrate the compliance of the Combo glucometer with the reference methods.

In more recent investigations, the combined invasive and non-invasive TensorTip Combo-Glucometer ($n = 100$) results showed that 99% of glucose measurements were in zones A and B (91.1 and 7.8%, respectively), and MARD was 18.1% for non-invasive technology. The authors conclude that this technology allows for painless monitoring of glucose levels in people with diabetes (78).

Against the background of a standardized experiment with food in 36 patients, including healthy individuals as well as those with diabetes, the performance of the TensorTip Combo-Glucometer in comparison with the YSI Stat 2300 Plus at home was assessed. For the non-invasive TensorTip Combo-Glucometer instrument, 96.6 and 3.4% of results were detected in zones A and B. The authors conclude that the measurements were reliable with the Combo glucometer (79).

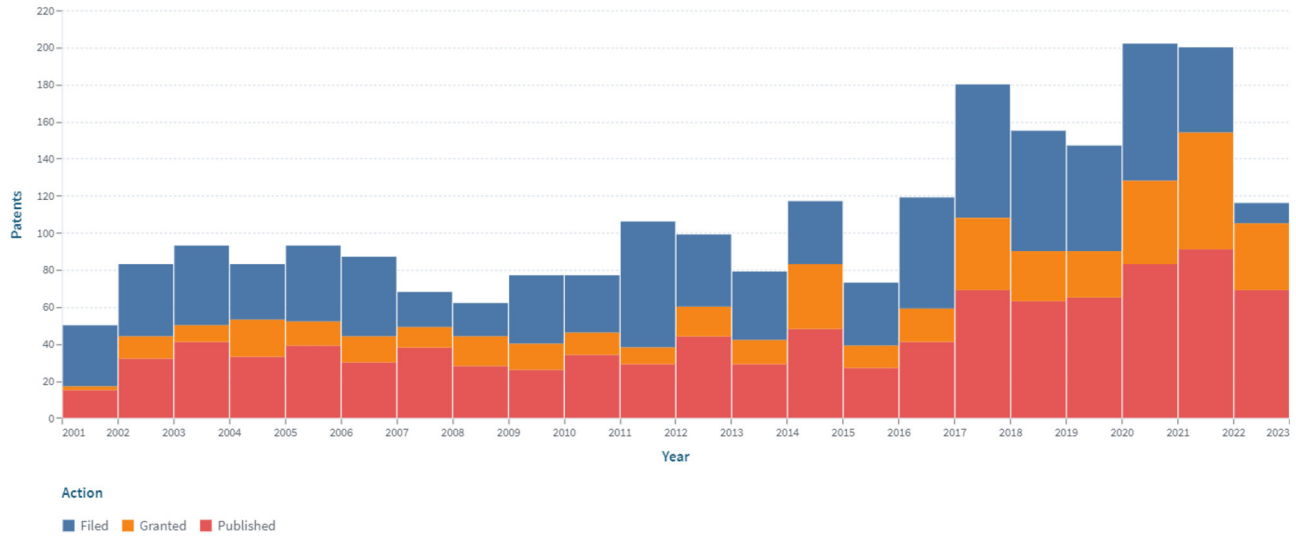

FIGURE 8
The dynamics of the patent landscape within the segment of non-invasive continuous glucose monitoring in the period 2000–2022.

The results of the studies performed showed the effectiveness and accuracy of measurements using the TensorTip Combo Glucometer in patients with DM1 and DM2 and in healthy volunteers, and patients after heart surgery. The TensorTip Combo Glucometer is the "world's first" hybrid glucometer with both non-invasive and invasive components.

Near infrared spectroscopy is used in a medical sensor for non-invasive glucose monitoring in the Helo Extense device developed by World Global Network and disclosed in patent application WO 2022/076395 (80). The device has not been approved by the FDA yet and does not have the CE mark. The informativeness of HELO Extense device publications is limited. No clinical trial data were identified at this time.

The Wizmi device manufactured by WEAR2B LTD is disclosed in patents US 11129556, and EP 3975831 (81, 82). The device also uses near-infrared reflectance spectroscopy.

In a prospective, observational, controlled clinical trial in 32 healthy pregnant women, the safety and precision of non-invasive continuous glucose monitoring with the Wizmi sensor were compared with plasma glucose values (83). Of the 224 paired measures, 208 (93%) were in Zone A, and 16 (7%) were in Zone B, both of which were clinically suitable zones for the Clarke error grid analysis. The Wizmi device is safe to use, with overall good accuracy when compared to a gold standard reference of plasma glucose, according to the scientists' findings. Clinical trials of the Wizmi device are underway.

A medical sensor for continuous glucose monitoring developed by DiaMonTech and using laser detection is of interest. The device is under research and development. The DiaMonTech device was not cleared by the FDA. The device has received CE mark approval. The essence of the sensor is disclosed in patent EP 3623795 (84). The device operates in the infrared range and measures the glucose level using laser detection. The proposed system comprises a device to emit an exciting light beam and a probing light beam. The probing light beam is oriented so that it allows the analysis of many different materials with different optical densities. The mobile phone communication option allows you to check the information and take the necessary measures.

In studies using 100 volunteers, a non-invasive glucometer prototype that combines skin stimulation by a mid-infrared quantum cascade laser with photothermal sensing was examined. Results showed that non-invasive blood glucose analysis is practical and accurate enough to replace finger pricking and minimally invasive glucometers (85). Currently, the clinical trial "Feasibility study of blood glucose monitoring with the non-invasive medical device D-Base (DiaMonTech)" is active (86).

FiberSense is a continuous glucose monitoring device developed by EyeSense. WO 2022/199765 discloses a FiberSense device that measures fluorescence in a tissue surrounding the transport fluid by means of a fiber optic probe (87). A FiberSense CGM clinical trial is currently underway [clinical trial NCT05133973, "Feasibility Study of a Transdermal Continuous Glucose Monitoring (CGM) System in Diabetic Patients"] (88).

Interesting is the development of GlucoWise by MediWise, based on radio wave spectroscopy technology. In determining the glucose level, electromagnetic radiation with a frequency of 60 GHz is used, which is applied to the area of the skin between the thumb and index finger or to the earlobe. This technique is disclosed in patent US11298052 (89). GlucoWise is still in research and development.

The GlucoWise device was evaluated for glucose monitoring in a pilot study with healthy male volunteers ($n = 10$). For two volunteers, the results showed good agreement between invasive and non-invasive techniques. Data gathered from the other eight volunteers revealed abnormalities in the radio-frequency signal that could have been caused by stress and indicated hand motion and incremental holder sliding during the session (90).

Nemaura Medical introduces the SugarBEAT continuous glucose monitoring device to the market. Patent US 10092224 states that the device uses a reverse iontophoresis technique to extract

glucose analytes from a patient's interstitial fluid (91). The patch system is in close contact with the patient's skin and contains electrochemical sensors. An electronic sensor collects readings and transmits them to a smartphone or SugarBEAT reader. Calibration requires a traditional finger-prick blood test.

Data from a clinical accuracy study of the SugarBEAT device in 75 patients with DM1 and DM2 are available. Over 12,000 pairs of data points, MARD was 7.96% for the 2-point calibration and 8.02% for the single finger prick calibration (92). Nemaura Medical, Inc. has received CE Mark approval for SugarBEAT.

OrSense Ltd. received CE approval for a continuous non-invasive glucose monitoring system by spectroscopy. This optical measurement technology is disclosed in EP 1292216 (93). This system was investigated in 23 patients with DM1 and DM2. A Clarke error grid analysis revealed that 95.5% of the data fell within the clinically acceptable A and B zones, and the mean relative absolute difference was 17.2%. The sensor was well-tolerated (94). However, the NBM-200G device has been discontinued by OrSense Ltd.

The non-invasive Symphony device is designed by Echo Therapeutics. Symphony includes a skin penetration tool, a transdermal sensor, a wireless transceiver, and data display technologies. Non-invasive glucose determination is performed using sonophoresis. The device is disclosed in numerous patents (including US 7963917 and US 8812071) (95, 96).

In critically ill cardiac surgery patients ($n = 15$), the Symphony continuous glucose monitor's accuracy has been investigated. An analysis of the glucose-error grid revealed that zones A and B were occupied by 99.6% of the measurements. MARD was at 12.3%. There were no known negative device impacts. The Symphony system, according to the involved scientists, can accurately measure glucose levels in the transdermal interstitial fluid of patients in cardiac surgery intensive care units (97).

Noteworthy is the development of GlucoTrack (GlucoTrack, Inc., formerly Integrity Applications). The device is disclosed in patent application WO 2022/020734 (98). The device combines three ways to measure blood glucose: ultrasonic, electromagnetic, and thermal. Integration of measurement data from three methods at the same time allows patients to get more accurate results. All these measurements are carried out using a miniature clip-on sensor, which is attached to the earlobe. GlucoTrack is a device that has received a CE Mark.

In recent years, data on the use of GlucoTrack has expanded significantly. Studies have been conducted on the accuracy of GlucoTrack in patients with DM1 and DM2, as well as on the influence of demographic factors.

For 2 days, GlucoTrack was compared to HemoCue in patients with DM1 and DM2 ($n = 91$). Clarke error grid analysis revealed that 96% of readings fall into acceptable zones A and B. The authors conclude that the high accuracy of GlucoTrack is achieved through the use of a combination of several technologies (99).

Of interest are also the GlucoTrack studies in patients ($n = 172$) with DM2 with various demographic characteristics related to age, sex, body weight, and the presence of a punctured earlobe. Studies conducted using the Clarke error grid analysis revealed that 97.6% of glucose readings were in zones A and B. The authors conclude that GlucoTrack measurements are independent of patient demographic profiles (100).

Lin et al. also investigated the accuracy of GlucoTrack according to the individual characteristics of patients ($n = 114$) with DM2 (101). The effect of such factors as duration of diabetes mellitus, HbA1c level, and smoking on the indicators of continuous glucose monitoring was assessed. 98.0% of glucose readings were found to be in zones A and B. Absolute relative difference values were independent of duration of diabetes, HbA1c, or smoking. The findings suggest that GlucoTrack's work is independent of diabetes duration, HbA1c levels, and smoking history.

The GlucoTrack medical sensor also exhibited stable performance in a trial of individuals ($n = 27$) with DM2, including those with prediabetes (102). It was found that 100% of the outcomes fell inside zones A and B (62.4 and 37.6%, respectively). MARD is 19.7% compared to YSI Stat2300plus and 17.5% compared to HemoCue.

Thus, the results of GlucoTrack studies showed its accuracy in both DM1 and DM2 diabetic individuals, independence from demographic factors (age, sex, body weight, and presence of a punctured earlobe), and individual characteristics of patients (duration of diabetes mellitus, HbA1c level, and smoking). GlucoTrack is also indicated for patients with prediabetes.

A fundamentally different approach for constant glucose monitoring is used by the developers of the Boydsense device. BoydSense Inc. is developing an exhalation analyzer using biomarkers to predict blood glucose levels. This technique is disclosed in EP 3830574 (103). Currently, clinical studies of the exhalation analyzer are under way. The clinical trial NCT05207020, "Development and Validation of the Blood Glucose Measurement Device by Air Analysis Expired (BOYDSENSE)" has a status of "Recruiting" (104).

Several studies have also investigated the potential of continuous monitoring of glucose in tear fluid. The inventors of the Akron Institute have developed diagnostic lenses for measuring glucose levels in tear fluid for patients with diabetes. If blood glucose rises, the lenses containing the boronic acid derivative change color. The invention is disclosed in patent CA 2774462, but the patent has now expired, and the development has not been widely used commercially (105). A glucose-sensitive contact lens was developed by Novartis and presented in the application WO 2003/075888 (106). It was also not commercialized.

Dongwoon Anatech has already received patent recognition for saliva glucose detection (D-SaLife) technology in South Korea, Japan, and China; an EP 3561507 patent application in Europe is pending (107). The sensor uses the glucose oxidase method.

The correlation and precision between the salivary glucose level measured with D-Salife and the capillary glucose level were examined in 114 people (108). Capillary glucose and D-Salife glucose had a direct association ($r = 0.93$), according to the regression analysis. According to error grid analysis, 33.3% of D-Salife were in zone B and 66.7% were in zone A. The authors came to the conclusion that the D-Salife performed well in accordance with ISO 15197. The company is planning further clinical trials of D-SaLife.

Other researchers have also proposed a system using salivary glucose screening. iQ Group Global has developed a medical sensor

to detect salivary glucose. This organic thin film transistor is disclosed in patent application US 2020/0057020 A1 (109). The film contains glucose oxidase, which, upon contact with sugar in saliva, generates an electric current. It is measured using a special chip built on transistors. The mobile device receives a signal that is transferred electrically. The collected data is processed by the application and displayed on the screen. The sensor is disposable and made in the form of a strip. Data from clinical studies of this medical sensor were not revealed.

To control glucose, scientists also propose to analyze sweat. An electronic patch has been developed to monitor sweat glucose levels. The technology is disclosed in patent application KR20180002550 (110). The patch is equipped with sensors for humidity, glucose, pH balance, and temperature. When measuring the glucose level in sweat, the enzyme type sensor takes into account pH and temperature values to increase the accuracy of the results.

There are data from pilot studies of sensors for monitoring sweat glucose levels in patients (111). The sweat glucose levels detected by the sweat glucose sensors are consistently correlated with the blood glucose levels estimated by a commercial glucose meter, according to statistical analysis. Moreover, it should be noted that the researchers proposed integrating the sensor for monitoring sweat glucose with the transdermal drug delivery module.

4. Discussion

The studies conducted revealed a stable increase in the patenting of sensors for continuous glucose monitoring in the period 2000–2022, to the greatest extent since 2006. New devices can be expected to appear in medical practice in the coming years since patenting precedes the launch of products on the market. The greatest geographical distribution of development patenting was discovered in the United States and Europe, as was the protection of inventions under the Patent Cooperation Agreement. Leading development companies are Dexcom Inc., Abbott Diabetes Care Inc., Medtronic Minimed Inc., Roche Diabetes Care Inc., Roche Diagnostics Operations Inc., Roche Diabetes Care Gmbh, and Ascensia Diabetes Care Holdings Ag, among others.

It should be noted that continuous monitoring currently still complements, but does not fully replace, blood glucose control by other methods. The continuous glucose monitoring system gives a more comprehensive picture of the state of carbohydrate metabolism compared to the determination of glycated hemoglobin (HbA1c) and self-monitoring data using a glucometer, and enables the recording of glycemic fluctuations in detail during the day. In addition, in clinical practice, continuous glucose monitoring allows to assess the effect of nutrition, exercise, concomitant diseases, different doses of sugar-lowering or other drugs, and other factors on glycaemia and its variability. This allows initiating changes in patients' therapy and giving more targeted recommendations on diet compliance and exercise.

The role of continuous glucose monitoring in the estimation of asymptomatic and nocturnal hypoglycemia is also important, as it allows for the risk of their occurrence to be reduced, contributing to the improvement of the patient's glycemic profile.

4.1. Minimally invasive continuous glycemic monitoring

Positive dynamics of the patent landscape in the segment of invasive and minimally invasive continuous glucose monitoring have been established for the period 2000–2022.

The patented minimally invasive continuous glycemic monitoring devices (Guardian Real-Time System, Medtronic MiniMed, Dexcom G7, Dexcom Inc., FreeStyle Libre, and Abbott Diabetes Care) use an electrochemical mechanism for sensing glucose concentration. Different concentrations of glucose in interstitial fluid and blood can result in measurement errors by minimally invasive sensors. It should also be noted that the method of monitoring glucose in interstitial fluid in conditions of increased oxygenation is not applicable because of the possibility of erroneous indications of hypoglycemia associated with a decrease in blood flow in the area of sensor installation (compression, hypothermia). In addition, the use of a number of minimally invasive sensors is associated with the need to calibrate the device as well as regularly self-monitor glycemia with a glucometer in a number of cases. The above-described patented sensors for minimally invasive glucose monitoring are presented for purposes of illustration and not to underline limitations.

The effectiveness of minimally invasive monitoring using such tools as Dexcom G7 (Dexcom Inc., California, USA), Guardian Real-Time (Medtronic MiniMed, US), and FreeStyle Libre (Abbott Diabetes Care, USA) has been confirmed in a number of clinical studies in patients with DM1, including high-risk individuals, and DM2, with insulin injections and insulin pump therapy, and in children and older adults, and during pregnancy. Exercise and body mass index, glucose variability, should be taken into account when using sensors for continuous glucose monitoring. A decrease in HbA1c was detected upon using such monitoring.

Thus, studies have revealed a positive patent trend for sensors for minimally invasive glucose monitoring. This monitoring significantly supplements the data from invasive monitoring and, as a result, increases the informativeness of diagnostic studies due to numerous measurements taken during various patient conditions: before and after eating, during and after physical activity, against the background of glucose variability, in the dietary treatment of patients without diabetes, during fasting, and during pregnancy. The possibility of using minimally invasive glucose monitoring in different age groups should also be noted. So, according to the instructions, the FreeStyle Libre sensor is designed to measure the level of glucose in interstitial fluid in patients with DM aged 4 years. Medtronic also has a pediatric version of the Guardian REAL-Time System. The Dexcom G5 system is approved for adults and children 2 years of age and older.

At the same time, among the disadvantages of minimally invasive constant glucose monitoring are: patients' discomfort due to the introduction of subcutaneous sensors; the need for calibration using invasive devices in a number of cases; and the usability of sensors for a limited number of days due to biofouling.

It has to be mentioned that for more than 10 years, continuous minimally invasive glucose monitoring has been used in medical practice. These sensors are well-tolerated with the exception of possible individual side reactions, including discomfort, skin irritation, the development of erythema, bleeding (especially in patients with hemophilia), and allergic reactions.

According to the conducted studies, clinical use of devices has confirmed their efficacy, favorable safety profile, and ability to significantly improve patients' quality of life. Promising areas for improving sensors for minimally invasive continuous glucose monitoring are increasing the accuracy of results, optimizing calibration frequency, improving the convenience of wearing a glucose sensor on the patient's body, and optimizing the sensor's life.

4.2. Non-invasive continuous glycemic monitoring

Patenting non-invasive sensors for continuous glucose monitoring also displays a positive trend. However, in comparison to invasive and minimally invasive analysis, the numbers of the developed and implemented technologies in this area are lower.

Numerous techniques have been presented for non-invasive determination of glycaemia, including analysis of biological fluids from various parts of the body and organs (fluid of the anterior chamber of the eye, lacrimal fluid, saliva, sweat, interstitial fluid of the skin, etc.) and the composition of exhaled air. A number of devices have received CE mark approval (TensorTip Combo-Glucometer, Cnoga Medical Ltd.; SugarBEAT, Nemaura Medical; GlucoTrack, and GlucoTrack Inc.). However, these devices have not yet been approved by the FDA.

A clear advantage of non-invasive continuous glucose monitoring is the diversity of sensors using various glucose detection methods. However, it should be noted that some of the patented non-invasive sensors for continuous glucose monitoring are under investigation and are not yet on the market.

Continuous non-invasive monitoring has characteristics that make it highly desirable in the treatment of diabetes; this approach does not require implantation and does not cause adverse reactions of the organism to a foreign body. It should be noted that there is the possibility of error as a result of differences in skin pigmentation, hydration, intake of certain medications, and diverse parameters of the used body fluid. Moreover, a number of medical devices use non-specific methods to determine glucose, there is an effect of temperature on results, and there is no high correlation between blood glucose concentrations and glucose concentrations in the respective biological fluids. Nevertheless, continuous non-invasive glucose monitoring can also be used as an adjunctive method.

The analysis shows that non-invasive continuous glucose monitoring provides a large amount of glucose profile data and slows complications. It is necessary for patients and doctors, and it allows for timely glucose adjustment. The development of systems that account for the lag between the glucose concentration in the blood and interstitial fluid while requiring a minimum number of calibrations is promising.

4.3. Implementation of digital technologies and medical devices regulation (EU) 2017/745—MDR

According to the patent analysis conducted since 2006, a new trend in the advancement of continuous glucose monitoring has intensified, namely the implementation of digital technologies.

It is noted that early systems for continuous glucose monitoring included a sensor to estimate glucose concentrations, a transmitter that sent measurements to the receiver. Recent developments often use smartphones as receivers. This increases compliance with treatment because patients can quickly check glucose levels and their trends on their smartphones, which, as a result, optimizes the assessment of glycemic control (112).

Vettoretti et al. noted that potential users of low-cost CGM products include those taking part in weight reduction programs or athletes, for whom the CGM system may be useful for monitoring metabolism and making informed nutritional selections (113).

It should be noted that a number of non-invasive devices have received the CE mark, confirming that the products comply with European standards in the field of health, safety and environmental protection. It guarantees electrical safety and other issues mentioned in the regulations, but not health as such. In the European Union, there are certificates specifically for medical devices. Manufacturers could obtain certificates (MDD) in accordance with the Medical Devices Directive (Council Directive 93/42/EEC of June 14, 1993). However, in 2017, a European Union regulation on clinical trials and marketing of human medical devices [Regulation (EU) 2017/745] entered into force (https://health.ec.europa.eu/medical-devices-new-regulations/overview_en). It repeals Directive 93/42/EEC (MDD), which concerns medical devices, and Directive 90/385/EEC, which concerns active implantable medical devices, on May 26, 2021. The new Medical Devices Regulation (2017/745/EU) (MDR) harmonizes EU legislation according to technological advances, changes in medical sciences, and regulatory progress. In order to avoid destabilizing the market and to allow a smooth transition from the Directives to the Regulation, several transitional provisions have been implemented. Certain products certified under the Directives (with AIMDD or MDD certificates) may be placed on the market until May 26, 2024, and be available until May 26, 2025. During the transition period, manufacturers may obtain new MDR certifications under Regulation (EU) 2017/745. Compared to existing Directives, the MDR places greater emphasis on a life cycle approach that is clinically validated in terms of product safety. The MDR establishes stricter requirements for the designation of notified bodies and increases control and monitoring by national competent authorities and the Commission. MDR also enhances transparency by providing product information and publishing research results in the European Medical Devices Database (EUDAMED).

Examples of patented sensors for continuous glucose monitoring are presented in Table 1.

The progress in the field of sensors for continuous glucose monitoring offers a good opportunity for the further development of effective and high-quality care for diabetes patients. The validation data presented in the table for specific sensors give

TABLE 1 Characteristics of patented sensors for continuous glucose monitoring.

Device, company name, and country	Measurement technology and device location	Accuracy rate	Digital care for patients with diabetes		Status of the device
			Diabetes mobile health apps	Communication platforms (between patient and healthcare professionals)	
1	2	3	4	5	6
Guardian Real-Time, Medtronic Minimed, US	Glucose oxidase-based electrochemical sensor; subcutaneous adipose tissue (the back of the upper arm, the upper buttocks).	Of the 3.941 paired measurements, 96% of the values fell within Zone A (61.7%) and Zone B (34.4%). Agreement between YSI and Guardian RT values tended to be closer when glucose values were in the mid-range, vs. high or low glucose levels (114).	A transmitter sends the measurements to a receiver. The Guardian Connect system is compatible with the mobile app. The Guardian Connect continuous glucose monitoring system allows patients to see glucose levels, trends, and alerts on their mobile device.	The CareLink system platform allows users to connect with care partners and healthcare professionals (HCPs) to enable care partner remote monitoring and HCP therapy optimization when connected to the internet via WI-FI or mobile data.	Approved FDA and commercialized.
Dexcom 7G, Dexcom Inc., US	Glucose oxidase-based electrochemical sensor; subcutaneous adipose tissue (the abdomen, the back of the upper arm, the upper buttocks).	With an 8.2% overall MARD for adults and an 8.1% MARD for children, 2 Dexcom G7 is the most accurate CGM system available (115).	Devices are compatible with the mobile app.	Dexcom Clarity allows patients to view trends, statistics, and day-by-day data and email them to healthcare professionals. Dexcom G6 and G7 let patients share their glucose levels with up to 10 people who use the separate Dexcom Follow app, giving patients an added layer of support.	FDA-approved, CE-marked, and commercialized. **EU Certificate MDD for Dexcom ONE Continuous Glucose Monitoring System.*
FreeStyle Libre Pro Flash Glucose Monitoring System, Abbott Diabetes Care, US	Amperometric electrochemical sensor; subcutaneous adipose tissue (the abdomen, the back of the upper arm).	Overall, the mean absolute relative difference was 12.3% for the comparison with the YSI reference. The median absolute relative difference shows that half of the time the system was within 10.1% of the YSI reference (116).	Mobile app. FreeStyle Libre Link allows patients to monitor glucose with their phones.	Mobile app. LibreLinkUp enables patients to share glucose data with friends and family and manage diabetes together. The LibreView platform enables patients to share their glucose reports with healthcare professionals between appointments in order to have more in-depth discussions about their diabetes management, as well as to provide clear, easy-to-understand reports and easy remote access.	FDA-approved, CE-marked, and commercialized

(Continued)

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TABLE 1 (Continued)

Device, company name, and country	Measurement technology and device location	Accuracy rate	Digital care for patients with diabetes		Status of the device
			Diabetes mobile health apps	Communication platforms (between patient and healthcare professionals)	
1	2	3	4	5	6
TensorTip Combo-Glucometer, Cnoga Medical Ltd., Israel	NIR photoplethysmography; finger	MARD of 14–17%; error grid analysis: 99% in zones A and B (91.1 and 7.8%, respectively) (78)	There is Singular mobile application for users' other devices of Cnoga Medical Ltd. (TensorTip VSM and TensorTip MTX).	There is Cnoga's doctor management platform for patients monitoring for users' other devices of Cnoga Medical Ltd.	CE-mark approved. Not cleared by FDA.
Helo Extense World Global Network, US	Near-Infrared Spectroscopy; finger.	No reliable data has been found.	The HELO Extense is compatible with the mobile app. There is a HeloAppStore, a dedicated site for apps developed by subject matter experts, exclusively for Helo device.	There is Lifelog, a partner platform powered by Helo data.	The FDA has not approved it. The CE-mark has not been received.
Wizmi, WEAR2B Ltd, Israel	Near-Infrared Spectroscopy; arm wrist.	Error grid analysis: 93% in zone A, 7% in zone B (83)	No data has been found.	No data has been found.	Clinical trials are underway.
D-Base, DiaMonTech, Germany	Laser detection; finger.	MARD: 11.3–12.1% Consensus error grid: 98.8% in zones A+B (85)	D-Base can be connected to a mobile phone.	No data has been found.	DiaMonTech has submitted a pre-submission application for D-Base to the FDA. CE-mark approved.
FiberSense, EyeSense, Switzerland	Fluorescence method; transdermal.	Clinical trials of the FiberSense device are underway.	FiberSense is compatible with the mobile app.	No data has been found.	The FDA has not approved it. The CE-mark has not been received.
GlucoWise MediWise, England	Radio wave spectroscopy technology; hand.	Clinical trials are underway.	A mobile application is being created.	Smart cloud technology is being created.	The FDA has not approved it. The CE-mark has not been received.
SugarBEAT, Nemaura Medical, US	Reverse iontophoresis technique; upper arm.	MARD was 7.96% for the 2-point calibration and 8.02% for the single finger prick calibration (92)	SugarBEAT is compatible with the mobile app.	There is a Beat Technology Platform. Transmitting data to healthcare professionals via a smartphone app, the technology will allow for medical conditions and chronic diseases to be monitored for better disease management or treatment.	CE-mark approved. FDA pending.
NBM-200G, OrSense Ltd., US	Occlusion spectroscopy, finger.	Error grid analysis: 95% in zones A and B (94)	No data has been found.	No data has been found.	CE-mark approved. Discontinued.

(Continued)

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TABLE 1 (Continued)

Device, company name, and country	Measurement technology and device location	Accuracy rate	Digital care for patients with diabetes		Status of the device
			Diabetes mobile health apps	Communication platforms (between patient and healthcare professionals)	
1	2	3	4	5	6
Symphony, Echo Therapeutics, US	Sonophoresis; transdermal.	Error grid analysis: 99.6% in zones A and B (97)	Symphony is compatible with the mobile app.	Echo glucose data will be displayed on the cloud service for ultimate user convenience and accessibility.	No reliable data has been found.
GlucoTrack, GlucoTrack Inc., Israel	Personal ear clip; ultrasonic, electromagnetic, and heat capacity techniques.	Error grid analysis: 96% in zones A and B (99)	The testing of the mobile app has been completed.	The testing of the cloud-based software has been completed.	CE-mark approved and commercialized.
Boydsense, BoydSense Inc., France	Identification, and quantification of volatile organic compound (VOC) patterns in human breath; exhalation analyzer.	Clinical trials are underway.	Public APIs for EMR, applications, and portal access are developing.	Public APIs for EMR, applications, and portal access are developing.	No reliable data has been found.
D-SaLife, Dongwoon Anatech, South Korea	Saliva glucose detection.	Clinical trials are underway.	D-SaLife is compatible with the mobile app.	No data has been found.	No reliable data has been found.
Saliva-based glucose test, iQ Group Global, Australia	Saliva glucose detection.	Data from clinical studies were not revealed.	Sensor is compatible with the mobile app.	No data has been found.	iQ Group files a pre-submission to the FDA for a saliva-based glucose test.
Biosensing device, Seoul National University, Institute for Basic Science, South Korea	Sweat-based glucose monitoring device.	Clinical trials are underway.	No data has been found.	No data has been found.	No reliable data has been found.

*EU Certificate MDD—certificate in conformity with European Directive 93/42/EEC on Medical Devices, submitted in the European Medical Database EUDAMED (accessed on July 18th, 2023).

**EU Certificates MDR—certificates in conformity with Regulation (EU) 2017/745, submitted in the European Medical Database EUDAMED have not been found (accessed on July 18th, 2023).

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general overview on their important features, without an exhaustive list of performed studies. Overall, it is necessary to conduct additional studies of the accuracy of the increased number of various sensors in more patients, including different groups of risk and age, including reliable results for periods over 14 days. Straightforward way to assurance of the unity and quality of results is to standardize the method validation procedure and the process of obtaining acceptance criteria for validation characteristics. The processes of obtaining criteria and conducting validation should constitute a mutually agreed-upon system based on a single scientific base.

Certification of systems for continuous glucose monitoring in accordance with Regulation (EU) 2017/745 is also required. The regulation contains a number of improvements: reinforcement of the criteria for designation and processes for oversight of notified bodies, improved transparency through a comprehensive EU database on medical devices, introduction of an "implant card" for patients, reinforcement of the rules on clinical evidence, reinforcement of the rules on clinical evidence, etc. (117).

Mobile phone users can access over 1,500 diabetes management apps, namely patient health tracking apps, applications that function as independent medical devices, and applications that use medical device data (118).

The conducted analysis confirms that the control of diabetes treatment is becoming increasingly digital through the use of both connected digital medical devices and telemedicine communication (119, 120). Digital healthcare is a relatively new direction, but it is actively developing. The high risk of complications in diabetic patients can be prevented using current methods of digital continuous glucose monitoring. Mobile applications and computer programs are important components of systems for continuous glucose monitoring.

To visually assess glucose changes, most digital technologies for continuous glucose monitoring utilize a graphical display of the daily glucose profile—studies with overlapping daily graphs. Digital technologies also provide the main glycemic control indicators. An individual glycemic profile of the patient is created based on the information uploaded to the cloud storage and allows a doctor or medical organization to systematize the data of all of their patients.

For example, using the cloud platform with the LibreView web interface, which allows doctors and patients to create and exchange reports, enables the medical institution to aggregate the glucose data of all patients associated with it, perform dynamic monitoring, and control. Di Molfetta et al. created algorithms for the digital diabetes platform LibreView for various groups of diabetics to ensure proper glucose monitoring data interpretation (121).

Sensors for continuous glucose monitoring help to improve diabetes management. Continuous glucose monitoring is increasingly using digital technologies. As a result, digital innovation is spreading and providing broad access to the latest information technology and resources.

5. Conclusions

Active patenting and implementation of minimally invasive and non-invasive sensors for continuous glucose monitoring have been identified. Continuous monitoring currently supplements, but does not replace, other methods of blood glucose control and allows for more efficient glycemic control assessment. The implementation of digital technologies is a promising direction in the development of continuous glucose monitoring for patients with diabetes mellitus.

Sensors for minimally invasive glucose monitoring are patented, registered, approved, and marketed more than non-invasive devices. The clinical use of minimally invasive sensors for continuous glucose monitoring confirmed their clinical effectiveness in both type 1 and type 2 diabetics, including young patients and pregnant women; on the background of a diet in patients without diabetes mellitus, during Ramadan; and their favorable safety profile and ability to significantly improve the quality of life of patients.

Since 2006, the implementation of digital sensors for continuous glucose monitoring, using smartphones as receivers and telemedicine communication, has intensified. It increases adherence to the treatment of diabetes and increases its effectiveness. The creation of systems, which include digital sensors for CGM, mobile applications, and web platforms for professional analysis of glycemic control and implementation of unified glycemic assessment principles in mobile healthcare, represent promising approaches for controlling glycaemia in diabetic patients.

The development and improvement of digital sensors is expected to effectively complement invasive monitoring data, contribute to achieving a high patients' quality of life, and reduce their mortality.

Author contributions

OL, AA, and HW: conceptualization. OL and AA: methodology. OL: formal analysis and writing—original draft preparation. OL, ME, AB, AY, EP, AM, JH, AA, and HW: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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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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Help-seeking during 1-year follow-up in Chinese patients diagnosed with type 2 diabetes mellitus comorbid major depressive disorder

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Introduction: Previous research has revealed a bidirectional relationship between type 2 diabetes mellitus (T2DM) and major depressive disorder (MDD). A very limited proportion of patients with T2DM comorbid MDD received adequate psychiatric intervention. This study investigated the help-seeking behaviors of patients with T2DM comorbid with MDD during one-year follow-up.

Methods: At a medical center in China, a cohort of outpatients with T2DM were assessed and diagnosed for comorbid depression at baseline and after one year. The Mini International Neuropsychiatric Interview was used to diagnose MDD, while The Patient Health Questionnaire-9 (PHQ-9) and The Hamilton Depression Scale 17-item (HAMD-17) were used for depression assessment. Mental health help-seeking behaviors of patients during follow-up period were also evaluated.

Results: Out of the 203 patients with T2DM at baseline, 114 (56.2%) completed the follow-up. The prevalence of MDD in participants with T2DM was 12.8% at baseline and 22.8% at follow-up. Patients who completed the follow-up had a lower baseline PHQ-9 score (test statistic -2.068, p=0.039), HAMD-17 score (test statistic -2.285, p=0.022) than those who did not complete the follow-up. A total of 26 patients had comorbid MDD during the follow-up period, among which 8 patients (30.8%) voluntarily visited psychiatric clinics, while others did not seek assistance. The level of HbA1c at follow-up was higher in patients who sought help than in those who did not (8.1 ± 1.8% *vs.* 7.0 ± 0.7%), although the difference was not statistically significant.

Conclusion: Voluntary psychiatric help-seeking for Chinese patients with comorbid T2DM and MDD is uncommon. It is crucial to increase awareness of depression among patients and healthcare professionals alike.

KEYWORDS

type 2 diabetes mellitus, major depressive disorder, comorbidity, cohort study, help seeking

1 Introduction

Diabetes and depression are both among the top causes of disability-adjusted life-years in the adult population (1). Patients diagnosed with Type 2 Diabetes Mellitus (T2DM) require long-term medical care, self-management, family support, and health education to prevent or delay the development of complications (2). However, chronic physical diseases often cause psychological distress in patients, which in turn affects patients' ability and motivation for disease management (3). The prevalence of major depressive disorder (MDD) in patients with T2DM was 7.4% in a multicenter study across 12 countries (4). Previous research has revealed a bidirectional relationship between diabetes and depression (5). Patients with T2DM have a higher prevalence of depression than the general population (6). Depression was found to be an independent risk factor for worse glycemic control and associated with a 1.7-2.0 fold higher prevalence of complications in diabetes (7). In a recent epidemiological study of mental disorders in the Chinese population, only 11.6% of patients with MDD actively sought any form of treatment and only 0.8% were considered to have received adequate treatment (8). There are few studies on psychiatric help-seeking in patients with T2DM. In this study, we focused on the help-seeking behaviors of patients with T2DM comorbid with MDD during 1-year follow-up.

2 Methods

2.1 Study design

This study was conducted as part of the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study, a two-year international longitudinal study carried out across 16 countries including Argentina, Bangladesh, Brazil, China, Germany, India, Italy, Kenya, Mexico, Pakistan, Poland, Russia, Serbia, Thailand, Uganda, and Ukraine. A comprehensive protocol outlining the study design and procedure for data collection in the INTERPRET-DD study has been previously published (9). The primary goals of the initial research were to assess the prevalence and incidence (over 12 months) of depressive disorders and emotional distress related to diabetes in adults with T2DM, as well as to investigate how frequently depression is documented/undocumented in individuals with T2DM and examine which care pathways are implemented for depression. Our current study aims to investigate the help-seeking behaviors of patients with comorbid T2DM and MDD during a 1-year follow-up period.

As one of the centers participating in the INTERPRET-DD study, we conducted convenient sampling to recruit participants from July 2014 to March 2015 in the outpatient clinic of the Department of Endocrinology at Peking Union Medical College Hospital, which is a tertiary general hospital located in Beijing, China. Inclusion criteria were: (1) 21-65 years of age, (2) outpatients, (3) diagnosed with T2DM at least 12 months before enrolment. Exclusion criteria were: (1) diagnosed with T2DM less than 12 months before enrolment, (2) unable to complete survey tools due to communication or cognitive difficulties, (3) inpatients, (4) any life-threatening or serious conditions, (5) pregnant women or women who gave birth within the last 6 months.

This study was approved by the Ethics Committee of Peking Union Medical College Hospital. Written informed consent was obtained from each participant.

2.2 Data collection

Measurements of medical and psychological characteristics were performed at enrolment and after one year. Upon enrolment, participants completed a survey on sociodemographic information including age, sex, level of education, occupation, and marital status. The researchers extracted clinical data for each participant from the hospital's electronic database including height, weight, level of HbAlc, course of disease, T2DM complications, family history, and medication plan. Psychological evaluation included self-rating questionnaires and structured clinical diagnostic interviews (see 2.3 Instruments). If a participant was diagnosed with MDD after the diagnostic interview, the researcher would inform the participant and suggest visiting the Department of Psychological Medicine in the hospital. One year after enrolment, participants were contacted and invited to revisit the Department of Endocrinology outpatient clinic and complete the follow-up survey. Patients diagnosed with MDD at baseline were also asked to share information on whether or not they had sought any kind of help with depression in the past year.

2.3 Instruments

2.3.1 The Mini International Neuropsychiatric Interview

A structured diagnostic tool for mental disorders developed by Sheehan and Lecrubier, which has been widely used in a range of different populations (10). In the validation study, MINI had a positive predictive value of 84.3% for MDD in Chinese patients (11). MINI assessments were conducted by two expert psychiatrists, who were blind to the medical and psychological status of the participants.

2.3.2 The Patient Health Questionnaire-9, PHQ-9

A 9-item self-rating screening scale for depressive symptoms. The presence of MDD was defined as PHQ-9 scores >9 in a validation study in Chinese outpatients (12).

2.3.3 The Hamilton Depression Scale 17-item, HAMD-17

A 17-item examiner-rating scale for depressive symptoms. Items are divided into five dimensions: psychomotor retardation, cognitive impairment, anxiety or somatization, sleep symptoms, and weight change. HAMD-17 scores >17 indicate the presence of depressive symptoms (13). Two trained psychiatrists performed HAMD-17 for all participants.

2.3.4 Problem Areas in Diabetes Scale, PAID

A 20-item self-rating scale compiled by Polonsky et al. in 1995, PAID involves questions about stress experienced by patients with diabetes. The Chinese version has four factors, emotional, therapeutic, dietary, and social support. A total score of >40 indicates disease stress with diabetes (14).

2.4 Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 21.0.0.0. (IBM Corp., Armonk, NY, USA). Quantitative variables are described as mean ± standard deviation or median (interquartile range) based on the normality of the variable. Categorical variables were described as frequencies (percentages). Student t-test and χ^2 test were used to compare continuous and categorical variables between groups. The Mann-Whitney test was used to compare non-normalized variables between groups. A value of $p < 0.05$ was considered statistically significant.

3 Results

A total of 203 patients with T2DM were included at baseline (Table 1). The average age of the patients was 53.5 ± 9.8 years, with 95 (46.8%) female patients. The median disease course of T2DM was 8 (4, 14) years, and the average HbA1c was 7.47 ± 1.90%. Complications were prevalent, with 44 (21.7%) experiencing cardiac issues, 33 (16.3%) renal complications, 70 (34.5%) ocular complications, and 44 (21.7%) peripheral nerve complications. In terms of patient-reported outcomes, the median PAID scale score was 15 (6, 27) points, compared to a median PHQ-9 score of 4 (2, 8) and a median HAMD-17 score of 5 (2, 11). 26 (12.8%) patients had comorbidity of MDD.

At 1-year follow-up, a total of 114 patients (56.2%) completed the study, with an average age of 54.2 years. Of these patients, 60 (52.6%) were female, and the majority (96.5%) were married. 26 (22.8%) of them were comorbid with MDD. Nine patients were newly diagnosed with MDD. Six patients reported clinical remission from a major depressive episode during the follow-up period, thus not meeting the criteria of MDD at follow-up. The 1-year incidence rate of MDD in this study was 13.2% (15/114).

3.1 Follow-up comparisons

Patients who completed the follow-up had a lower baseline PHQ-9 score (test statistic -2.068, p=0.039), HAMD-17 score (test statistic -2.285, p=0.022), and PAID score (test statistic -2.047, p=0.041) than those who did not complete the follow-up. There

TABLE 1 Comparisons of clinical characteristics of participants at baseline and follow-up.

At baseline	Participants who completed follow-up (n=114)	Participants who did not complete follow-up (n=89)	p	At follow-up	Participants with comorbid MDD and T2DM (n=17)	Participants without comorbid MDD and T2DM (n=97)	p
HbA1c(%)	7.4 ± 1.8	7.6 ± 2.0	>0.05	HbA1c(%)	7.3 ± 1.6	7.2 ± 1.2	>0.05
BMI (kg/m^2)	25.6 ± 3.6	25.9 ± 3.6	>0.05	BMI (kg/m^2)	25.6 ± 3.1	25.8 ± 3.6	>0.05
Hyperlipidemia	83(72.8)	69(77.5)	>0.05	Hyperlipidemia	11(64.7)	91(93.8)	<0.001
PHQ-9	3(1,8)	5(3,9)	0.039	PHQ-9	17(9,21)	3(1,5)	<0.001
HAMD-17	4(1,11)	7(3,12)	0.022	HAMD-17	23(19,29)	7(3,15)	<0.001
PAID	12(5,22)	19(7,31)	0.041	PAID	20(11,48)	7(2,15)	0.006
MDD	17(14.9%)	9(10.1%)	>0.05				

MDD, Major depressive disorder; T2DM, Type 2 diabetes mellitus; PHQ-9, The Patient Health Questionnaire-9; HAMD-17, The Hamilton Depression Scale 17-item; PAID, Problem Areas in Diabetes Scale. Quantitative variables are described as mean ± standard deviation or median (interquartile range).

were no significant differences in age, sex, marital status, occupation, level of education, body mass index, disease course, HbA1c, complications, and prevalence of MDD between the two groups.

Of the 26 patients diagnosed with MDD at baseline, 17 (65.4%) completed follow-up at 1 year. Differences between patients with or without comorbid MDD in HbA1c, complications, clinic visits, and frequency of hospitalization were not statistically significant. Patients with comorbid MDD at baseline had a higher PHQ-9 score (test statistic 4.164, $p<0.001$), PAID score (test statistic 2.728, $p=0.006$), and HAMD-17 score (test statistic 3.997, $p<0.001$) at follow-up than those without comorbidity.

3.2 Psychiatric help-seeking of patients with T2DM comorbid MDD

There were no significant differences in sociodemographic characteristics, scores of depressive symptoms, and scores of diabetes distress between patients who sought psychiatric help and patients who did not. The level of HbA1c at follow-up was higher in patients who sought help than in those who did not (8.1 ± 1.8% *vs.* 7.0 ± 0.7%), although the difference was not statistically significant.

Of the 17 patients with MDD at baseline who completed follow-up, five engaged in active self-help and did not meet the diagnosis of MDD at 1 year thus considered to be in remission of depression. Five patients visited psychiatric clinics after baseline assessment. However, they did not achieve remission at follow-up. Seven patients had never sought help for depression and gave different reasons (Table 2). Three of the nine patients newly diagnosed with MDD at follow-up had acquired psychiatric help from clinics. The other six were unaware of their comorbidities and did not seek help.

4 Discussion

Depressive symptoms and disease distress are common in patients with T2DM (15–17). Previous studies have noted discrepancies between the prevalence of depressive symptoms and the diagnosis of MDD (18). Self-rating depression scores may be influenced by concomitant diabetes-specific distress (4, 18). Our study included both psychiatric diagnoses of MDD and self-rating depression scores, providing concrete information on the prevalence of comorbid MDD and T2DM. Help-seeking behavior reflects one's attitude and awareness of the state of health, which in turn affects the treatment process and outcome of one's disease (19). Therefore, it is necessary to investigate help-seeking behavior in patients with chronic diseases whose management requires continuous effort and good coherence. Few studies have specifically focused on those with T2DM and MDD comorbidity (16, 20). In our study, we also included the mental health help-seeking characteristics of patients with T2DM, hoping to provide more information on this topic.

It is noteworthy that the prevalence of MDD in participants with T2DM in our study at baseline (12.8%) and follow-up (22.8%) were both higher than the 12-month prevalence of MDD (3.9%) in the general Chinese population (8). Results from the INTERPRET-DD study in 12 countries (China not included) suggested that the incidence rate of MDD in T2DM was 7.4%, including both baseline and follow-up data of 1616 patients, the highest found in Ukraine (35.4%), Pakistan (10.8%), and India (9.5%) (4). In a multi-center cross-sectional study of 2538 Chinese outpatients of T2DM, 6.1% had depression, which was defined as a PHQ-9 score > 9 (7). The high prevalence of MDD in our study may stem from a relatively small sample, loss of follow-up in some patients, and differences in hospital settings.

Similar to most diseases, etiology of T2DM or MDD is complex, not simply "There's something wrong with my body/mind," but

TABLE 2 Help-seeking of 26 patients with comorbid T2DM and MDD.

Participants who sought help (13)	Time of diagnosis	Description of help	Participants who did not seek help (13)	Time of diagnosis	Reasons for not having sought psychiatric help
2 (in remission)	Baseline	Changes in attitudes and coping strategies towards T2DM	2	Baseline	Prefer self-help
1 (in remission)	Baseline	Actively manage T2DM symptoms	2	Baseline	Do not acknowledge diagnosis of MDD
1 (in remission)	Baseline	Actively improve marital relationships	1	Baseline	Medical insurance does not cover mental health
1 (in remission)	Baseline	Antidepressants (self-prescribed)	1	Baseline	Difficult to get appointments
5	Baseline	Psychiatric clinic (antidepressants and/or psychotherapy)	1	Baseline	Unwilling to go to a psychiatric clinic
3	Follow-up	Psychiatric clinic (antidepressants and/or psychotherapy)	6	Follow-up	Not aware of MDD diagnosis

T2DM, Type 2 Diabetes Mellitus; MDD, Major Depressive Disorder.

often involves multiple bio-psychosocial factors. The same is true of why patients do not seek help, not simply "I don't want to go." Only 19.2% of patients with comorbid MDD in our study accepted referral to a psychiatric clinic where they received treatment for depression. With the exception of patients who were not aware of their mental status being considered depressive and therefore did not visit psychiatric clinics, the rest majority showed reluctance to see a psychiatrist. Help-seeking in patients with MDD may be a good example to explain the bio-psychosocial factors. Biologically, diagnostic criteria for MDD include decreased physical strength and motivation, as well as impaired cognitive function, all of which may act as biological barriers to help-seeking behavior. Psychosocially, attribution, cognition and perception of disease, doctor-patient relationship, and coping strategies all affect one's help-seeking behavior. Patients' attribution and cognition of symptoms or diseases often affect their help-seeking behavior (21, 22). Some of the patients in our study attributed depression either to difficulties in T2DM management, i.e. illness distress, or psychosocial distress such as relationship problems. In the meantime, they also attributed the remission of depression to the elimination of the distress mentioned. Another factor is the stigma associated with the diagnosis of mental disorder, still present in China and many countries (22–25), which may explain to some extent why a patient in this study would rather self-administer antidepressants than obtain adequate intervention from psychiatric clinics. Some patients prefer to describe emotional feelings using terms such as "tension," "stress," instead of medical terms such as "depression" and "anxiety" (26). Others tend to express concerns about physical symptoms rather than emotional symptoms (27). These phenomena may affect the physician's interpretation of the patient's underlying condition. Certain physical symptoms, such as gastrointestinal symptoms, exist in both T2DM and MDD, making differential diagnosis an even more difficult task for physicians. In our study, the researchers directly recommended that participants visit psychiatric clinics upon diagnosis of MDD, which is different from clinical settings, where usually the treating physician would decide whether or not to refer a patient. Doctor-patient rapport plays an important role in patient coherence, and a good doctor-patient relationship usually promotes patient help-seeking behavior (19). It has been reported that in general hospitals in China, the recommended referral rate for patients with depression was only 19.4% (28), while in low- and middle-income countries, about 80-90% of patients with depression have not been diagnosed or treated (29). As shown in our study, if neither physicians nor patients themselves were aware of patients' mental health condition, the idea of referral to the psychiatric department would not spontaneously occur in patients with T2DM. Given the significance of treating comorbid MDD (7), it is important to include routine screening and assessment of psychological and social status in patients with T2DM, as indicated in the American Diabetes Association (ADA) treatment guidelines (2). Coping strategies, or coping resources, refer to efforts to manage the demands created by stressful events, such as chronic disease, in which social support plays an important role (30). A meta-analytic review suggested that as individuals in Asia or with Asian origins may be affected by collectivistic cultural orientation, they tend to deal with difficulties first within a core unit such as family (31), rather than reaching out for other resources. It was also suggested that treatment-seeking was associated with perceived failure of coping strategies (21). Some participants in our study expressed a preference for self-help, which could be interpreted as the need for autonomy and self-esteem. It is also possible that they did not experience depression as a serious condition, as the severity of the illness was found to be a factor affecting help-seeking behavior (17, 19, 22). Sample size limits the interpretation of some results. For example, it is possible that patients with worse glycemic control would be more proactive in seeking medical advice, which includes referral to another department. Although the proactive pursuit of medical and psychiatric support typically indicates good coherence, which tends to facilitate better glycemic management, there is evidence to suggest otherwise, as our study has demonstrated. In our view, patients experiencing poorer glycemic control are likely to suffer a greater degree of physical and psychological distress, leading them to actively seek assistance more urgently.

Despite the limited sample size, our study observed a relatively high drop-out rate. Previous research has examined potential predictors of drop-out for diabetes patients in cohorts. One program for T2DM management in Germany spanning over two years saw only 5.5% of 10,989 participants discontinue their enrollment, attributed to numbers of assessed factors upon program entry (32). Another study found that initial high HbA1c levels were more indicative of eventual drop-out, with a rate of 13.2% among diabetes patients (33). However, our study did not observe significant differences in HbA1c levels between those who completed follow-up and those who dropped out, which suggests glycemic control may not be the primary contributor to drop-out. A fever surveillance cohort study suggests that participants' background characteristics and perceptions can influence drop-out rates (34). Our study's low psychiatric help-seeking rates and observation of lower depressive symptoms in those who dropped out suggest that our limited participant group may have been unwilling to continue with follow-up, regardless of their condition being diabetes or depression.

Our study has several strengths. The first is the use of diagnostic interviews to assess depression, which provides a more accurate prevalence of MDD in this group of patients with T2DM. Secondly, the prospective design of follow-up allows us to learn about patients' help-seeking behaviors during the period between enrolment and follow-up. Third, we provided both qualitative and quantitative data on participants. However, the relatively small sample size, the study design of a single center, and the loss of follow-up of more than 40%, all limit the generalizability of our study.

5 Conclusions

In conclusion, the comorbidity of MDD in patients of T2DM is not uncommon in China, but few seek for psychiatric help. To provide adequate psychiatric intervention for patients with comorbidity, it is important to take a comprehensive multidisciplinary approach to raising awareness of depression among both patients and physicians.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Committee of Peking Union Medical College Hospital. 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

WG: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. YJ: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. XH: Conceptualization, Supervision, Writing – review & editing. WZ: Supervision, Writing – review & editing. JR: Data curation, Writing – review & editing. CL: Supervision, Writing – review & editing. NS: Supervision, Writing – review & editing. JW: Conceptualization, Supervision, 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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Burden of type 1 and type 2 diabetes and high fasting plasma glucose in Europe, 1990-2019: a comprehensive analysis from the global burden of disease study 2019

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Introduction: With population aging rampant globally, Europe faces unique challenges and achievements in chronic disease prevention. Despite this, comprehensive studies examining the diabetes burden remain absent. We investigated the burden of type 1 and type 2 diabetes, alongside high fasting plasma glucose (HFPG), in Europe from 1990-2019, to provide evidence for global diabetes strategies.

Methods: Disease burden estimates due to type 1 and type 2 diabetes and HFPG were extracted from the GBD 2019 across Eastern, Central, and Western Europe. We analyzed trends from 1990 to 2019 by Joinpoint regression, examined correlations between diabetes burden and Socio-demographic indices (SDI), healthcare access quality (HAQ), and prevalence using linear regression models. The Population Attributable Fraction (PAF) was used to described diabetes risks.

Results: In Europe, diabetes accounted for 596 age-standardized disability-adjusted life years (DALYs) per 100,000 people in 2019, lower than globally. The disease burden from type 1 and type 2 diabetes was markedly higher in males and escalated with increasing age. Most DALYs were due to type 2 diabetes, showing regional inconsistency, highest in Central Europe. From 1990-2019, age-standardized DALYs attributable to type 2 diabetes rose faster in Eastern and Central Europe, slower in Western Europe. HFPG led to 2794 crude DALYs per 100,000 people in 2019. Type 1 and type 2 diabetes burdens correlated positively with diabetes prevalence and negatively with SDI and HAQ. High BMI (PAF 60.1%) and dietary risks (PAF 34.6%) were significant risk factors.

Conclusion: Europe's diabetes burden was lower than the global average, but substantial from type 2 diabetes, reflecting regional heterogeneity. Altered DALYs composition suggested increased YLDs. Addressing the heavy burden of high fasting plasma glucose and the increasing burden of both types diabetes necessitate region-specific interventions to reduce type 2 diabetes risk, improve healthcare systems, and offer cost-effective care.

KEYWORDS

Europe burden of disease, type 1 and type2 diabetes, chronic noncommunicable diseases, population attributable fraction, high fasting plasma glucose, risk factors

1 Introduction

Chronic non-communicable diseases (NCDs) were a leading cause of death worldwide. The United Nations (UN) and the World Health Organization (WHO) prioritized the prevention of chronic non-communicable diseases, focusing on five major disease groups: cardiovascular diseases, cancers, chronic obstructive pulmonary diseases, diabetes, and mental health (1). It was estimated that in 2019 there were 463 million people with diabetes globally, with about 15.4% in Europe. The prevalence of diabetes was projected to increase by 50% by 2045 (2). From 1990 to 2019, the burden of diabetes had continually risen, imposing substantial healthcare and economic burdens globally (3). Type 2 diabetes patients represented the majority of people with diabetes, while type 1 diabetes accounted for only 5-10%. Both types of diabetes presented varying degrees of disease burden. Moreover, high fasting plasma glucose (HFPG), one of the diagnostic criteria for diabetes, impacts the disease burden of other diseases, particularly chronic non-communicable diseases (4).

Due to early industrialization and urbanization, most regions and countries in Europe were economically advanced. However, significant differences existed between Eastern, Central, and Western Europe in terms of geography, culture, population, and diabetes management strategies (5). Europe entered an aging demographic earlier, bearing a heavier risk of disease burden associated with chronic diseases. Currently, no related studies focus on the disease burden of diabetes in Europe. A comprehensive analysis of the overall disease burden of diabetes in Europe will not only provide a basis for preventing and controlling the disease burden of diabetes in Europe but will also be of significant reference value to areas globally where the disease burden of diabetes is high.

Our study aimed to utilize the Global Burden of Diseases Study 2019 (GBD 2019) data to describe the disease burden of type 1 and type 2 diabetes and high fasting plasma glucose in various regions, timelines, and populations across Europe. Additionally, it sought to explore the associated factors to fill this knowledge gap and provide valuable insights for global diabetes prevention and control.

2 Materials and methods

2.1 Data sources

GBD 2019 systematically assessed the epidemiological characteristics of 369 diseases and injuries, and 87 risk factors in 204 countries and territories from 1990 to 2019 (6, 7). GBD 2019 provided mortality, prevalence, incidence, years of life lost (YLLs), Years lived with disability (YLDs), and disability-adjusted life years (DALYs), segmented by genders, ages, periods, geographies, and causes. This study leveraged data from GBD 2019 to analyze the burden of diabetes in 44 European countries over the same period. All data were extracted from the GBD results tool (https://vizhub.healthdata.org/gbd-results/). Additionally, the Healthcare Access and Quality (HAQ) Index and the Socio-demographic Index (SDI) can be accessed from the GBD 2019 data resource homepage (https://ghdx.healthdata.org/gbd-2019).

2.2 Countries of European regions

GBD 2019 classified Europe into Eastern, Central, and Western Europe. Eastern Europe included Belarus, Estonia, Latvia, Lithuania, Moldova, Russia, and Ukraine. Central Europe included Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Montenegro, North Macedonia, Poland, Romania, Serbia, Slovakia, and Slovenia. Western Europe included Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Spain, Sweden, Switzerland, and the UK.

2.3 Disease hierarchies and risk factors

We investigated non-communicable diseases at the secondary level and their associated subgroups. In GBD 2019 diseases and injuries were classified into 4 hierarchies. Level 1 included infectious

diseases, maternal diseases, neonatal diseases, nutritional diseases, non-communicable diseases like diabetes, cancer, cardiovascular diseases, neurological disorders, sensory organ diseases; and injuries. Level 2 refined to level 1 into 22 disease groups: Diabetes and Chronic Kidney Disease (CKD), cardiovascular diseases; neoplasms (e.g., colon, liver, breast, ovary, pancreas, lung), sense organ diseases, neurological disorders; and tuberculosis. Level 3 detailed diabetes and CKD categories. Level 4 was subdivided into type 1 diabetes and type 2 diabetes.

We investigated risk factors at the secondary level. In GBD 2019 risk factors were classified into 4 hierarchies Level 1 included environmental/occupational factors, behavioral factors, and metabolic factors. Level 2 comprised 19 risk groups, including air pollution, inappropriate temperature, tobacco usage, dietary factors, physical inactivity, high fasting plasma glucose, and high BMI.

2.4 Data extraction

We extracted estimates of the death rates, DALYs, YLDs, and YLLs associated with diabetes in Eastern, Central, and Western Europe from 1990 to 2019 in GBD 2019. YLL is calculated by multiplying deaths by the remaining life expectancy. YLD derives from multiplying disease prevalence by the respective disability weight, adjusted for complications. DALYs is the sum of YLLs and YLDs. We also extracted the Population Attributable Fractions (PAFs) of type 1 and type 2 diabetes burden due to each of its risk factors. The SDI indicates developmental status, encompassing per capita income, total fertility rate (age <25 years), and average educational attainment (for those age ≥15 years), with values between 0-1 (6). The HAQ index evaluates individual healthcare access and quality per country, based on risk-standardized death rates in conditions that shouldn't lead to death when high-quality healthcare is available. The index ranges from 0-100, and higher scores indicate better healthcare accessibility and quality (8).

2.5 Statistical analysis

Based on the GBD 2019 database, our study utilized descriptive statistical analysis to examine the temporal, spatial, and demographic distribution of diabetes disease burden in Europe from 1990 to 2019. The Joinpoint regression model was utilized to analyze the trends in age-standardized death rates and age-standardized DALYs globally, across Europe, and specifically within Eastern, Central, and Western Europe, over the span of 1990-2019. We employed a linear regression model to assess the impact of SDI, HAQ, and diabetes prevalence on the diabetes burden. A two-sided P-value less than 0.05 was considered statistically significant. Given that the age-standardized DALYs of 44 European countries did not meet the criteria for normal distribution, they were log-transformed to fit a normal distribution. Hence, linear regression analysis was performed with SDI, HAQ, diabetes prevalence, and the logarithm (Lg) of DALYs, yielding the regression coefficient. The research was accomplished by SPSS (version 24.0), Joinpoint (version 5.0.2) and R (version 4.2.1).

3 Results

3.1 Burden of type 1 and type 2 diabetes

In 2019, both types of diabetes caused 995 (95% UI 780-1240) crude DALYs per 100,000 people across Europe, with type 2 diabetes accounting for 93.2%. The burden of both types of diabetes was notably higher in males than females in Europe, and it escalated with age increment. The age-standardized mortality rate and DALYs rate for type 1 diabetes in Europe in 2019 were 0.6 per 100,000 people and 53.8 per 100,000 people respectively, decreasing by 40.1% (AAPC -1.74) and 2.4% compared to 1990. From 1990 to 2019, the global age-standardized death rate for type 2 diabetes increased by 10.8% (AAPC 0.36), whereas it decreased by 18.8% (AAPC -0.72) in Europe. However, during the same period, the age-standardized DALYs rate in Europe increased by 18.2% (AAPC 0.58), which was consistent with the global trend.

From 1990 to 2019, compared to Western Europe (12.2%, AAPC 0.94), the age-standardized DALYs of diabetes grew more rapidly in Eastern Europe (29.6%, AAPC 0.63) and Central Europe (21.2%, AAPC 0.37). During this period, the age-standardized mortality rate of type 1 diabetes in Eastern Europe demonstrated an oscillatory trend, reaching its apex in 1994, which signified a notable inflection point of change, followed by a trend towards reduction. Concurrently, Central Europe reported a decline of 42.2% (AAPC -1.89) in age-standardized death rate for type 1 diabetes, with a more precipitous decrease noted from 1990 to 2014. On the contrary, in Eastern Europe, age-standardized mortality rates of Type 2 diabetes presented an undulating increase, amplifying by 48.3% (AAPC 0.46). Particular periods such as 1990-1994 and 2010-2016 witnessed significant rises with APCs at 6.11 and 9.69 respectively, while a pronounced upward trajectory was observed in Central Europe between 2001 and 2007 (APC 1.76). From 1990 to 2019, Western Europe recorded substantial reductions in age-standardized mortality rates for both type 1 and type 2 diabetes, showing decreases of 50.1% (AAPC -2.39) and 34.6% (AAPC -1.49) respectively, with a rapid decline from 1990 to 2014 followed by a gradual state of increment. As of 2019, Central Europe topped European ranks for age-standardized DALYs rates for both type 1 and type 2 diabetes, standing at 54.4 per 100,000 and 730.2 per 100,000 respectively. The countries in Central Europe with the heaviest burden of type 1 diabetes were Bulgaria and Montenegro, while Bosnia and Herzegovina and North Macedonia, also in Central Europe, bore the greatest burden of type 2 diabetes. However, compared to the 1990 levels, Central Europe saw a reduction of 18.8% (AAPC -0.72) in age-standardized DALYs rates for type 1 Diabetes, highlighted by a swift decline during 1997-2000 (APC -2.77) (Tables 1, 2; Table S2; Figures S2-5, Figure 1).

In 1990, YLLs and YLDs were nearly equally represented in Europe's diabetes burden. However, by 2019, this burden shifted towards YLDs as Central and Western Europe regions reported an increased YLD proportion in DALYs over the period 1990-2019, while the YLLs fraction decreased. Eastern, Central, and Western Europe all registered YLDs ratios above 50%, peaking at 58.8% in Western Europe. For type 1 diabetes in 1990, the European YLLs rate exceeded the YLDs rate, which was contrastingly lower for type 2 diabetes. In 2019, the YLLs proportion in type 1 diabetes receded

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TABLE 1 Age-standardized rates of deaths and DALYs due to type 1 and type 2 diabetes in Europe in 1990 and 2019, and percentage changes from 1990 to 2019.

	Age-standardized death rate per 100000			Age-standardized DALYs rate per 100000		
	1990	2019	Percentage change 1990-2019	1990	2019	Percentage change 1990-2019
T1DM						
Global	1.2 (1.0,1.4)	1.0 (0.9,1.2)	-20.4% (-31.4,-2.7)	62.3 (51.3,71.7)	57.4 (49.1,67.2)	-7.8% (-18.5,5.5)
Europe	1.0 (0.8,1.1)	0.6 (0.5,0.7)	-40.1% (-47.1,-27.2)	55.1 (46.8,64.6)	53.8 (41.8,69.4)	-2.4% (-14.8,10.2)
Eastern Europe	0.7 (0.6,0.9)	0.6 (0.5,0.9)	-16.0% (-28.6,7.0)	49.1 (42.1,57.8)	52.3 (42.2,64.8)	6.6% (-3.5,17.0)
Central Europe	1.6 (1,3,1.9)	0.9 (0.8,1.2)	-42.2% (-52.0,-28.9)	66.9 (76.2,58.0)	54.4 (44.3,67.3)	-18.8% (-30.0,-6.9)
Western Europe	0.8 (0.6,0.9)	0.4 (0.3,0.5)	-50.1% (-55.3,-37.4)	48.0 (58.6,39.1)	52.5 (38.1,71.5)	9.3% (-6.3,26.0)
T2DM						
Global	16.7 (15.7,17.5)	18.5 (17.2,19.7)	10.8% (4.4,17.4)	628.3 (537.2,730.9)	801.5 (670.6,954.4)	27.6% (22.0,33.0)
Europe	11.8 (11.0,12.2)	9.6 (8.7,10.2)	-18.8% (-22.7,-14.4)	459.2 (380.3,551.2)	542.6 (419.1,680.7)	18.2% (9.7,24.8)
Eastern Europe	4.1 (3.9,4.3)	6.1 (5.4,6.8)	48.3% (32.3,65.5)	281.5 (221.9,347.8)	376.0 (295.1,468.2)	33.6% (28.1,39.2)
Central Europe	11.7 (11.2,12.2)	11.9 (10.4,13.6)	1.7% (-10.7,14.7)	580.4 (470.4,703.7)	730.2 (559.0,923.1)	25.8% (17.0,32.8)
Western Europe	13.1 (12.1,13.6)	8.5 (7.6,9.1)	-34.6% (-37.8,-32.0)	458.4 (381.2,551.6)	515.8 (389.5,663.9)	12.5% (1.8,21.3)

below the YLDs proportion. Furthermore,Eastern, Central and Western Europe saw an approximate 50% distribution between YLLs and YLDs (Figure 2).

3.2 Burden of high fasting plasma glucose

In 2019, HFPG resulted in 2864 crude DALYs per 100,000 people in Europe, with 35.6% of this burden originating from type 1 and type 2 diabetes. As outlined in the GBD 2019, the significant impact of HFPG predominantly manifested in non-communicable chronic diseases, such as cardiovascular diseases, chronic kidney disease, neoplasms, neurological disorders, tuberculosis, and other sensory disorders. Significantly, cardiovascular diseases attributable to HFPG constituted a remarkable 50.3% of the overall burden in Europe. Amongst all regions, Central Europe bore the maximum burden of HFPG, while considerable regional variations were observed in the cardiovascular disease burden attributable to HFPG, with Eastern and Central Europe notably surpassing Western Europe.

TABLE 2 The annual average percent change of age-standardized rates of deaths and DALYs due to type 1 and type 2 diabetes in Europe from 1990 to 2019.

	Age-standardized death rate			Age-standardized DALYs rate		
	AAPC (95%CI)	T value	P value	AAPC (95%CI)	T value	P value
T1DM						
Global	-0.76 (-0.83, -0.7)	-22.069	<0.001	-0.27 (-0.33, -0.22)	-9.571	<0.001
Europe	-1.74 (-1.92, -1.56)	-18.754	<0.001	-0.07 (-0.27, 0.14)	-0.635	0.525
Eastern Europe	-0.4 (-1.53, 0.74)	-0.693	0.488	0.29 (-0.2, 0.79)	1.163	0.244
Central Europe	-1.89 (-2.07, -1.7)	-19.864	<0.001	-0.72 (-0.84, -0.6)	-11.696	<0.001
Western Europe	-2.39 (-2.6, -2.18)	-22.036	<0.001	0.3 (0.19, 0.4)	5.605	<0.001
T2DM						
Global	0.36 (0.32, 0.41)	16.033	<0.001	0.82 (0.73, 0.9)	19.63	<0.001
Europe	-0.72 (-0.91, -0.53)	-7.408	<0.001	0.58 (0.45, 0.7)	9.21	<0.001
Eastern Europe	1.46 (0.68, 2.25)	3.683	<0.001	1.04 (0.82, 1.26)	9.477	<0.001
Central Europe	0.07 (-0.08, 0.22)	0.869	0.385	0.77 (0.67, 0.86)	15.908	<0.001
Western Europe	-1.49 (-1.58, -1.41)	-33.79	<0.001	0.39 (0.3, 0.48)	8.675	<0.001

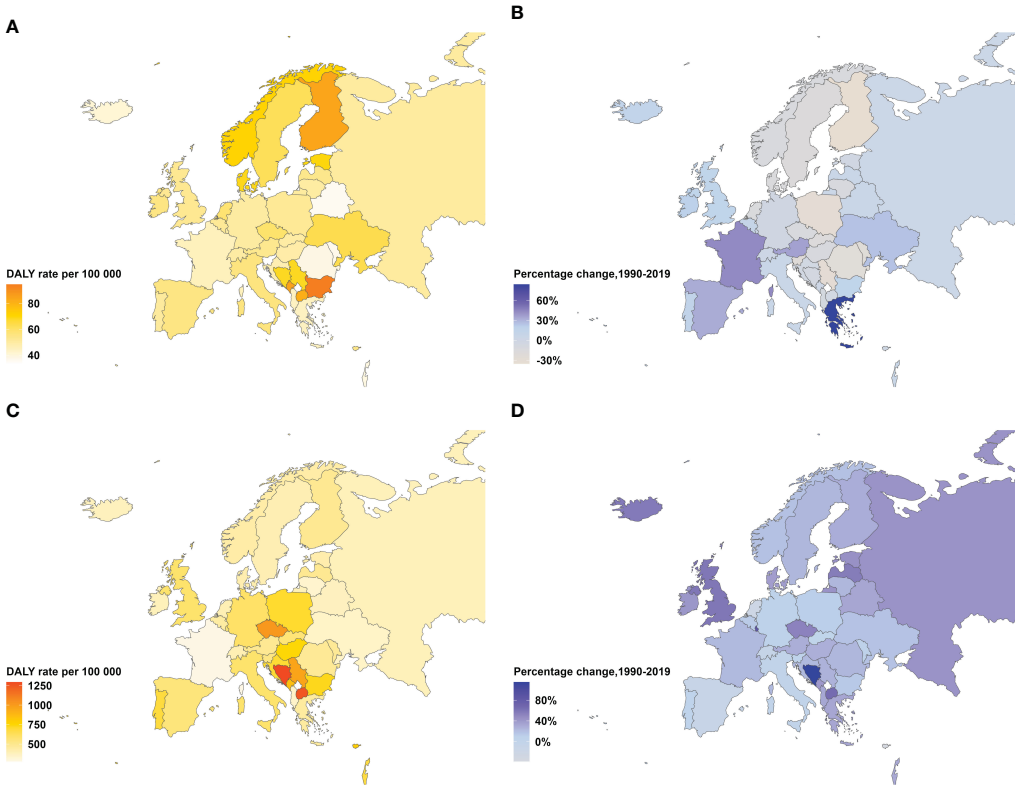

FIGURE 1
Age-standardized DALYs rate in 2019 and percentage change in DALYs rate from 1990–2019 for type 1 and type 2 diabetes, both sexes. **(A)** Age-standardized type 2 diabetes DALYs rate per 100,000 people in 2019. **(B)** Percentage change in age-standardized type 2 diabetes DALYs rate, 1990–2019. **(C)** Age-standardized type 1 diabetes DALYs rate per 100,000 adults aged 20 years or older in 2019. **(D)** Percentage change in age-standardized type 1 diabetes DALYs rate, 1990–2019. DALYs=disability-adjusted life-years.

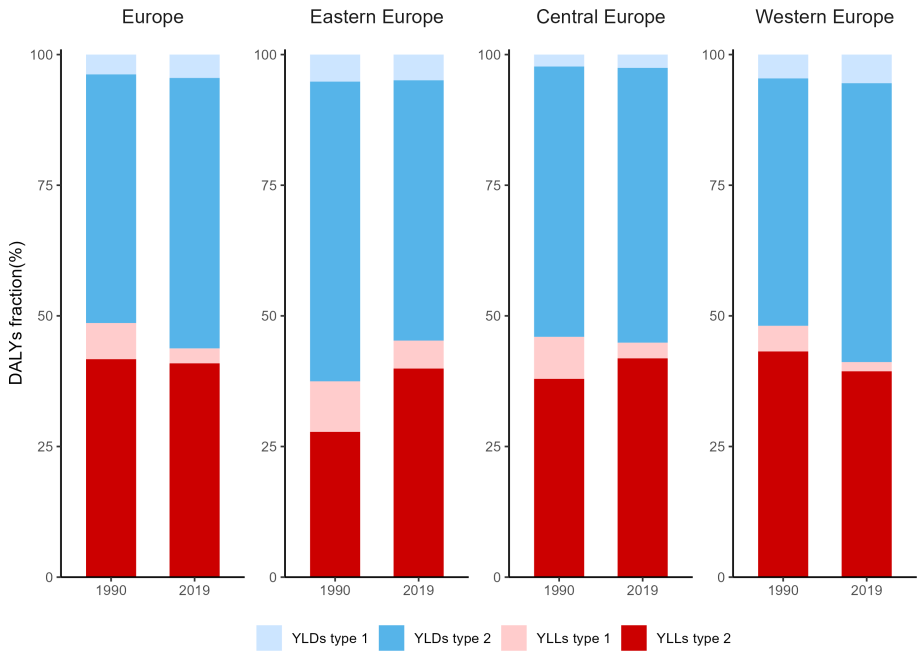

FIGURE 2
Fractions of YLLs and YLDs for type 1 and type 2 diabetes in 1990 and 2019. YLLs, Years of life lost; YLDs, years lived with disability.

Specifically, Central Europe and Eastern Europe attributed 53.3% and an alarming 70.2% of their cardiovascular disease burden to HFPG, respectively (Table S4; Figure 3).

3.3 Determinants: SDI, HAQ, and diabetes prevalence

Linear regression analysis revealed that the logarithm of age-standardized DALYss (Lg DALYss) was associated with SDI and diabetes prevalence. There was a negative correlation between SDI and Lg DALYs (R2 = 0.096, P=0.037). Higher SDI values indicated lower diabetes burdens, as evidenced in Western Europe countries with high SDI and relatively low diabetes burden. There's no significant correlation between HAQ and Lg DALYs (R2 = 0.006, P=0.611). However, after excluding data from Eastern Europe countries that deviated from the regression line, a negative correlation between the HAQ index and Lg DALYs emerged (R2 = 0.310, P<0.001). Diabetes prevalence correlated positively with Lg DALYs (R2 = 0.659, P<0.001). Higher diabetes prevalence leads to greater diabetes disease burdens (Figure 4).

Given the strong positive correlation between European diabetes prevalence and Lg DALYss, we explored the prevalence and incidence of type 1 and type 2 diabetes. In 2019, type 1 diabetes prevalence exceeded the global average, while type 2 diabetes prevalence was below it. Regional differences were observed in the rates of both types. Western Europe showed the highest standardized prevalence for type 1 diabetes and the most significant growth (69.3%). Central Europe exhibited the highest age-standardized prevalence for type 2 diabetes. Increases in prevalence were paralleled with the rise in incidence rates for both Type 1 (69.1%) and Type 2 (47.4%) diabetes (Table S3).

3.4 Risk factors

In 2019, high body mass index (BMI) emerged as the leading risk factor for the burden of type 2 diabetes in Europe. The influence of this factor varied across regions, ranging from 53.3% in Western Europe to 68.2% in Eastern Europe. Dietary risks accounted for 34.6% of DALYs, including excessive consumption of red and processed meats, sugary beverages, insufficient whole grains, fruits, dietary fibers, seeds, and nuts. Tobacco and air pollution emerged as the third and fourth leading contributors, respectively. Across different European regions, the prevalent risk factors, in descending order, were high BMI, diet, tobacco, air pollution, low physical activity, and non-optimal temperatures. Of particular note was the fact that Western Europe had the highest proportion of diabetes burden attributable to dietary factors and physical inactivity, yet the lowest linked to high BMI. In contrast, Eastern Europe recorded the highest percentage of disease burden associated with air pollution (Figure 5).

4 Discussion

From 1990 to 2019, both the age-standardized rates of death and DALYs for type 1 and type 2 diabetes in Europe were below global levels. This was contrary to expectations given the significant aging population in Europe (9), which should theoretically bear a

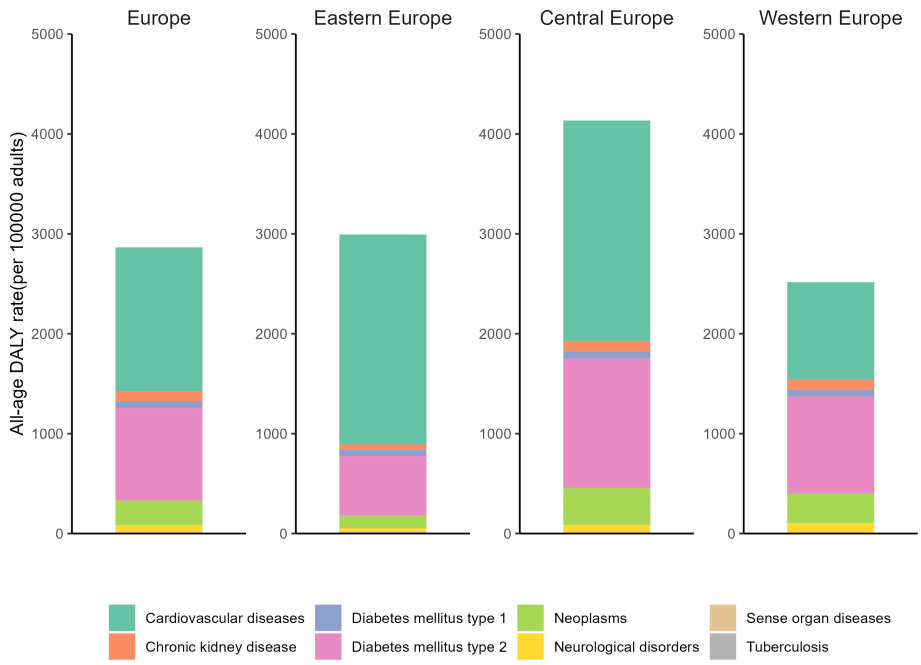

FIGURE 3
All-age DALYs rate due to high fasting plasma glucose in Europe by cause in 2019.

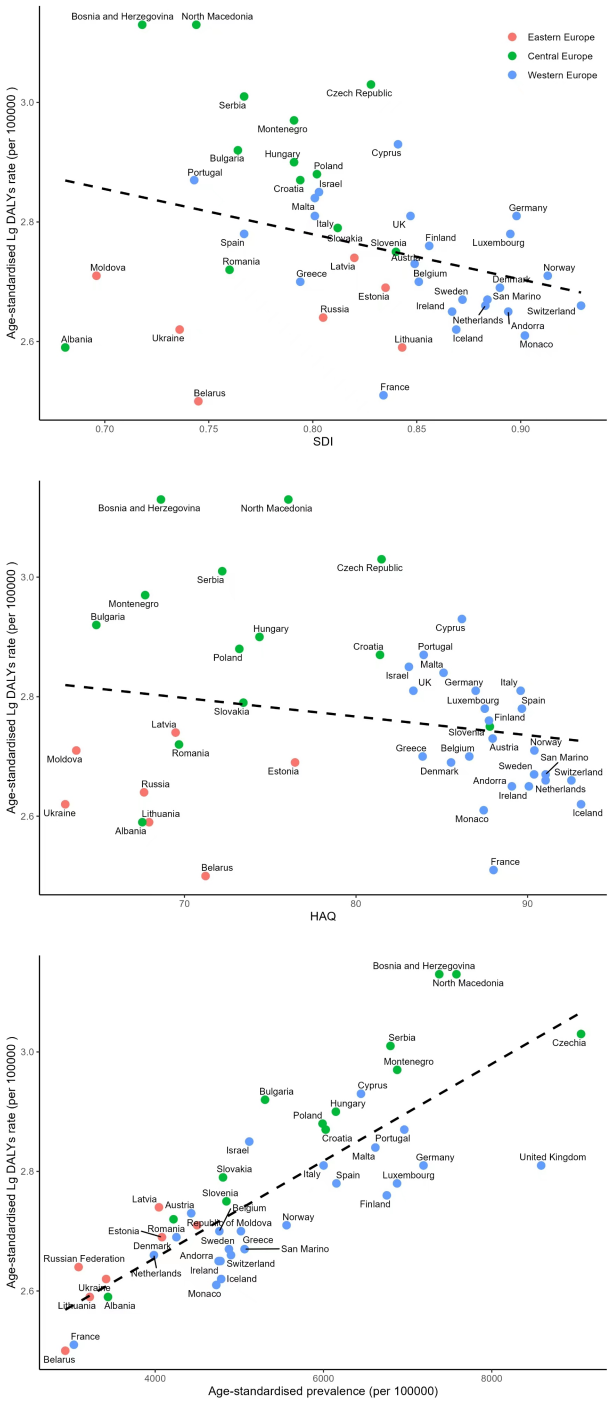

FIGURE 4
Association of the Socio-demographic Index (SDI), the Healthcare Access and Quality Index (HAQ) and prevalence with DALYs due to diabetes.

severe burden of diabetes. This fact indicated that Europe had achieved commendable results in managing diabetes against the backdrop of an aging population, possibly due to economic growth and developments in healthcare. Compared to type 1 diabetes, type 2 diabetes contributed a heavier burden to the total DALYs from diabetes (93.2%). Therefore, future diabetes prevention and control strategies in Europe should still lean towards type 2 diabetes.

The burden of diabetes varied across different regions in Europe. From 1990 to 2019, the age-standardized death rates for type 1 diabetes have significantly decreased in Eastern, Central, and Western Europe. While the exact reasons for this decrease were unclear, insulin supplements (10), genetics (11), and environmental risk factors (12) played crucial roles in enhancing life expectancy. However, age-standardized death rates for type 2 diabetes showed regional variations: they were growing in Eastern and Central Europe while decreasing by 34.6% in Western Europe. The decline in mortality rates from type 1 and type 2 diabetes in Western Europe, along with the prevalence of acute and chronic complications (13, 14), had led to an increase in the proportion of YLDs component within total DALYs, far exceeding the YLLs component. age-standardized DALYs rates for type 1 diabetes increased by 6.6% and 9.3% in Eastern and Western Europe respectively, while decreasing by 18.8% in Central Europe. At the same time, age-standardized DALYs rates for type 2 diabetes continued to grow in all three regions of Europe, albeit at a slower pace in Western Europe.

The study results showed that SDI and HAQ were significant factors affecting the burden of diabetes, and they explained the variations in the distribution and changes in the burden of diabetes across different regions of Europe. Firstly, the 2019 SDI and HAQ data for Eastern, Central, and Western Europe demonstrated that the levels of economic development and healthcare in Eastern and Central Europe lag behind those in Western Europe, resulting in heavier burdens of diabetes. Compared to Western European countries (13), Eastern and Central European countries lacked the corresponding infrastructure and capabilities, suffered from inadequate discretionary health expenditure (15, 16) and public resources (17, 18), hence preventing them from introducing advanced diabetes treatment technologies such as the Hybrid Closed-Loop (HCL) system. A key issue with adopting novel medical technologies was the shortage of funds to purchase new medical equipment. Economic constraints also affected the level of education accessible by physicians and diabetic patients, hindering their understanding and absorption of innovative medical technologies, and impacting the establishment of professional diabetes care in medical institutions. Therefore, the main task to alleviate the growing burden of diabetes, which increased as diabetes prevalence rose, was to tackle public health issues in relatively underdeveloped countries in Eastern and Central Europe. Secondly, looking at the changes in SDI from 1990 to 2019 in Eastern, Central, and Western Europe, Western Europe had entered a plateau phase, while Eastern and Central Europe maintained rapid development. Specifically, Central Europe was progressively bridging the economic disparity with Western Europe, spurred by its accelerated growth. In the foreseeable future, it is likely to emerge as a subsequent parallel to Western Europe. However, to avoid falling into the same predicament of diabetes burden as Western Europe, Central Europe can learn from the situation in Western Europe and adjust their diabetes management strategies as needed.

During the period of 1990 to 2019, the mortality rate trend associated with type 2 diabetes in Europe was in contrast to the global pattern, while the age-standardized Disability Adjusted Life

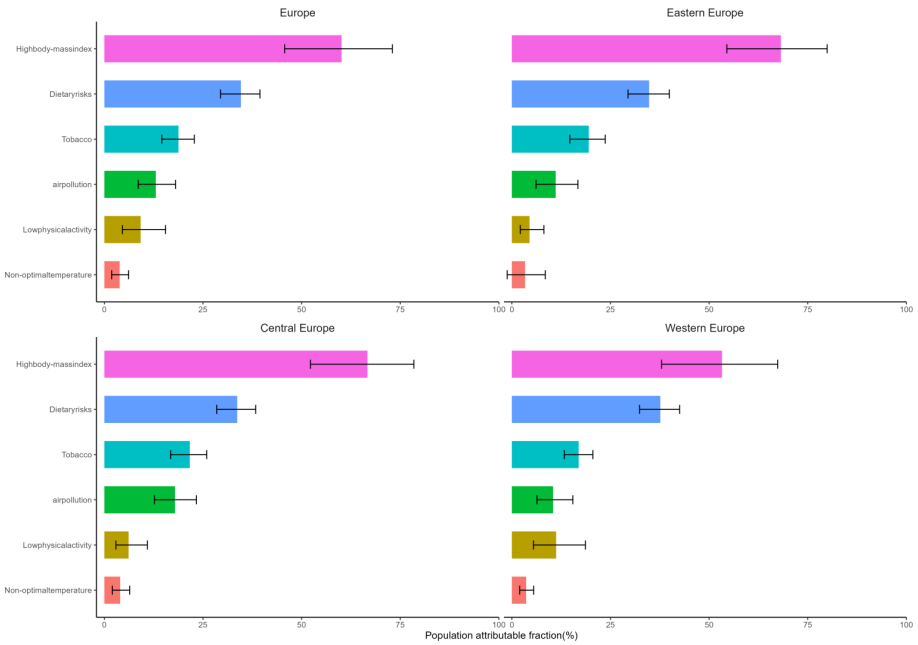

FIGURE 5
Population attributable fraction of crude DALYs due to type 2 diabetes for the main risk factors identified by GBD 2019, by region.

Years (DALYs) continued on an upward trajectory. This signifies that apart from the aging demographic, additional risk components contribute substantially to the burden of type 2 diabetes. Given that type 2 diabetes contributed considerably to the overall burden of diabetic diseases, and the risk factors for type 2 diabetes also served as significant prognostic factors for type 1 diabetes, research had demonstrated the feasibility and effectiveness of prevention and treatment programs for type 2 diabetes (19, 20). Therefore, primary prevention of diabetes is of great importance. The risk factors for type 2 diabetes discussed in our study included high BMI, dietary factors, tobacco use, lack of exercise, and air pollution. High BMI has been proven to be one of the major factors in the development of diabetes (21), serving as an essential indicator for measuring overweight and obesity. In recent decades, almost all European countries have seen an increase in overweight/obesity rates (22). If no intervention measures were taken, it is expected to escalate further (23). Lifestyle improvements could help prevent high-risk individuals (24). Existing research evidence suggested that a healthy lifestyle was the best measure for preventing and managing diabetes (25). Consequently, implementing health education targeting individuals with diabetes could serve as a crucial strategy for diabetes management and prevention, fostering a shift in health perception leading to self-initiated healthy activities. We should adhere to healthy eating habits, mirroring models like the Mediterranean diet and Nordic dietary patterns (26), and control our energy intake while focusing on nutritional balance to ensure sufficient nutrient intake. It was important to participate in physical exercise actively and maintain a stable frequency and intensity of workouts, thereby enhancing physical vitality and metabolic capacity. We could maintain a stable and healthy weight through diet and exercise, reducing the likelihood of overweight and obesity.

In recent years, numerous studies had demonstrated that air pollution could lead to insulin resistance (5), while particulate matter and persistent organic pollutants could increase the risk of diabetes (27, 28) and obesity (29). As such, air pollution has emerged as one of the risk factors for diabetes. Therefore, it is necessary to restrict the emission of polluting gases through more stringent legislation, strictly enforce air pollutant emission standards, intensify penalties, and improve related environmental engineering projects to mitigate the harm of air pollution to human health. Additionally, efforts to promote smoking cessation through education should be increased, along with further refinement of laws and regulations related to smoking bans in public places.

HFPG was considered the primary risk factor for CNDs. It could exert influences not only on diabetes as well other various diseases, acting as a pivotal risk factor contributing to the increased global and regional disease burden (30). Compared to the burden of diabetes alone, the overall burden of HFPG was heavier, effectively doubling in magnitude. As indicated by data from Europe, diabetes and cardiovascular diseases were the primary causes of health loss in the region. A cohort study based on biobank data testified that prediabetes and type 2 diabetes were linked with cardiovascular diseases, chronic kidney disease, and heart failure (31). Furthermore, high glycemia-induced oxidative stress may cause cardiovascular damage, establishing a relationship between hyperglycemia and an increased risk of cardiovascular diseases (32). Additionally, there existed an inextricable link between cardiovascular diseases (CVDs) and diabetes; CVDs were the leading cause of morbidity and mortality in patients with both type 1 and type 2 diabetes (33, 34). The onset of cardiovascular disease as a complication of diabetes resulted in a doubled mortality rate and reduced life expectancy by at least 12 years (35).

Consequently, in order to alleviate the disease burden in the European region, emphasis must be put on managing these two conditions. Furthermore, given that HFPG was a risk factor for numerous diseases, efforts should be made to mitigate this risk, while also considering the impact of low FPG values.

To sum up, there existed substantial heterogeneity in the burden of diabetes across Europe: 1) Variation in diabetes type. Type 2 diabetes continued to constitute the crux of future prevention and control strategies in Europe; 2) Geographical discrepancies. Central Europe stood at the forefront of diabetes burden within Europe; 3) Differentials in the composition of diabetes burden. Owing to the falling mortality rate from diabetes and the high prevalence of acute and chronic complications, YLDs accounted for a significant share of the diabetes burden in Western Europe. Despite Europe's onset of ageing dating back to the 19th century, its age-standardized death rate from diabetes and DALYs remained below global averages. Although the rise in diabetes burden has markedly decelerated in Western Europe - the most economically advanced region of Europe, the proportion of YLDs was escalating swiftly. This serves as both a caution and model for other rapidly developing European regions and countries worldwide that are witnessing an ageing demographic. To counteract the burden of diabetes and HFPG levels, it is imperative to initiate primary healthcare interventions targeting the diabetic population with the aim of mitigating diabetes risk, whilst simultaneously ensuring efficient management of diabetes-associated complications, notably cardiovascular diseases.

Our study has its limitations, some of which are inherent to the GBD study (6). Firstly, certain European countries lack accurate, high-quality data; therefore, it becomes necessary to rely on data from other countries that have been adjusted for covariates. However, this inevitably introduces bias into the obtained results, a situation frequently observed during the evaluation process for type 1 diabetes and non-fatal burden. Secondly, Within the context of the GBD, we lean towards using ample data sources and embracing the effects brought by adjustments, rather than exclusively relying on limited high-quality data sources. Although utilizing other case definitions for diabetes as adjustment strategies can garner more data sources for analysis, it also signifies introducing measurement bias. Finally, there are seven countries in Eastern Europe, a small number, of which resulted in no correlation between the diabetes disease burden in Europe and the Healthcare Access and Quality (HAQ) Index. However, when data from Eastern Europe was excluded and linear regression analysis was applied solely to Central and Western European countries, a strong correlation existed between the HAQ Index and diabetes burden. The HAQ Index, within the GBD, served as a covariate for estimating the fatal and non-fatal burden of diabetes in countries with sparse data, hence the association between the index and the diabetes burden may be overstated.

Data availability statement

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

Author contributions

DL: Writing – original draft, Writing – review & editing. XC: Writing – original draft. Writing – review & editing. QG: Writing – review & editing. YO: Writing – review & editing. XZ: Writing – review & editing. XL: 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.2023.1307432/full#supplementary-material

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Association between illness perception and medication adherence in patients with diabetes mellitus in North Shoa, Zone: cross-sectional study

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Background: Although the impact of illness perception on medication adherence is well-established, its specific influence on medication adherence in Ethiopia remains unclear. Consequently, the objective of this study was to examine the association between illness perception and medication adherence among patients with diabetes mellitus in the North Shoa Zone.

Methods: An institution-based cross-sectional study was conducted from 24 May to 25 June 2022 in the North Shoa zone. The study included a random sample of 552 individuals with diabetes from four public hospitals. Data was collected and entered into Epi Data V.3.1, and analysis was performed using SPSS version 22. Descriptive statistics were used to summarize continuous variables as means with standard deviations, while categorical variables were presented as percentages. The study variables were analyzed using binary logistic regression models to assess the associations between illness perception and medication adherence. In the bivariable analysis, variables with p-values less than 0.20 were entered into a multivariable logistic regression model. Associations with a p-value $\leq$0.05 and an odds ratio with a 95% confidence interval were considered statistically significant.

Results: The study results revealed that medication adherence was 64.4% (95% CI: 60.1, 67.9), while illness perception was 54.7% (95% CI, 41.2, 49.4). There was a significant and strong association between illness perception and medication adherence ($p < 0.0001$). In the adjusted model, the illness perception components of consequence showed a significant association with medication adherence (AOR = 3.10, 95% CI: 2.11, 4.55). Similarly, personal control (AOR = 1.77, 95% CI: 1.20, 2.61) and emotional representation of diabetes (AOR = 2.26, 95% CI: 1.54, 3.32) were also significantly associated with medication adherence in patients with diabetes.

Conclusion: The findings of this study indicate a positive association between higher illness perception and increased medication adherence and practice. Therefore, when engaging in discussions about diabetic self-management, diabetes educators should employ psychoeducational approaches that take into account the illness perceptions of patients.

KEYWORDS

medication adherence, illness perception, patient with diabetes, perception towards medication, North Shoa Zone

Background

Diabetes is a significant global health issue, with a considerable impact on the adult population. In 2021, it was estimated that approximately 537 million adults worldwide were affected by diabetes. Projections indicate a steady rise, with an expected increase to 643 million by 2030 and 783 million by 2045. The prevalence of diabetes in Africa is also a concern, with an estimated 24 million adults affected in 2021. Alarmingly, this number is projected to rise to 55 million by 2045, highlighting the urgent need for effective prevention and management strategies in the region (1). Diabetes is increasingly becoming a significant public health challenge in Ethiopia, with a national prevalence rate of 2.8% in 2022 (2) and gradually increasing from 1% in 2000 (3) to 3.3% in 2020, according to the Report of the International Diabetes Federation (1).

The long-term social, health, and economic impacts of diabetes on individuals and countries are substantial. Consequently, treatment adherence serves as a crucial indicator of healthcare quality in the effective management of diabetes (4). Adherence to treatment refers to the voluntary cooperation of patients in following the prescribed dosage, timing, and frequency of medication as directed by healthcare professionals (5, 6).

Medication adherence plays an important role in glycemic control and prevention of complications (7) and the effectiveness of treatment also depends on adherence to recommended medication (8). Low adherence to medications in people with diabetes is significantly associated with poor glycemic control (9). Although a wide range of antidiabetic drugs is available, many patients with diabetes still fail to control blood glucose levels associated with diabetes (10). Patients' adherence to prescribed medications is influenced by personal beliefs about chronic diseases (11). Adherence to antidiabetic medications improves with better illness perception (12). Illness perception (IP) is characterized as the patient's implicit and common sense beliefs regarding their illness (10).

Illness perception plays a key role in the study of patients' perceptions of their illness and significantly impacts medication adherence (13). Individuals with diabetes are more motivated to adhere to their treatment regimen when they hold the belief that their medications are effective and that their disease is well-managed (14, 15). IP plays an important role in managing adherence and is related to adherence in diabetes (16). Research findings indicate that having knowledge about one's illness positively influences self-care behaviors, which in turn help individuals with diabetes to mitigate the consequences of the disease (14).

Hence, it is crucial to manage illness perception among individuals with diabetes as it has the potential to enhance treatment adherence. Research evidence strongly indicates a significant relationship between illness perception and treatment adherence in diabetes, resulting in improved management and control of the disease (13, 17). Patient perception is a psychological factor in diabetes that directly or indirectly influences treatment adherence, emphasizing the need for additional research to investigate the role of psychological factors in diabetes management (18). Patient perception, as a psychological aspect, should be integrated into diabetes care and effectively communicated across all levels of the healthcare system.

To the best of our knowledge, there are no studies that have investigated the relationship between illness perception and treatment adherence in Ethiopia. The hypothesis put forth is that a positive recognition of diabetes as an illness may have a favorable influence on medication adherence. Therefore, the objective of this study was to examine the association between disease perception and treatment adherence in the Northern Shoa.

Methods

Study design and setting

The facility-based cross-sectional study design was performed at public hospitals in the North Shoa Zone from 24 May to 25 June 2022. North Shoa is one of the thirteenth zones of the Amhara region located in northern Ethiopia. There are 24 districts, 3 municipalities, and 13 hospitals. All public hospitals have diabetes care and follow-up services.

Subjects and sample selection

The sample size was determined using the formula for the proportion of the single population considering the proportion of medication adherence of 68% in Ethiopia (19) with a precision level of 5 and 15% for non-response and a design effect of 1.5, resulting in 552 subjects. Diabetic subjects aged ≥18 years who had been followed for more than three months were included in the study. The mean of Fasting Blood Sugar (FBS) measurements in three consecutive months was used for FBS analysis. Patients who were medically judged unable to participate in the study (e.g., acute illness, mental illness, and dementia) and patients with severe visual impairment were excluded from the study. Study participants were recruited from four hospitals, selected according to a proportional allocation among hospitals. Study participants were selected using a systematic randomization procedure. Because each patient had at least one appointment within one month, we waited up to one month for a selected study participant.

Abbreviations: CI, confidence interval; DM, diabetes mellitus; IP, Illness perception; IPQ-R, modified illness perception questionnaire; SD, standard divisions.

Data measurement and tool

Medication adherence was evaluated through a set of four questions, including: Have you ever forgotten to take a prescribed medication? Do you sometimes discontinue taking your medication? Are there instances when you are not diligent about taking your medicine? And if you experience worsening symptoms after taking your medication, do you cease taking it?

The scoring method for this questionnaire focuses solely on item four. A response of "Yes" is assigned a score of 1, while a response of "No" is given a score of 0. The total score is obtained by summing the scores of all items in the questionnaire. The total score ranges from zero to four, where a score above 1 suggests low compliance, while a score of 0 indicates high compliance. The questionnaire underwent face and content validity assessment by experts, and its reliability was measured using the Cronbach's alpha method, resulting in values ranging from 0.75 to 0.81.

The evaluation of individuals' perception of their illness utilized the modified Illness Perception Questionnaire (IPQ-R). This questionnaire consists of seven subscales and a 38-item version (20). The instrument employed in this study consists of 38 items that assess seven domains of illness perception (20, 21). Each domain of illness perception was treated as an independent variable and examined to assess its influence on medication adherence. Participants providing their perception of illness using a 5-point Likert scale for each question within each domain. The responses were summed to calculate an average score for each domain. Furthermore, individual scores were computed for each component, and an overall score was computed to the overall level of illness perception. A higher score indicates stronger feelings associated with each aspect of illness perception (20, 22). The Cronbach's alpha coefficients for the subscales ranged from 0.70 to 0.89.

The data collection process was carried out by four trained data collectors, all of whom held bachelor's degrees. These collectors conducted interviews to gather the required data. Prior to data collection, both the data collectors and their supervisors underwent comprehensive training on the research objectives, questionnaire content, and the importance of maintaining confidentiality and privacy throughout the data collection process. To ensure data quality, all authors and supervisors performed daily checks to verify completeness, accuracy, and consistency of the collected data. The principal investigator closely monitored the data collection activities on a daily basis, ensuring questionnaire completeness and providing further clarification when needed. Detailed review of patients' medical records was conducted, capturing essential information such as fasting blood sugar (FBS) levels, diabetic complications, comorbidities, and the medications being taken.

Data management and analysis

The collected data was entered into Epi Data version 4.6 and then exported to SPSS version 25 for analysis. Descriptive analysis was utilized to present the frequency distribution of each variable in the study. Continuous variables were reported as mean ± standard deviation, while categorical variables were presented as percentages.

To examine the relationship between illness perception and medication adherence, binary logistic regression analysis was conducted. Multicollinearity was assessed using the variance inflation factor, with a threshold value of less than 10 considered acceptable. The goodness of fit of the model was evaluated using the Homer-Lemeshow test.

Variables that demonstrated a *p*-value of less than 0.20 in the bivariate analysis were included in the subsequent model analysis. The significance of the associations was determined using the *p*-value and 95% confidence interval (CI) for the odds ratios (OR).

Results

Socio-demographic and clinical characteristics of respondents

The study included 539 individuals diagnosed with diabetes, resulting in a high response rate of 98%. The gender distribution was nearly equal among the participants. A majority of respondents (52.1%) fell within the age range of 41 to 60 years, and a significant proportion (45.6%) were married. Moreover, a majority of the participants had received formal education.

Among all the study participants, a substantial percentage (80.1%) had fasting blood sugar (FBS) levels that were uncontrolled, surpassing 130 mg/dL. Regarding diabetic complications, 35.8% of the participants had developed chronic complications, with retinopathy (32.8%) being the most prevalent. Additionally, 145 individuals (26.9%) had comorbidities, with hypertension (51.0%) being the most frequently reported comorbidity (Table 1).

Participant's perception of their diabetes illness

In the study, the overall illness perception was found to be 54.7% (95%CI: 41.2–49.4%). The mean score for illness perception was 135.6 ± 8.7 SD. Among the various dimensions of illness perception, illness perception/personal control ability had the highest mean score of 20.5 ± 3.7 SD, followed by emotional illness response with a mean score of 20.8 ± 3.1 SD. On the other hand, illness identity had the lowest mean score of 8.3 ± 2.3 SD.

Table 2 presents the frequency distribution of the reported illness perceptions. The most commonly reported illness perceptions were perception of consequences (59.9%), treatment control (58.1%), and emotional expression (57.9%) (Table 2).

Relationship between illness perception and medication adherence

In the study, the overall adherence to antidiabetic medication was determined to be 64.4%, with a mean of 0.67 ± 1.02 SD. Chi-square test analysis revealed a significant association between illness perception and adherence to antidiabetic medication ($\chi 2 = 4.01$; $p < 0.05$). Several domains of illness perception were found to be significantly associated with medication adherence. These domains included perception of acute/chronic timeline ($p = 0.025$), perception of diabetic consequences ($p < 0.0001$), perception of personal control ($p = 0.001$), and perception of emotional representation ($p < 0.0001$) (Table 3).

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TABLE 1 Socio-demographic and clinical characteristics of respondents in North Shoa, 2022.

Variables	Category (n = 539)	Frequency	Percent (%)
Sex of the respondent	Male	260	48.2
	Female	279	51.8
Age (years) of the respondent	18–40	169	31.4
	41–60	246	45.6
	>60	124	23.0
Marital status of the respondent	Single	134	24.9
	Married	335	62.2
	Divorced	34	6.3
	Widowed	36	6.7
Level of education	Unable to read and write	133	24.7
	Can read and write	77	14.3
	Primary school	117	21.7
	Secondary school	105	19.5
	College and above	107	19.9
Place of residence of the respondent	Urban	222	41.2
	Rural	317	58.8
Family history of diabetes	Yes	156	28.9
	No	383	71.1
Average FBS (mg/dl)	≤130	107	19.9
	>130	432	80.1
Type of DM	Type I DM	231	42.9
	Type II DM	308	57.1
Duration of diabetes (years)	≤5	299	55.5
	>5	240	44.5
Presence of co-morbid conditions	Yes	145	26.9
	No	394	73.1
Co-morbid conditions	Hypertension	98	51.0
	Ischemic heart disease	34	17.7
	Kidney disease	14	7.3
	Dyslipidemia	37	19.3
	Other (Arthritis, HIV Thyrotoxicosis, and Asthma)	9	4.7
Presence of diabetes complications	Yes	193	35.8
	No	346	64.2
Encountered complications	Retinopathy	77	32.8
	Nephropathy	60	25.5
	Neuropathy	50	21.3
	Coronary artery disease	48	20.4

DM: diabetes mellitus; HIV: human immunodeficiency virus.

Association between only illness perception domain and medication adherence

In the adjusted model, patients who had higher perceptions of diabetic consequences were found to be three times more likely to adhere to treatment compared to other patients (adjusted odds ratio [AOR] = 3.10, 95% CI: 2.11, 4.55). Similarly, individuals with a sense of personal control over their diabetes (AOR = 1.77, 95% CI: 1.20, 2.61) and those with an emotional perception (AOR = 2.26, 95% CI: 1.54, 3.32) were more inclined to adhere to treatment (Table 4).

Association of medication adherence with illness perception and background information

The final model included sociodemographic, patient-related, care-related, clinical, and medication-related variables. Variables that demonstrated a p-value of less than 0.20 in the bivariate analysis were considered for inclusion. After adjusting for potential confounding factors, it was observed that patients with a higher perception of diabetic consequences (AOR = 2.5, 95% CI: 1.64, 3.72), patients with good personal control over their diabetes (AOR = 1.78, 95% CI: 1.19, 2.68), and those with an emotional perception (AOR = 2.39, 95% CI: 1.59, 3.58) were more likely to adhere to their treatment (Table 5).

Discussion

The current study aimed to examine the relationship between illness perception and medication adherence in the North Shao Zone. The findings revealed a significant association between illness perception and adherence to antidiabetic medication (X2 = 4.01; $p < 0.05$). These results align with previous research indicating a positive relationship between illness perception and treatment adherence (13, 16, 23–26). Illness perception influences treatment adherence by affecting patients' behavior and actions (14, 27, 28). Interpersonal problems and illness perceptions significantly influence the emotional adjustment of individuals with diabetes (29).

Although illness perception has been found to have a positive impact on treatment adherence and diabetes management, a considerable number of patients in this study (54.7%) reported suboptimal illness perception. Given the significance of illness perception, it is crucial to prioritize this aspect in educational interventions aimed at improving adherence. It is essential to integrate patient illness perception into diabetes care at all healthcare levels. Furthermore, patients with negative perceptions of their disease can benefit from practical interventions, such as psychoeducational and cognitive-behavioral approaches. By addressing illness perception comprehensively, healthcare providers can contribute to better patient outcomes in diabetes care (11).

This study aimed to examine the influence of illness perception domains on medication adherence. The results demonstrated significant associations between medication adherence and three domains of illness perception: acute/chronic timelines ($p = 0.025$), consequences ($p < 0.0001$), and emotional representation ($p < 0.0001$).

TABLE 2 Illness perception of respondents in North Shoa, 2022 ($n = 539$).

Variables	Category	Frequency	Percent (%)	Mean score ± SD
Identity	Low	290	53.8	8.3 ± 2.3
	High	249	46.2	
Timeline acute/chronic	Low	246	45.6	19.5 ± 2.3
	High	293	54.4	
Consequence	Low	216	40.1	19.8 ± 2.5
	High	323	59.9	
Personal control	Low	253	46.9	20.5 ± 3.7
	High	286	53.1	
Treatment control	Low	226	41.9	19.8 ± 2.0
	High	313	58.1	
Illness coherence	Low	263	48.8	14.7 ± 3.3
	High	276	51.2	
Timeline cyclical	Low	287	53.2	12.2 ± 3.8
	High	252	46.8	
Emotional representation	Low	227	42.1	20.8 ± 3.1
	High	312	57.9	
Overall illness perception	Low	244	45.3	135.6.6 ± 8.7
	High	295	54.7	

TABLE 3 Relationship of illness perception and medication adherence of diabetic patients in North Shoa 2022 ($n = 539$).

Variable	Category	Medication adherence		X2	*p*-value
		Adherent	Non-adherent		
Identity	High	166 (66.7%)	83 (33.3%)	1.057	0.304
	Low	181 (62.4%)	109 (37.6%)		
Timeline acute/chronic	High	201 (68.6%)	92 (31.4%)	4.991	0.025*
	Low	146 (59.3%)	100 (40.7%)		
Consequence	High	241 (74.6%)	82 (25.4%)	36.815	<0.0001*
	Low	106 (49.1%)	110 (50.9%)		
Personal control	High	203 (71%)	83 (29%)	11.576	0.001*
	Low	144 (56.9%)	109 (43.1%)		
Treatment control	High	201 (64.2%)	112 (35.8%)	0.008	0.927
	Low	146 (64.6%)	80 (35.4%)		
Illness coherence	High	190 (66.4%)	96 (33.6%)	1.122	0.289
	Low	157 (62.1%)	96 (37.9%)		
Timeline cyclical	High	169 (67.1%)	83 (32.9%)	1.488	0.223
	Low	178 (62%)	109 (38%)		
Emotional representation	High	226 (72.4%)	86 (27.6%)	20.973	<0.0001*
	Low	121 (53.3%)	106 (46.7%)		
Overall illness perception	High	201 (68.1%)	94 (31.9%)	4.011	0.045*
	Low	146 (59.8%)	98 (40.2%)		

The findings of this study are consistent with previous research (23, 24), reinforcing the importance of understanding illness perception in order to enhance medication adherence. The results of the study highlight the significance of gaining insights into individuals' perceptions of their illness, as it can guide the development of strategies to improve medication adherence.

Based on the final model, medication adherence showed a positive association with illness consequences, personal control, and

TABLE 4 Binary logistic regression analysis of the relationship of illness perception and medication adherence in North Shoa, 2022 ($n = 539$).

Variable	Category	Medication adherence		COR (95%CI)	AOR (95% CI)
		Adherent	Non-adherent		
Identity	High	166 (66.7%)	83 (33.3%)	1.2 (0.85, 1.72)	1.16 (0.79, 1.70)
	Low	181 (62.4%)	109 (37.6%)	1	1
Timeline acute/chronic	High	201 (68.6%)	92 (31.4%)	1.5 (1.05, 2.13)	1.38 (0.94, 2.03)
	Low	146 (59.3%)	100 (40.7%)	1	1
Consequence	High	241 (74.6%)	82 (25.4%)	3.1 (2.12, 4.40)	3.10 (2.11, 4.55)**
	Low	106 (49.1%)	110 (50.9%)	1	1
Personal control	High	203 (71%)	83 (29%)	1.9 (1.30, 2.64)	1.77 (1.20, 2.61)**
	Low	144 (56.9%)	109 (43.1%)	1	1
Treatment control	High	201 (64.2%)	112 (35.8%)	0.98 (0.69, 1.41)	0.84 (0.56, 1.25)
	Low	146 (64.6%)	80 (35.4%)	1	1
Illness coherence	High	190 (66.4%)	96 (33.6%)	1.21 (0.85, 1.72)	1.22 (0.83, 1.80)
	Low	157 (62.1%)	96 (37.9%)	1	1
Timeline cyclical	High	169 (67.1%)	83 (32.9%)	1.25 (0.87, 1.78)	1.17 (0.80, 1.72)
	Low	178 (62%)	109 (38%)	1	1
Emotional representation	High	226 (72.4%)	86 (27.6%)	2.30 (1.61, 3.30)	2.26 (1.54, 3.32)**
	Low	121 (53.3%)	106 (46.7%)	1	1

Statistically significant variables ** at $p < 0.05$ in multivariable analysis; CI: confidence interval at 95%; 1 reference variable; COR: crude odds ratio; AOR; adjusted odds ratio.

perception of emotional representation. Individuals with diabetes who have a comprehensive understanding of their condition are more likely to adhere to their prescribed medication. Particularly, patient-perceived illness consequences emerged as a significant factor influencing diabetes medication adherence, which is in line with previous research findings (16, 30). The influence of patient-perceived illness consequences on diabetes medication adherence can be attributed to various factors, including motivation, personal relevance, and sense of control, emotional responses, and patient-provider collaboration. Recognizing these factors can assist healthcare providers in customizing interventions and support strategies to improve medication adherence among patients with diabetes.

In this current study, patients who had a positive perception of personal diabetes control were more likely to take diabetes medication. This result is consistent with studies conducted in Saudi Arabia (16), Tripoli (24), and Iran (13). These results suggest that positive perceptions of diabetes control can promote better health outcomes. Perceived personal control is closely related to a patient's commitment and confidence in their capacity to manage their disease and take their medications as prescribed. People are becoming more aware of their condition and health, and they feel more accountable to adhere to treatment regimens more closely. As a result, patients are confident in their ability to control their illness, which influences adherence to medications.

According to this study, a stronger perception of emotional representation was linked to a higher probability of taking diabetic medicine as prescribed. Similar results were obtained in Ghana (30), however different results were obtained in Malaysia (17). This suggests that interventions to improve emotional representation could help improve treatment adherence. Interventions could include better communication between health care providers and patients, improved patient education, and better recognition of emotional needs. In addition, we need to understand how patients perceive diabetes, because without emotional representation, treatment may not be appropriately tailored to the patient's needs.

One of the strengths of this study is its examination of the relationship between various dimensions of illness perception and medication adherence. This highlights the need for healthcare professionals to target specific aspects of illness perception when addressing medication adherence. However, it is important to acknowledge the limitations of this study. Firstly, self-reported measures are susceptible to response bias, which may lead to an overestimation of behavioral performance. Additionally, participant recall bias regarding antidiabetic medication adherence could influence the study's results. Moreover, the instrument used in the study should be further refined to ensure accurate and reliable data, taking into account the local context.

The implication of the study

Research examining the association between illness perception and medication adherence in patients with Diabetes mellitus has made significant contributions to the field. By understanding how individuals perceive their illness and how it impacts their adherence to medication regimens, valuable insights have been gained for healthcare professionals, leading to the development of effective interventions. Illness perception refers to an individual's cognitive and emotional understanding of their illness, including their beliefs, expectations, and perceived consequences. Studies have shown that patients with positive illness perceptions are more likely to adhere to their medication regimens. This includes patients who have a better understanding of the chronic nature of diabetes, believe in the effectiveness of their treatment, and feel empowered to manage their condition.

TABLE 5 Logistic regression analysis of medication adherence with illness perception and background information among the participants in North Shoa Zone, 2022.

Variable	Category	Medication adherence		COR (95%CI)	AOR (95% CI)
		Adherent	Non-adherent		
Family history	Yes	107 (68.6%)	49 (31.4%)	1.30 (0.88, 1.93)	1.44 (0.92, 2.27)
	No	240 (62.7%)	143 (37.3%)	1	1
Presence of co-morbid conditions	Yes	81 (55.9%)	64 (44.1%)	0.61 (0.41,0.90)	1.10 (0.60, 2.00)
	No	266 (67.5%)	128 (32.5%)	1	1
Availability	Yes	178 (73.3%)	65 (26.7%)	2.06 (1.43, 2.97)	1.99 (1.32, 3.01)**
	No	169 (57.1%)	127 (42.9%)	1	1
Counseling/education	Yes	150 (68.8%)	68 (31.2%)	1.39 (0.97, 2.00)	1.29 (0.85, 1.95)
	No	197 (61.4%)	124 (38.6%)	1	1
Age	18–40	114 (67.5%)	55 (32.5%)	2.78 (1.72, 4.49)	2.18 (1.28, 3.72)**
	41–60	180 (73.2%)	66 (26.8%)	3.65 (2.32, 5.75)	3.32 (2.00, 5.51)**
	>60	53 (42.7%)	71 (57.3%)	1	1
Duration of treatment	≤5	212 (67.1%)	104 (32.9%)	1.33 (0.93, 1.90)	0.46 (0.19, 1.13)
	>5	135 (60.5%)	88 (39.5%)	1	1
Number of drugs taken per day	One	131 (71.6%)	52 (28.4%)	2.70 (1.71, 4.28)	2.35 (1.18, 4.69)**
	Two	147 (69%)	66 (31%)	2.39 (1.54, 3.70)	2.07 (1.12, 3.80)**
	Three or more	69 (48.3%)	74 (51.7%)	1	1
Duration of diabetes	≤5	206 (68.9%)	93 (31.1%)	1.56 (1.09, 2.22)	2.26 (0.92, 5.56)
	>5	141 (58.8%)	99 (41.2%)	1	1
Timeline acute/chronic	High	201 (68.6%)	92 (31.4%)	1.50 (1.05, 2.13)	1.41 (0.94, 2.12)
	Low	146 (59.3%)	100 (40.7%)	1	1
Consequence	High	241 (74.6%)	82 (25.4%)	3.05 (2.12,4.40)	2.47 (1.64, 3.72)**
	Low	106 (49.1%)	110 (50.9%)	1	1
Personal control	High	203 (71%)	83 (29%)	1.85 (1.30, 2.64)	1.78 (1.19, 2.68)**
	Low	144 (56.9%)	109 (43.1%)	1	1
Emotional representation	High	226 (72.4%)	86 (27.6%)	2.30 (1.61, 3.30)	2.39 (1.59, 3.58)**
	Low	121 (53.3%)	106 (46.7%)	1	1

For statistically significant variables * at $p < 0.05$ in multivariable analysis. CI: confidence interval at 95%; 1 reference variable; COR: crude odds ratio; AOR; adjusted odds ratio.

The comprehensive understanding of illness perception and its impact on patient behavior has paved the way for the development of personalized interventions that address the unique needs of each patient, ultimately improving long-term treatment outcomes. It emphasizes the importance of incorporating illness perception as a key focus in educational interventions aimed at enhancing adherence. These research findings have significant implications for clinical practice. Healthcare professionals can utilize this knowledge to tailor interventions and enhance medication adherence in patients with Diabetes mellitus. By addressing patients' illness perceptions, correcting misconceptions through education, and fostering a sense of control and self-efficacy, healthcare providers can make strides in improving medication adherence and, subsequently, patient outcomes. Gaining insight into the influence of illness perception on patient adherence and developing appropriate strategies should be a priority for healthcare professionals.

In summary, research on the association between illness perception and medication adherence in patients with Diabetes mellitus has shed light on the psychological factors that influence adherence behaviors. This valuable knowledge has the potential to inform interventions, support patient-centered care, and ultimately enhance the management of diabetes.

Conclusion

The current study demonstrates a positive association between higher illness perception and increased medication adherence and practice. Specifically, personal control, illness consequences, and emotional representation were identified as significant aspects of illness perception strongly linked to enhanced medication adherence.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Ethics statement

The studies involving humans were approved by Asrat Woldeyes Health Science Campus, Debre Berhan University, and Institutional Review Board. 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

BG and AE: conceptualization, formal analysis, project administration, and writing – original draft. AE, BG, GA, BaT, EM, BeT, DZ, TD, TK, and YA: investigation, methodology, and writing – review & editing. All authors contributed to the article and approved the submitted version.

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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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Association between type 2 diabetes mellitus and body composition based on MRI fat fraction mapping

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Purpose: To explore the association between type 2 diabetes mellitus (T2DM) and body composition based on magnetic resonance fat fraction (FF) mapping.

Methods: A total of 341 subjects, who underwent abdominal MRI examination with FF mapping were enrolled in this study, including 68 T2DM patients and 273 non-T2DM patients. The FFs and areas of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and abdominal muscle (AM) were measured at the level of the L1-L2 vertebral. The FF of bone marrow adipose tissue (BMAT) was determined by the averaged FF values measured at the level of T12 and L1 vertebral, respectively. The whole hepatic fat fraction (HFF) and pancreatic fat fraction (PFF) were measured based on 3D semi-automatic segmentation on the FF mapping. All data were analyzed by GraphPad Prism and MedCalc.

Results: VAT area, VAT FF, HFF, PFF of T2DM group were higher than those of non-T2DM group after adjusting for age and sex ($P < 0.05$). However, there was no differences in SAT area, SAT FF, BMAT FF, AM area and AM FF between the two groups ($P > 0.05$). VAT area and PFF were independent risk factors of T2DM (all $P < 0.05$). The area under the curve (AUC) of the receiver operating characteristic (ROC) for VAT area and PFF in differentiating between T2DM and non-T2DM were 0.685 and 0.787, respectively, and the AUC of PFF was higher than VAT area ($P < 0.05$). Additionally, in seemingly healthy individuals, the SAT area, VAT area, and AM area were found to be significantly associated with being overweight and/or obese (BMI $\geq$ 25) (all $P < 0.05$).

Conclusions: In this study, it was found that there were significant associations between T2DM and VAT area, VAT FF, HFF and PFF. In addition, VAT area and PFF were the independent risk factors of T2DM. Especially, PFF showed a high diagnostic performance in discrimination between T2DM and non-T2DM. These findings may highlight the crucial role of PFF in the pathophysiology of T2DM, and it might be served as a potential imaging biomarker of the prevention and treatment of T2DM. Additionally, in individuals without diabetes, focusing on SAT area, VAT area and AM area may help identify potential health risks and provide a basis for targeted weight management and prevention measures.

KEYWORDS

ectopic fat deposition, abdominal muscle, bone marrow adipose tissue, magnetic resonance imaging, imaging biomarker

1 Introduction

The global prevalence of diabetes has continued to increase over the past few decades. According to the International Diabetes Federation, as of 2021, the global prevalence of diabetes has exceeded 10%, of which 90% is type 2 diabetes mellitus (T2DM). It is estimated that by 2045, the prevalence of diabetes will increase to 12.2% and will continue to rise in the future (1, 2). T2DM and its complications have posed a serious threat to global public health.

Previous studies have showed that excessive fat accumulation may increase Insulin resistance (IR), which was considered as the key pathogenesis of T2DM (3–5), consequently promoting the onset and progression of T2DM (6). It was found that the accumulation of visceral adipose tissue (VAT) and ectopic fat deposition, such as liver, pancreas, heart, skeletal muscle, are closely related to IR and T2DM (7, 8). However, there is still controversy surrounding the relationship between ectopic fat deposition and T2DM, particularly in pancreatic fat deposition (9–13). The reasons may be attributed to differences in study population, ethnicity, disease status, and the quantitative techniques employed. Therefore, quantitative assessment of fat accumulation is crucial for the prevention and treatment of T2DM.

In addition to adipose tissue, recently, the relationship of T2DM with muscle and bone, two other important components of body composition, has received increasing attention. Waddell et al. (14) found that skeletal muscle mass of T2DM patients was significantly reduced compared with the non-T2DM group. Additionally, a cross-sectional study in a multi-ethnic population demonstrated that skeletal muscle mass may have an independent role compared to body size or VAT in regulating blood glucose in T2DM (15). Furthermore, Hofbauer et al. (16) emphasized that T2DM may lead to deposition of bone marrow adipose tissue (BMAT), thereby increasing the risk of diabetic fragility fractures.

Although previous studies have highlighted the relationship between body composition and T2DM, most of them were primarily focused on specific components of body composition, such as adipose tissue, muscle or bone, rather than considering them as a holistic concept and evaluating multiple factors of body composition simultaneously (15, 17, 18). It is still unclear which factor serves as the optimal biomarker for identifying T2DM. Therefore, research on comprehensive and quantitative assessment of such body composition factors are of great significance for a deep understanding of the pathogenesis of T2DM and the development of more effective prevention and treatment strategies.

Magnetic resonance imaging (MRI) enables fat fraction (FF) mapping through chemical shift encoding, and the FF is commonly defined as the percentage of proton density of fat molecules relative to the combined proton density of water and fat molecules (19, 20). Compared with traditional imaging techniques such as dual-energy x-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA), FF mapping by MRI can provide fast and accurate evaluation of the fat composition of the whole body, and it has been widely applied in the assessment of abdominal muscle (AM) (21–24), BMAT (23–25), and ectopic fat deposition (25, 26).

Therefore, the purpose of this study is to use MRI FF mapping to explore the association between T2DM and body composition, including the AM, BMAT content and ectopic adipose deposition, and to identify potential imaging biomarkers for prediction of T2DM.

Abbreviations: T2DM, type 2 diabetes mellitus; IR, insulin resistance; VAT, visceral adipose tissue; BMAT, bone marrow adipose tissue; MRI, magnetic resonance imaging; FF, fat fraction; DXA, dual-energy x-ray absorptiometry; BIA, bioelectrical impedance analysis; AM, abdominal muscle; FPG, fasting plasma glucose; SAT, subcutaneous adipose tissue; HFF, hepatic fat fraction; PFF, pancreatic fat fraction; ROI, region of interest; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ICC, intraclass correlation coefficient; ROC, receiver operating characteristic; AUC, area under the ROC curve.

2 Methods

2.1 Study design and participants

This single-center, retrospective study collected inpatients who underwent 1.5 or 3.0 T MRI examination of upper abdomen between January 2017 and March 2021, and the scan sequences include MRI FF mapping. Exclusion criteria: 1. lack of clinical data; 2. Age $<$ 18 years; 3. a history of alcoholism (alcohol intake $\geq$ 210 g/week for men and 140 g/week for women in the past 10 years); 4. cirrhosis, decompensated liver disease, liver malignant tumor, large benign liver tumor, post-hepatectomy and other liver diseases (such as viral hepatitis, drug-induced liver injury, autoimmune liver disease, etc.); 5. history of pancreatic and bile duct diseases (e.g., acute or chronic pancreatitis, autoimmune pancreatitis, pancreatic tumor, pancreatic surgery, pancreatic trauma, biliary and pancreatic duct dilatation, etc.); 6. ascites, abdominal edema, huge abdominal mass, mesenteric surgery, postoperative history of abdominal ostomy, etc.; 7. history of radiotherapy and chemotherapy; 8. weight changes more than 5% within 1 month; 9. vertebral body injury, vertebral body occupation, vertebral body surgery etc.

T2DM was defined as fasting plasma glucose (FPG) $\geq$ 7.0 mmol/L or being treated with oral hypoglycemic drugs or insulin. Participants who met the diagnostic criteria of T2DM were divided into the T2DM group; otherwise were divided into the non-T2DM group. To further analyze the association between seemingly healthy population and body composition, a stratified analysis was conducted based on BMI, with the non-T2DM group divided into BMI $<$ 25 and BMI $\geq$ 25 subgroups.

This single-center, retrospective study was approved by the ethics committee of the First Affiliated Hospital of Dalian Medical University, and a waiver of informed consent was remitted.

2.2 MRI examinations

Abdominal MRI examinations were performed in supine position with 8-channel phased array coils and abdominal breathing gating (compensation) on a 1.5 or 3.0 T MRI scanner (Signa HDxt, GE Healthcare, Waukesha, WI, USA), or in supine position with 16-channel phased array coils on a 3.0 T MRI scanner (Ingenia CX, Philips Healthcare, Best, the Netherlands). Patients

were instructed to fast for 4–6 h, and were trained to exhale and hold their breath before MRI scans. We obtained the MRI fat fraction mapping using IDEAL-IQ sequence and mDixon Quant sequence, with the specific parameters as follows (Table 1): 1.5 T MRI IDEAL-IQ sequence: TR = 13.4 ms, TE = 4.8 ms, FOV = 36 × 36 cm^2, matrix = 256 × 160, NEX = 1, slice thickness = 10 mm, flip angle = 5°. 3.0 T MRI IDEAL-IQ sequence: TR = 6.9 ms, TE = 3 ms, FOV = 36 × 36 cm^2, matrix = 256 × 160, NEX = 1, slice thickness = 10 mm, flip angle = 3°. 3.0 T MRI mDixon Quant sequence: TR = 6 ms, TE = 1.05 ms, FOV = 37 × 30 cm^2, matrix = 176 × 130, NEX = 1, slice thickness = 5 mm, flip angle = 3°. Multiple acquired echoe signals were collected during a single breath-hold, and the water-phase, fat-phase, in-phase, out-phase, R2* and fat fraction mapping were generated after reconstruction.

2.3 Data measurements

2.3.1 Visceral adipose tissue, subcutaneous adipose tissue, hepatic fat fraction, and pancreatic fat fraction measurement

VAT and subcutaneous adipose tissue (SAT) were semi-automatically measured by Image J (National Institutes of Health, USA) (https://imagej.nih.gov/ij), and hepatic fat fraction (HFF) and pancreatic fat fraction (PFF) were semi-automatically measured based on the 3D semi-automatic segmentation using the multimodality tumor tracking software on the Philips post-processing workstation (Intellispace Portal, ISP v9.0), and the VAT area, SAT area, VAT FF, SAT FF, HFF and PFF were automatically calculated according to previous studies (20, 27).

2.3.2 Abdominal muscle measurement

AM was manually delineated on MRI axial fat fraction maps at L1-L2 level by using Image J (19, 28, 29), including bilateral erector spinae muscles, quadratus lumborum, psoas major, internal and external oblique muscles, transverse abdominis and rectus abdominis, and then the area and FF for all these muscles were automatically calculated (Figure 1A).

2.3.3 Vertebral bone marrow adipose tissue measurement

The BMAT FF was measured at T12 and L1 vertebral bodies on the Philips post-processing workstation (Intellispace Portal, ISP V9.0) (30). On the axial fat fraction mapping, the region of interests (ROIs) were placed in the center of T12 and L1 vertebral bodies, respectively. And ROIs were drawn along the inner edge of the boundary of the vertebral bodies to contain as many vertebral body area as possible, while avoiding confounding structures such as cortical bone, proliferative osteophyte and other tissues outside the vertebral body. The T12 and L1 spine FF were automatically measured, and the mean spine FF was calculated (Figure 1B).

2.3.4 Other data measurements

All participants were required to fast for ≥12 h before blood drawing and collect blood samples in the morning. FPG, triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were measured by the laboratory staff in our hospital using standard laboratory procedures. The height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) of all subjects were measured by professionally trained nurses in accordance with international standards. Height was measured using a stadiometer with participants removing their cap and shoes, standing upright in the center of the platform, body relaxed, arms naturally drooping down. The measurement accuracy was ±0.1 cm, and two consecutive measurements were taken and averaged. Weight was measured using an electronic scale with participants removing their cap and shoes, wearing light clothing. The measurement accuracy was ±0.1 kg, and two consecutive measurements were taken and averaged. Body mass index (BMI) was calculated using the formula BMI = weight (kg)/height^2 (m^2). SBP and DBP in sitting position of the left upper arm were measured using a calibrated mercury sphygmomanometer. Participants were required to maintain a seated position for at least 5 min before measurement. Two consecutive measurements were taken with a 1–2 min interval, and the average was calculated. The clinical information, including gender, age, smoking status and current alcohol use were acquired from the patient's electronic medical records.

2.4 Inter- and intra-observer variability

The intra- and inter-observer variability of the MRI-acquired fat measurements was determined by repeated analysis of 30 randomly selected patients more than 4 weeks apart by the same observer and by the MRI-acquired fat measurements of the same patient by a second independent observer. Two radiologists were blinded to the grouping information.

2.5 Statistical analysis

All data were analyzed by GraphPad Prism (Version 8.4.0, GraphPad software, LLC) and MedCalc (Version 20.022, MedCalc Software bvba, Ostend, Belgium). The intraclass correlation coefficient (ICC) was used to assess the consistency of measured data. The Kolmogorow-Smironov test was used to analyze the normality of continuous variables.

Normally distributed data were represented by mean ± standard deviation, and non-normally distributed data were represented by median (25th quantile value, 75th quantile value). Categorical variables were expressed as the number of cases and percentage.

Comparisons between T2DM and non-T2DM groups were determined using the two-sided independent sample *t*-test or the non-parametric Mann–Whitney *U*-test for normally or non-normally distributed continuous variables, and the chi-square test for categorical variables.

To assess the correlations between various body compositions, the adjustment coefficient (*r*) among ectopic fat deposition, AM and BMAT parameters after correction for age, sex and BMI were

TABLE 1 MRI fat fraction mapping scan parameters.

MR sequences	TR (ms)	TE (ms)	FOV (cm^2)	Matrix	NEX	Slice thickness (mm)	flip angle (°)
IDEAL-IQ (1.5 T)	13.4	4.8	36 × 36	256 × 160	1	10	5
IDEAL-IQ (3.0 T)	6.9	3.0	36 × 36	256 × 160	1	10	3
mDixon quant (3.0 T)	6.0	1.05	37 × 30	176 × 130	1	5	3

TR, repetition time; TE, echo time; FOV, field of view; NEX, number of excitation.

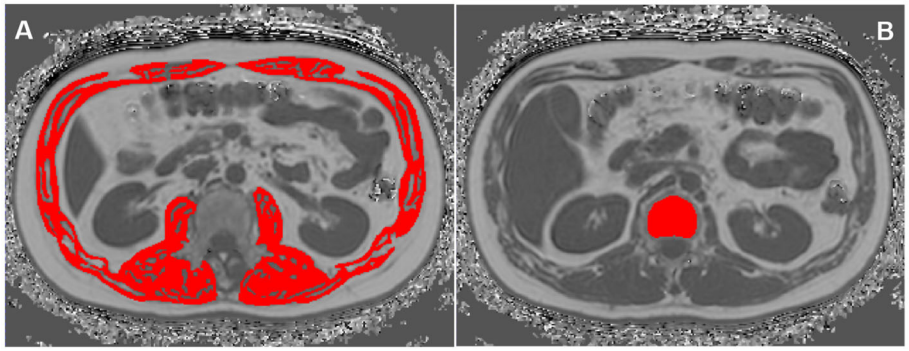

FIGURE 1
Region of interests (ROIs) of abdominal muscle (AM) **(A)** and vertebral bone marrow adipose tissue (BMAT) **(B)** on the MRI fat fraction (FF) mapping.

computed. Correlation coefficients were interpreted as follows: weak, 0–0.4; moderate, 0.4–0.7; strong, 0.7–1.0.

The associations between the body compositions and T2DM were assessed by logistic regression analysis. Receiver operating characteristics (ROC) analysis was performed to calculate the area under the ROC curve (AUC) for body compositions to identify T2DM patients. Additionally, the cut-off value, sensitivity and specificity were also estimated using Youden index. Delong test was used to compare the AUC values.

A two tailed $P < 0.05$ were considered statistically significant.

3 Results

3.1 Study subjects characteristics

A total of 341 participants were finally enrolled in this study, including 68 patients in the T2DM group (40 men and 28 women) and 273 patients in the non-T2DM group (117 men and 156 women). The average age and BMI of patients in T2DM group were significantly higher than those in non-T2DM group ($P < 0.05$). There were more male patients in the T2DM group (58.8 vs. 42.9% in the non-T2DM group) ($P < 0.05$). The detailed clinical characteristics were shown in Table 2.

3.2 Consistency analysis

The data consistency was shown in Table 3. The ICC values were all higher than 0.75, which suggested good inter-observer and intra-observer agreement.

3.3 Correlations among ectopic fat deposition, AM and BMAT parameters

SAT area, SAT FF, VAT area, VAT FF, HFF, PFF, AM area, AM FF and BMAT FF were correlated after adjusting for age, sex and BMI ($P < 0.05$), but patterns of these correlations were different. It was found that both VAT area and FF were correlated with other quantitative parameters ($P < 0.05$) (Figure 2).

3.4 Comparison of body composition parameters between the T2DM group and non-T2DM group

VAT area, VAT FF, HFF, PFF, BMAT FF, AM area and AM FF of the T2DM group were 187.89 cm^2, 78.99%, 4.12%, 13.05%, 46.56%, 119.49 cm^2, 28.85%, respectively, which were higher than those of the non-T2DM group (139.95 m^2, 76.66%, 3.40%, 6.70%, 42.91%, 104.93 cm^2, and 25.32%, respectively), but SAT FF was lower in the T2DM group than in the non-T2DM group (79.77 vs. 82.21%, $P < 0.05$). However, after adjusting for age and gender, the differences between the two groups in SAT FF, AM area, AM FF, and BMAT FF were no longer significant ($P > 0.05$). Additionally, there was no significant difference in SAT area between the two groups, regardless of whether age and gender were adjusted for ($P > 0.05$) (Table 2; Figure 3).

TABLE 2 Characteristics of the study subjects.

Variables	T2DM ($n = 68$)	Non-T2DM ($n = 273$)	*P*-value	*P*-value*
Clinical characteristics				
Age, years	63.81±12.35	57 (49, 64)	**<0.001**	–
Sex, *n* (%)			**0.018**	–
Male	40 (58.80)	117 (42.90)	–	–
female	28 (41.20)	156 (57.10)	–	–
BMI, kg/m^2	25.49 ± 2.54	24.41 ± 3.09	**0.008**	**0.012**
SBP, mmHg	137.10±19.54	120 (113, 130)	**<0.001**	**<0.001**
DBP, mmHg	80 (70, 90)	80 (70, 80)	**0.014**	0.067
FPG, mmol/L	7.48 (6.42, 9.30)	4.99 (4.65, 5.42)	**<0.001**	**<0.001**
TG, mmol/L	1.63 (1.18, 2.49)	1.12 (0.84, 1.58)	**<0.001**	**<0.001**
TC, mmol/L	4.87 (4.32, 5.76)	4.91 ± 1.14	0.399	**0.035**
HDL-C, mmol/L	1.14 ± 0.38	1.31 (1.02, 1.47)	**0.002**	**0.005**
LDL-C, mmol/L	2.80 (2.35, 3.43)	2.70 ± 0.83	0.064	**0.006**
Current smoking status, n (%)	6 (8.80)	28 (10.30)	0.724	0.531
Current alcohol use, *n* (%)	2 (2.90)	13 (4.80)	0.745	0.527
Diabetes treatment, *n* (%)	45 (66.20)	–	–	–
Postmenopausal status, *n* (%)	25 (89.30)	118 (76.60)	0.133	0.445
Body composition parameters				
SAT area, cm^2	118.19 (91.81, 167.93)	123.17 (96.02, 158.43)	0.836	0.172
SAT FF, %	79.77 ± 4.94	82.21 (79.13, 84.66)	**0.007**	0.910
VAT area, cm^2	187.89 ± 74.01	139.95 ± 66.94	**<0.001**	**0.001**
VAT FF, %	78.99 (75.85, 80.89)	76.66 (73.07, 79.94)	**0.011**	**0.024**
HFF, %	4.12 (2.92, 7.15)	3.40 (2.60, 5.50)	**0.029**	**0.012**
PFF, %	13.05 (9.80, 19.15)	6.70 (4.20, 9.80)	**<0.001**	**<0.001**
AM area, cm^2	119.49 ± 28.55	104.93 (87.69, 130.59)	**0.016**	0.070
AM FF, %	28.85 (22.86, 33.89)	25.32 (19.78, 32.23)	**0.033**	0.080
BMAT FF, %	46.56 ± 10.51	42.91 ± 11.83	**0.021**	0.429

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SAT, subcutaneous adipose tissue; FF, fat fraction; VAT, visceral adipose tissue; HFF, hepatic fat fraction; PFF, pancreatic fat fraction; AM, abdominal muscle; BMAT, bone marrow adipose tissue.

Data were expressed as mean ± SD, median (25th and 75th percentiles) or *n* (%); *P*-value shows comparison of the T2DM and non-T2DM groups.

*Adjusted for age and sex. The bold values indicates statistically significant.

3.5 Association between T2DM and body compositions

Multivariate analysis showed that VAT area (OR: 1.005, 95% CI: 1.001–1.010) and PFF (OR: 1.062, 95% CI: 1.025–1.100) were independently associated with T2DM after adjusting for the confounding factors of age, sex, BMI, VAT FF, HFF (Table 4).

It was found that the AUC of VAT area for identifying T2DM was 0.685 (0.633–0.734) with the sensitivity and specificity of 67.65 and 63.37%, respectively, when using the cut-off value of 159.18 cm^2. The AUC of PFF for identifying T2DM was 0.787 (0.740–0.830) with the sensitivity and specificity of 75.00 and 77.29%, respectively, when using the cut off value of 10.10% (Table 5; Figure 4).

Furthermore, Delong test was used to compare the diagnostic performance of VAT area and PFF for prediction of T2DM. It demonstrated that PFF has significantly higher diagnostic efficacy for T2DM than VAT area ($P < 0.05$) (Figure 5).

3.6 Relationship between non-T2DM and body compositions

There was no statistically significant difference in age between the BMI < 25 and BMI ≥ 25 groups ($P > 0.05$), while the difference in gender between the two groups was statistically significant ($P < 0.05$). Moreover, the SAT area, SAT FF, VAT area, VAT FF, HFF, PFF,

TABLE 3 Two-observer measurement consistency.

Body composition parameters	Radiologist A1	Radiologist A2	ICC 1*	Radiologist B	ICC 2*
SAT area, cm^2	131.28 (109.95, 149.86)	128.54 (107.38, 154.27)	0.996	130.72 (110.23, 153.03)	0.993
SAT FF, %	82.16 (80.52, 84.14)	83.02 (79.14, 84.85)	0.912	83.45 (79.52, 84.59)	0.902
VAT area, cm^2	137.26 ± 75.46	139.30 ± 74.58	0.997	139.43 ± 75.77	0.998
VAT FF, %	78.18 (73.85, 80.96)	77.36 (72.55, 80.24)	0.756	77.28 (72.76, 80.07)	0.832
HFF, %	3.50 (2.55, 5.55)	3.80 (2.85, 5.55)	0.987	3.50 (2.75, 5.55)	0.991
PFF, %	6.30 (4.05,11.20)	6.40 (4.25, 10.70)	0.992	6.30 (4.20, 11.75)	0.996
AM area, cm^2	116.14 ± 28.87	115.54 ± 26.83	0.966	115.39 ± 27.12	0.972
AM FF, %	25.96 (19.79, 30.84)	23.66 (18.44, 29.73)	0.900	24.32 (19.05, 29.28)	0.918
BMAT FF, %	46.32 (39.56, 50.31)	46.29 (39.86, 50.42)	0.987	43.85 ± 10.37	0.928

*ICC 1 shows ICC value of Intra-observer and ICC 2 shows ICC value of inter-observer.

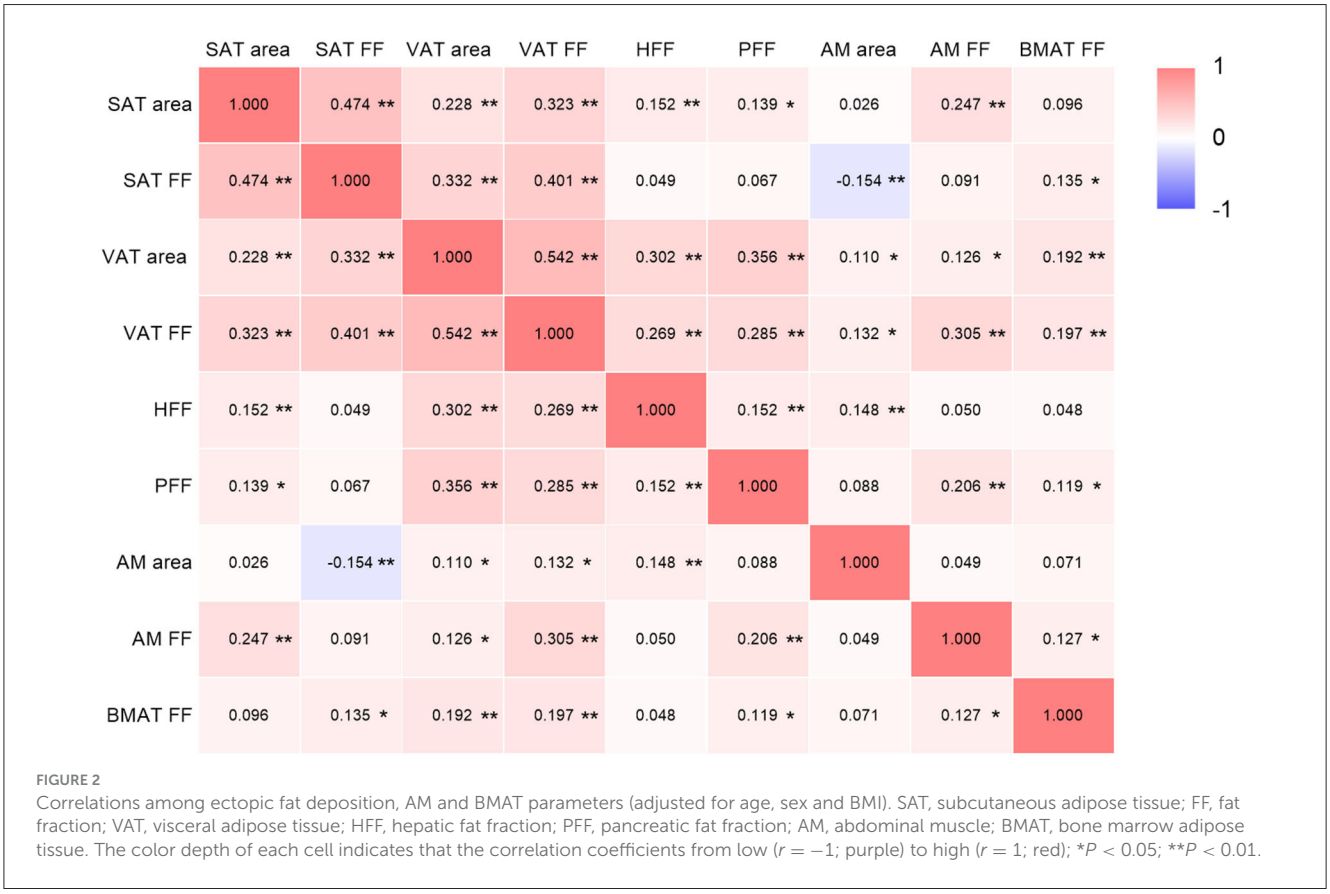

FIGURE 2
Correlations among ectopic fat deposition, AM and BMAT parameters (adjusted for age, sex and BMI). SAT, subcutaneous adipose tissue; FF, fat fraction; VAT, visceral adipose tissue; HFF, hepatic fat fraction; PFF, pancreatic fat fraction; AM, abdominal muscle; BMAT, bone marrow adipose tissue. The color depth of each cell indicates that the correlation coefficients from low ($r = -1$; purple) to high ($r = 1$; red); *$P < 0.05$; **$P < 0.01$.

and AMAT area of the BMI ≥ 25 group were significantly higher than those of BMI < 25 group ($P < 0.05$). However, there was no statistically significant differences in AM FF and BMAT FF between the two groups ($P > 0.05$). It is noteworthy that this relationship remains unchanged even after adjusting for sex (Table 6; Figure 6).

Multivariate analysis showed that SAT area (OR: 1.016, 95% CI: 1.005–1.026), VAT area (OR: 1.016, 95% CI: 1.008–1.024) and AM area (OR: 1.047, 95% CI: 1.026–1.069) were independently associated with BMI ≥ 25 after adjusting for the confounding factors of sex, SAT FF, VAT FF, HFF, PFF (Table 7).

4 Discussion

In this study, we found that there were significant associations of T2DM with VAT area, VAT FF, HFF and PFF. In addition, VAT area and PFF were independent risk factors of T2DM, with PFF showing the highest efficacy in prediction of T2DM. Additionally, in seemingly healthy individuals, the SAT area, VAT area, and AM area were found to be significantly associated with being overweight and/or obese (BMI ≥ 25). The findings highlight that PFF hold promise as a imaging biomarker to identify individuals

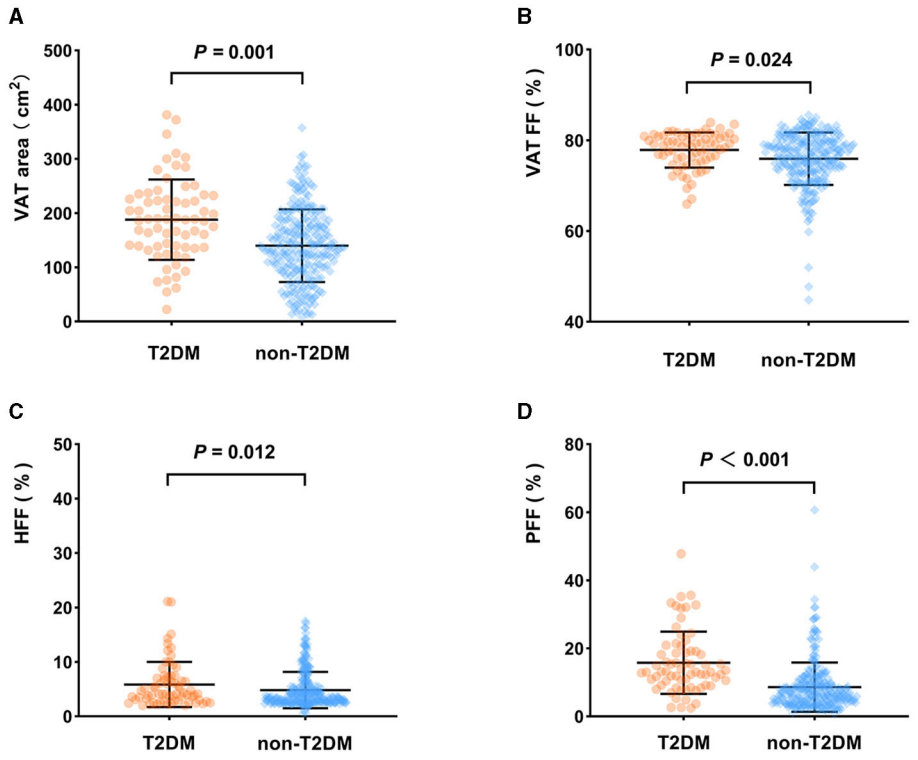

FIGURE 3
Comparison of body composition parameters between the T2DM group and non-T2DM group (adjusted for age and sex). VAT area **(A)**, VAT FF **(B)**, HFF **(C)**, PFF **(D)** of the T2DM group were higher than those of the non-T2DM group ($P < 0.05$).

TABLE 4 **Association between T2DM and body compositions (adjusted for age, sex, and BMI).**

Variables	Multivariate analysis	
	OR (95% CI)	*P*-value
VAT area	1.005 (1.001–1.010)	**0.020**
VAT FF	0.972 (0.899–1.051)	0.478
HFF	1.051 (0.966–1.143)	0.248
PFF	1.062 (1.025–1.100)	**0.001**

VAT, visceral adipose tissue; FF, fat fraction; HFF, hepatic fat fraction; PFF, pancreatic fat fraction; OR, odds ratio; CI, confidence interval. The bold values indicates statistically significant.

at risk of T2DM and being overweight and/or obese. Monitoring PFF may assist clinicians in formulating more precise strategies for prevention and treatment. Additionally, in individuals without diabetes, focusing on SAT area, VAT area and AM area may help identify potential health risks and provide a basis for targeted weight management and prevention measures.

The human body's fat storage is primarily composed of SAT and VAT, with SAT accounting for the majority of human adipose tissue (31, 32). Aside from the main subcutaneous and visceral fat depots, *de novo* adipogenesis will also occur in other parts (31). When the fat accumulation exceeds the expansion capacity of the SAT, excess lipid can accumulate in ectopic fat depots such as bone, liver, pancreas, and skeletal muscle (33). These fat depots might not exist independently and are influenced by age, gender and BMI, etc. In our study, it was showed that after adjusting for age, sex and BMI, there were varying degrees of correlations among these fat depots, particularly, VAT was correlated with all the other quantitative parameters. These findings indicated that VAT may be a marker of ectopic fat deposition (8).

Previous studies have showed that the accumulation of VAT is an risk factor of T2DM, while the expansion of SAT may be a protective factor (34, 35). However, abnormal expansion of SAT may also be a part of the pathological process. The insufficient capacity of SAT to recruit and/or differentiate available precursor cells may lead to hypertrophic expansion of the cells, resulting in IR and an increased risk of T2DM (33). As expected, in this study, we observed higher levels of VAT in the T2DM group, and VAT area is an independent identifying factor of T2DM, with an AUC value of 0.685. These findings were consistent with previous studies (36–38).

Compared to SAT, VAT exhibits higher metabolic activity and plays an more important role in regulating whole-body metabolism (39). The accumulation of VAT increases the risk of T2DM, which may be related to the following mechanisms. The venous blood of VAT drains into the liver through the portal vein, supplying the liver with free fatty acids and adipokines secreted by VAT cells. As a result, VAT accumulation can expose the liver to high concentrations of free fatty acids and glycerol, which will lead to reduced uptake of insulin by the liver (aggravating hyperinsulinemia), increased triglyceride-rich lipoproteins, and excessive stimulation of hepatic gluconeogenesis, ultimately increasing the risk of T2DM and hyperglycemia (8,

TABLE 5 The efficacy analysis of VAT area and PFF for predicting T2DM.

Parameters	AUC (95%CI)	Cut-off value	Sensitivity (%)	Specificity (%)	*P*-value
VAT area, cm^2	0.685 (0.633–0.734)	159.18	67.65	63.37	<0.001
PFF, %	0.787 (0.740–0.830)	10.10	75.00	77.29	<0.001

AUC, area under the curve; CI, confidence interval; VAT, visceral adipose tissue; FF, fat fraction; PFF, pancreatic fat fraction.

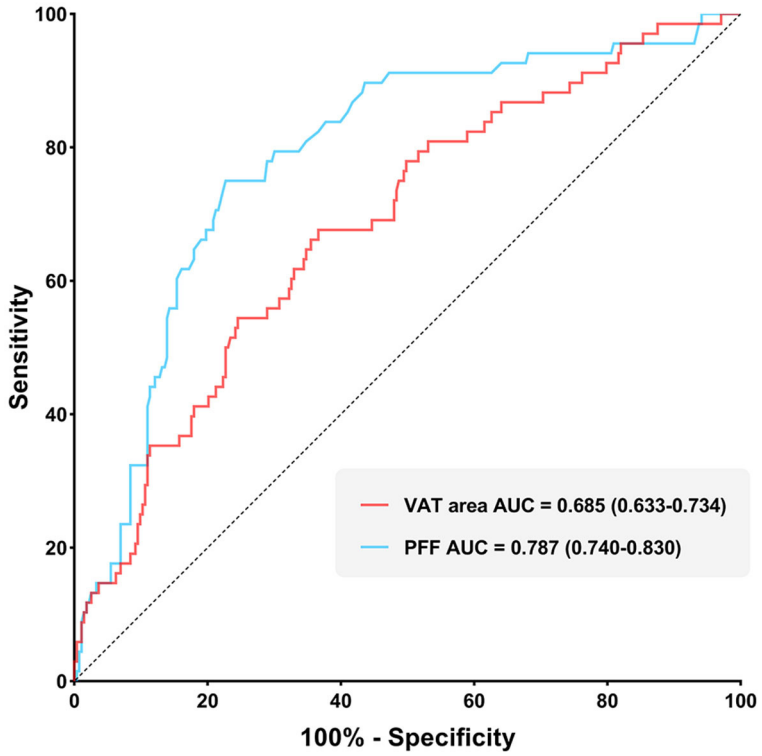

FIGURE 4
Receiver operating characteristic (ROC) curves of VAT area and PFF for predicting T2DM.

39, 40). In addition, VAT accumulation is accompanied by more inflammatory cell infiltration, which leads to an imbalance in the expression of pro-inflammatory and anti-inflammatory adipokines, thus interfering with glucose metabolism and increasing the risk of T2DM (8, 39, 41). Therefore, controlling and reducing the accumulation of VAT can reduce the risk of T2DM by improving insulin sensitivity, reducing the level of inflammation and reducing the release of fatty acids.

In the present study, we observed that the SAT area is not associated with T2DM, which is consistent with previous findings (9). Additionally, we observed that SAT FF in T2DM patients was lower than in non-T2DM patients. However, the difference in SAT FF between the two groups was no longer significant after adjusting for age and sex. This suggests that factors such as age and gender may play a certain role in interfering with this association.

Hepatic fat deposition is characterized by the accumulation of TG within hepatocytes (42). Previous studies have shown an association between hepatic fat deposition and T2DM. In this study, we found that patients with T2DM had higher HFF compared to non-T2DM patients. Sarma et al. (43) revealed that T2DM is related to the increase of fat deposition in liver, pancreas and viscera, and may be a contributing factor to IR in T2DM. Levelt et al. (7) found that diabetes, regardless of obesity, is associated with an increase in hepatic triglyceride content. Cao et al. (26) observed that patients with T2DM and prediabetes have higher HFF compared to individuals with normal glucose tolerance. Our findings were consistent with these results. However, it was found that HFF was not the independent risk factor for T2DM, which is consistent with the findings of Zheng et al. (9). We speculate that hepatic fat deposition may not be an independent mechanism in the pathogenesis of T2DM, and its role may be influenced by VAT, which collectively play important modulatory roles in T2DM development. Previous studies have indicated that the metabolites of VAT are mainly metabolized through portal vein circulation. Excessive accumulation of VAT will lead to the liver being exposed to high concentrations of free fatty acids and glycerol. When hepatic lipid supply exceeds the rate of lipid oxidation and output, the accumulate of TG in the liver as lipid droplets, resulting in the development of fatty liver (8, 39, 40, 44). Therefore, the relationship between HFF and T2DM may be mediated by VAT. However, we also recognized that there is significant heterogeneity in the pathogenesis of hepatic fat accumulation, leading to varying

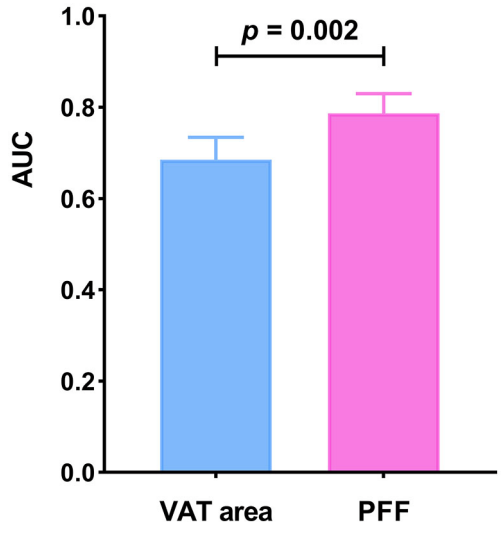

FIGURE 5
Comparison of diagnostic efficacy among VAT area and PFF for prediction of T2DM ($P < 0.05$).

relationships between fatty liver and glucose metabolism. Previous studies has indicated that higher liver fat content may not increase the risk of IR and diabetes in certain patients with a genetic predisposition to hepatic steatosis. Conversely, severe IR and high risk of T2DM have been observed in patients with hepatic steatosis caused by an unhealthy lifestyle and excessive accumulation of VAT (45). Furthermore, Stefan and colleagues have identified that the characteristic of IR associated with metabolically unhealthy fatty liver is elevated levels of fetuin-A, and this phenotype may differ from that of IR associated with visceral obesity, which is primarily characterized by low plasma adiponectin levels (46). Therefore, adopting new risk stratification approaches to distinguish between hepatic fat deposition and visceral obesity may contribute to a better understanding of the relationship between hepatic fat accumulation and T2DM, and provide more targeted prevention and treatment strategies.

Compared to the liver, the pancreas appears to be more susceptible to fat accumulation (47). Increasing evidence suggests that pancreatic fat deposition may be associated with lipotoxicity, IR and inflammation, which could contribute to the development of glucose metabolism disorders (48). So far, the evidence about the relationship between pancreatic fat accumulation and T2DM is not consistent. Some cross-sectional studies based on CT and MRI have indicated that compared with non-T2DM patients, T2DM patients have higher PFF (9, 10, 12, 43, 49). Our research has reached the similar conclusion. In addition, Yi et al. (50) indicated that T2DM patients with longer disease duration have higher levels of pancreatic fat accumulation compared to those with shorter duration. However, a recent MRI study, which based on age, gender, and BMI matched T2DM patients (131 cases) and non-T2DM patients (135 cases), did not observe the difference of PFF between the two groups by placing ROIs in the head, body, and tail of the pancreas on MRI FF mapping (14). This finding contradicts our research results. This discrepancy may be attributed to variations in the methods used to assess pancreatic fat deposition, uneven distribution of pancreatic fat deposition, as well as differences in race, gender, and genetic factors. It is gratifying to note that in this study, we discovered an independent association between PFF and T2DM, with PFF demonstrating the best performance in identifying T2DM. This suggests that an increase in PFF may more accurately reflect the deterioration of adipose tissue quality, and thus indicating the raising risk of T2DM development. These findings underscore the critical role of PFF in the pathophysiology of T2DM and offer new insights for the prevention and treatment of T2DM. The fat content of pancreatic endocrine cells is considered a key factor in the pathogenesis of T2DM (51). Previous studies have indicated that elevated levels of triglycerides have lipotoxic effects on islet β-cells, leading to impaired endocrine function and reduced insulin secretion (52). Furthermore, exposure of the pancreatic islets to high levels of fatty acids may result in β-cell dedifferentiation, which is also considered a potential mechanism for T2DM (51). Ectopic fat accumulation within endocrine and exocrine organs occurs after the obesity-associated exhaustion of the adipogenic capacity of adipocyte precursors within bona fide fat depots (53). The paracrine action of lipids within adipocytes and acinar cells may contribute to local inflammation and impairment of β-cell function through the release of adipokines and other metabolite (51, 54, 55). Therefore, controlling or reducing pancreatic fat content may contribute to better glycemic control and improved metabolic health.

BMAT, a metabolically active and insulin-sensitive unique fat depot, may play a role in whole-body energy metabolism and glucose homeostasis (56, 57). Similar to other fat depots, marrow adipocytes release various adipokines (such as leptin, adiponectin, etc.) and free fatty acids through endocrine and paracrine pathways, regulating insulin sensitivity and mediating IR (58, 59). In addition, pro-inflammatory cytokines released by marrow adipocytes might mediate systemic chronic inflammation, which is considered a pivotal factor in the progression of T2DM and its complications (60, 61). In our study, we observed significant differences in BMAT content between patients with and without T2DM. This finding aligns with previous research (30, 62, 63), indicating higher levels of BMAT in patients with T2DM. Yet, the study by de Araújo et al. (18) showed different results, and they observed that there was no difference in BMAT content at the L3 vertebra between T2DM (28 cases) and control groups (24 cases) by magnetic resonance spectroscopy. Possible reasons for this disparity could include differences in measurement methods and locations, as well as their limited sample size. However, after adjusting for age and gender, the difference in BMAT FF between the T2DM group and non-T2DM group was no longer significant. We speculate that this may be due to the older age of the patients in the T2DM group and the possibility that bone marrow may not be the primary site of fat accumulation in T2DM.

As the main effector organs of insulin, skeletal muscle plays an important role in maintaining local and overall glucose homeostasis and IR. The existing research on the relationship between body composition and T2DM has primarily focused on adipose tissue, with limited understanding of the independent role of skeletal muscle in predicting or diagnosing T2DM. Our study demonstrated that the both AM FF and AM area were higher in T2DM patients compared to non-T2DM patients. This results

TABLE 6 Characteristics of the non-T2DM subjects.

Variables	All subjects ($n = 273$)	BMI < 25 ($n = 165$)	BMI ≥ 25 ($n = 108$)	*P*-value	*P*-value*
Clinical characteristics					
Age, years	57 (49, 64)	57 (49, 64)	55.95 ± 12.47	0.888	
Sex, *n* (%)				**0.029**	
Male	117 (42.86)	62 (37.58)	55 (50.93)	–	
Female	156 (57.14)	103 (62.42)	53 (49.07)	–	
BMI, kg/m^2	24.41 ± 3.09	22.76 (21.09, 23.84)	26.83 (26.12, 28.25)	**<0.001**	0.957
SBP, mmHg	120 (113, 130)	120 (110, 130)	130 (120, 140)	**<0.001**	**0.014**
DBP, mmHg	80 (70, 80)	80 (70, 80)	80 (72, 87.5)	**0.001**	**0.006**
FPG, mmol/L	5.06 ± 0.63	4.92 ± 0.51	5.28 ± 0.72	**<0.001**	**<0.001**
TG, mmol/L	1.12 (0.84, 1.58)	1.01 (0.77, 1.47)	1.31 (0.93, 1.88)	**<0.001**	**0.004**
TC, mmol/L	4.91 ± 1.14	4.72 (4.13, 5.59)	4.94 ± 1.18	0.512	0.429
HDL-C, mmol/L	1.31 (1.02, 1.47)	1.36 (1.04, 1.47)	1.26 ± 0.39	0.179	0.617
LDL-C, mmol/L	2.70 ± 0.83	2.62 (2.16, 3.11)	2.71 ± 0.82	0.491	0.657
Current smoking status, *n* (%)	28 (10.20)	20 (12.10)	8 (7.40)	0.209	**0.034**
Current alcohol use, *n* (%)	13 (4.70)	8 (4.80)	5 (4.60)	0.934	0.566
Postmenopausal status, *n* (%)	118 (43.20)	74 (73.30)	44 (83.00)	0.174	0.178
Body composition parameters					
SAT area, cm^2	123.17 (96.02, 158.43)	114.47 (84.13, 133.52)	155.86 ± 52.77	**<0.001**	**<0.001**
SAT FF, %	82.21 (79.13, 84.66)	81.63 (78.38, 84.20)	83.00 (80.38, 85.52)	**0.001**	**<0.001**
VAT area, cm^2	139.95 ± 66.94	114.19 ± 59.54	179.30 ± 58.08	**<0.001**	**<0.001**
VAT FF, %	76.66 (73.07, 79.94)	75.45 (70.89, 78.16)	79.61 (75.00, 81.65)	**<0.001**	**<0.001**
HFF, %	3.40 (2.60, 5.50)	3.10 (2.50, 4.20)	4.45 (3.30, 8.20)	**<0.001**	**<0.001**
PFF, %	6.70 (4.20, 9.80)	5.80 (3.50, 8.80)	8.25 (5.65, 12.15)	**<0.001**	**<0.001**
AM area, cm^2	104.93 (87.69, 130.59)	96.93 (83.57, 117.87)	124.77 ± 30.33	**<0.001**	**<0.001**
AM FF, %	25.32 (19.78, 32.23)	24.30 (18.79, 32.23)	26.05 (21.35, 32.18)	0.161	0.058
BMAT FF, %	42.91 ± 11.83	42.66 ± 12.90	43.31 ± 10.01	0.639	0.618

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SAT, subcutaneous adipose tissue; FF, fat fraction; VAT, visceral adipose tissue; HFF, hepatic fat fraction; PFF, pancreatic fat fraction; AM, abdominal muscle; BMAT, bone marrow adipose tissue.

Data were expressed as mean ± SD, median (25th and 75th percentiles) or n (%); *P*-value shows comparison of the BMI < 25 and BMI ≥ 25 groups.

*Adjusted for sex. The bold values indicates statistically significant.

is consistent with previous research findings (15, 64). Currently, the underlying mechanisms of skeletal muscle in IR and the development of T2DM remain unclear. Previous studies have suggested that IR in skeletal muscle may manifest prior to β-cell failure and elevated blood glucose in T2DM (65). IR in liver and muscle can lead to increased lipolysis and release of free fatty acids, as well as hyperglycemia. This process further stimulates ectopic fat deposition in the liver and muscles. To cope with the IR of the periphery and liver, the pancreas secretes more insulin, which leads to hyperinsulinemia. This process stimulates ectopic fat deposition in the liver and muscles again, forming a vicious circle (66, 67). In skeletal muscle and liver, the increase of fat storage may be related to the increase of IR, which results in the inhibition of glucose uptake in muscle cells, the increase of hepatic gluconeogenesis and the decrease of glycogen synthesis (66, 68). In addition, cytokines and adipokines released by adipose tissue can also regulate insulin sensitivity in liver and skeletal muscle (66). Given the significant differences in age and gender distribution between the two groups, which may have an impact on the experimental results, we performed age and gender adjustments. After adjustment, we found that the differences in the AM area and FF between the two groups were no longer significant. To

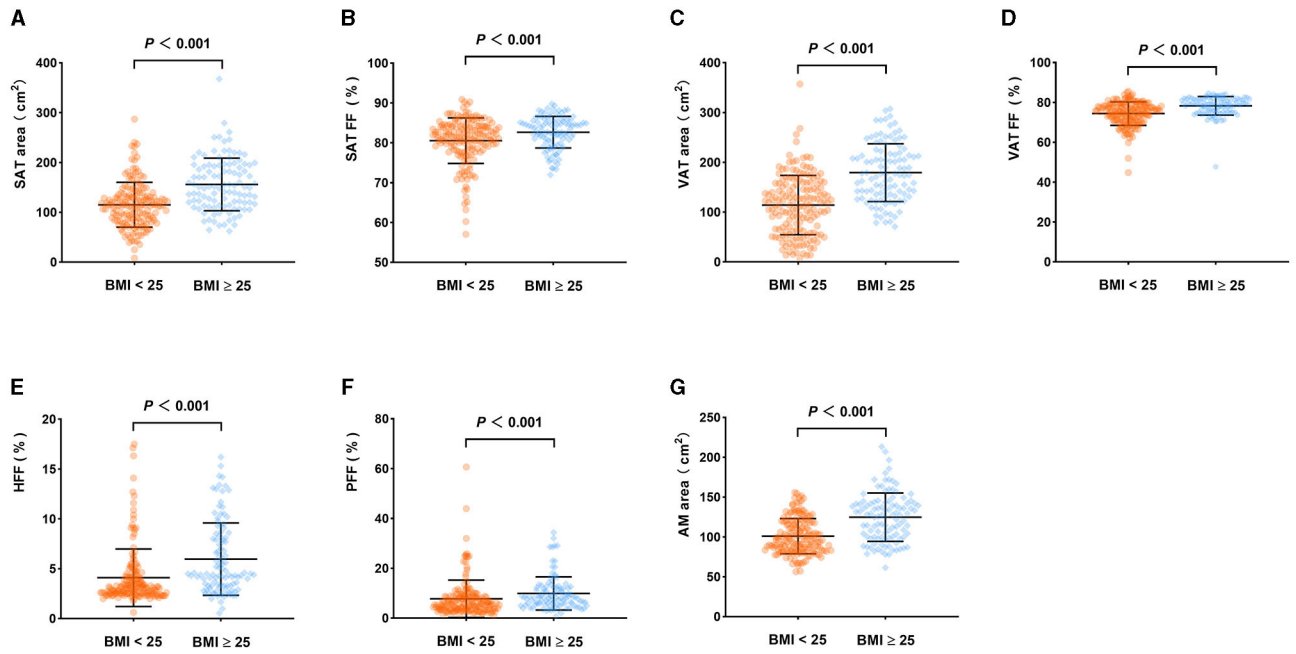

FIGURE 6
Comparison of body composition parameters between the BMI < 25 group and BMI ≥ 25 group (adjusted for sex). SAT area **(A)**, SAT FF **(B)**, VAT area **(C)**, VAT FF **(D)**, HFF **(E)**, PFF **(F)**, AMAT area **(G)** of the BMI ≥ 25 group were higher than those of the BMI < 25 group ($P < 0.05$).

TABLE 7 The correlation between non-T2DM and body compositions (adjusted for sex).

Variables	Multivariate analysis	
	OR (95% CI)	*P*-value
SAT area	1.016 (1.005–1.026)	**0.003**
SAT FF	1.027 (0.926–1.138)	0.617
VAT area	1.016 (1.008–1.024)	**<0.001**
VAT FF	0.948 (0.875–1.027)	0.191
HFF	1.015 (0.916–1.125)	0.773
PFF	0.966 (0.919–1.017)	0.188
AM area	1.047 (1.026–1.069)	**<0.001**

SAT, subcutaneous adipose tissue; FF, fat fraction; VAT, visceral adipose tissue; HFF, hepatic fat fraction; PFF, pancreatic fat fraction; AM, abdominal muscle; OR, odds ratio; CI, confidence interval. The bold values indicates statistically significant.

further investigate the predictive value of different fat depots for T2DM in different age and gender groups, it is necessary to expand the sample size and conduct subgroup analysis stratified by age and gender.

To explore the associations between seemingly healthy individuals and multiple body compositions, we further divided the patients in the non-T2DM group into two subgroups based on BMI. We observed that a close correlation between higher SAT, VAT, and AM areas and overweight and/or obesity. Therefore, focusing on the SAT area, VAT area, and AM area in non-diabetic patients may help identify potential health risks and provide a foundation for targeted weight management and preventive measures.

5 Strengths and limitations

The strength of our study is that we used MRI FF mapping to non-invasively and accurately assess body composition, including AM, BMAT, and ectopic fat deposits, and to explore the relationship between multiple body composition factors and T2DM. To avoid the influence of uneven distribution of hepatic fat and pancreatic fat contents, we employed a 3D semi-automatic segmentation method based on MRI FF mapping to quantify whole hepatic fat and whole pancreatic fat. Furthermore, DeLong test was employed to compare the differences of the AUC values of VAT area, and PFF, evaluating their diagnostic performance in T2DM. Our results emphasize the critical role of PFF in the onset and progression of T2DM, and hold promise as a potential imaging biomarker for the prevention and treatment of T2DM. However, there were several limitations to our study. First of all, our study is based on a cross-sectional design, which cannot establish causality. Therefore, further longitudinal studies are needed to validate the findings of our research. Secondly, subjects in our study were from a single central hospital in China, and larger scale studies are needed to verify whether our results can be extrapolated to other ethnic populations. Thirdly, the distribution of fat in T2DM patients differs by gender, thus it is necessary to further expand the sample size and subgroup analysis stratified by age and gender to explore the predictive value of different adipose depots for T2DM in different ages and sexes. Finally, it is not feasible to evaluate the impact of drug treatment on body composition parameters due to the small sample size of T2DM patients undergoing treatment and the absence of a comparison of these parameters before and after treatment. Therefore, further large-scale and prospective studies

are necessary to comprehensively and thoroughly investigate the influence of diabetes treatment on the body composition of T2DM patients.

6 Conclusions

In this study, we investigated the associations of ectopic fat deposition, AM, and BMAT with the incidence of T2DM. Our results showed that VAT area and PFF were independent risk factors for prediction of T2DM, and PFF showed the best diagnostic performance. Therefore, PFF based on MRI FF mapping could be a potential radiological biomarker to help clinicians to more accurately screen high-risk T2DM individuals, provide more personalized treatment, and monitor the therapeutic effect. However, in order to better apply PFF to clinical practice, further prospective studies are needed to investigate the role of PFF in the pathological mechanism of T2DM. Additionally, in individuals without diabetes, focusing on SAT area, VAT area and AM area may help identify potential health risks and provide a basis for targeted weight management and prevention measures.

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 Ethics Committee of the First Affiliated Hospital of Dalian Medical University. 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 informed consent is exempted.

Author contributions

QA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing—original draft, Writing—review & editing. Q-HZ: Conceptualization, Methodology, Writing—original draft, Writing—review & editing. YW: Investigation, Project administration, Writing—original draft. H-YZ: Investigation, Writing—original draft. Y-HL: Investigation, Writing—original draft. Z-TZ: Investigation, Writing—original draft. M-LZ: Investigation, Writing—original draft. L-JL: Writing—review & editing. HH: Writing—review & editing. Y-FY: Writing—review & editing. PS: Writing—review & editing. Z-YZ: Writing—review & editing. Q-WS: Writing—review & editing. A-LL: Conceptualization, Writing—review & editing.

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COPD and T2DM: a Mendelian randomization study

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Introduction: Type 2 diabetes (T2DM) stands as a global chronic illness, exerting a profound impact on health due to its complications and generating a significant economic burden. Recently, observational studies have pointed toward a potential link between Chronic Obstructive Pulmonary Disease (COPD) and T2DM. To elucidate this causal connection, we employed the Mendelian randomization analysis.

Method: Our study involved a two-sample Mendelian randomization (MR) analysis on COPD and T2DM. Additionally, tests for heterogeneity and horizontal pleiotropy were performed.

Results: For the MR analysis, 26 independent single nucleotides polymorphisms (SNPs) with strong associations to COPD were chosen as instrumental variables. Our findings suggest a pronounced causal relationship between COPD and T2DM. Specifically, COPD emerges as a risk factor for T2DM, with an odds ratio (OR) of 1.06 and a 95% confidence interval ranging from 1.01 to 1.11 (P = 0.006). Notably, all results were devoid of any heterogeneity or pleiotropy.

Conclusion: The MR analysis underscores a significant causal relationship between COPD and T2DM, highlighting COPD as a prominent risk factor for T2DM.

KEYWORDS

type 2 diabetes mellitus, Chronic Obstructive Pulmonary Disease, Mendelian randomization (MR) analysis, GWAS data, causal relationship

1 Introduction

Over the past three decades, the prevalence of Type 2 diabetes (T2DM) and its associated complications have surged globally, especially in low- and middle-income nations. This expansion represents a burgeoning crisis that poses severe threats to both global health and economic prospects. It is estimated that over 9% of the global adult population is diagnosed with T2DM. Those affected by T2DM face an average reduction in life expectancy of 8 years in the US, accompanied by a myriad of complications that

compromise their quality of life. Significantly, nearly 12% of the world's health expenditures in 2015 were dedicated to addressing T2DM and its consequential complications (1). The etiological factors underlying T2DM are diverse, intertwining genetic, epigenetic, and lifestyle determinants within an expansive physical-socio-cultural milieu.

Chronic Obstructive Pulmonary Disease (COPD) represents a significant global health challenge. As of 2015, an estimated 7.3 billion individuals worldwide were affected by COPD. With an aging population and persistent smoking habits, the prevalence of such chronic diseases is expected to rise (2). Notably, numerous studies indicate a higher incidence of diabetes in COPD patients (3–6). For instance, a retrospective investigation led by Mario Cazzola, which encompassed 341,329 Italian participants from the Health Search Database (HSD), discerned that individuals without COPD bore a significantly reduced prevalence of diabetes than their COPD-afflicted counterparts. However, the occurrence of metabolic syndrome remained stable irrespective of COPD, underscoring the hypothesis that COPD, rather than metabolic syndrome, amplifies the risk of diabetes (6). This pattern suggests a potential pathophysiological intertwining between COPD and T2DM.

A recent systematic review underscored that COPD could be a harbinger for the advancement of diabetes, emphasizing that individuals with severe to very severe COPD face a heightened risk of diabetes onset (7, 8). However, a prospective analysis reported no discernible link between obstructive pulmonary function impairment and T2DM (9). Even though the systematic review probed the potential nexus between COPD and diabetes, its conclusions remain inconclusive. Many investigations centering on COPD encompass a restricted cohort, and subjects diagnosed with AECOPD/T2DM frequently exhibit other pronounced co-morbidities, clouding the interpretation of metrics such as hospital stay durations and mortality rates. Furthermore, the perceived interrelation between COPD and diabetes could be a byproduct of external influencers like smoking (10), as opposed to intrinsic pathophysiological ties (8). Such nuances introduce biases when scrutinizing outcomes tethered to both ailments, obfuscating the delineation of a direct linkage between COPD and T2DM.

Mendelian Randomization (MR) is an innovative analytical tool that employs genetic variables to elucidate causal dynamics between exposures and outcomes (11, 12). By harnessing the association between genetic variants and specific modifiable exposures, MR affords insights into the causal ramifications of such exposures. Given the inherent randomness of genetic inheritance during conception, MR stands insulated from external confounders. Furthermore, the immutable nature of genetic variations, fixed at conception, shields the analysis from subsequent health or lifestyle influences (13). In contrast to conventional observational studies, MR offers a fortified stance against typical confounders and biases, grounding causal inferences in a more solid bedrock. Due to the predetermination of genetic variations, MR sidesteps pitfalls like reverse causation. It also leverages these variations as surrogates for prolonged exposures, refining assessments and countering the errors and biases typical of observational research (14). Under the appropriate conditions, MR can be harnessed in expansive research frameworks to probe if COPD indeed acts as a precursor to T2DM.

In our research, we employed Mendelian randomization analyses on separate samples for COPD and T2DM with the goal of elucidating a causal link between these two disorders. If such a causal association is substantiated, strategies aimed at treating COPD could potentially be leveraged to mitigate the onset and progression of T2DM.

2 Method

2.1 Exposure populations

For our COPD susceptibility investigation, we analyzed data from 257,811 individuals spanning 25 studies, all of European ancestry. We defined COPD specifically using prebronchodilator spirometry criteria: a Forced Expiratory Volume in the first second (FEV1) less than 80% of the predicted value, along with a FEV1 to Forced Vital Capacity (FVC) ratio under 0.7., we pinpointed 82 SNPs, distinguishing 35,735 COPD cases from 222,076 controls. This GWAS took intoaccount age, age^2, gender, height, principal components, and smoking habits (14).

2.2 Outcome populations

In our research on T2DM, we utilized GWAS summary data from Japan, corresponding to IEU identifier: ebi-a-GCST010118, encompassing 433,540 individuals predominantly from East Asian backgrounds. To define the T2DM case-control, each included study adhered to at least one or more of these established criteria (1): A confirmed doctor's diagnosis or ongoing diabetes medication regimen (2), fasting blood glucose levels of ≥126mg/dL (3), fasting blood glucose levels exceeding 200mg/dL (4), random blood glucose readings of ≥200mg/dL, or (5) HbA1c levels of ≥6.5%. Following these guidelines, our sample consisted of 77,418 T2DM diagnosed patients and 356,122 control subjects. It's noteworthy that the GWAS factored in adjustments for age, gender, and body mass index [16]. The research design is shown in Figure 1. For further details on the GAWS phenotype definitions related to COPD and T2DM, as well as baseline data, please refer to the Supplementary Material (15).

2.3 Mendelian Randomization analysis

Mendelian Randomization (MR) studies are grounded in three core assumptions: a. The genetic variants utilized as Instrumental Variables (IVs) should have a robust association with the targeted risk factors. b. These IVs should not correlate with other potential confounders affecting the link between risk factors and outcomes. c. The connection between the IV and the outcomes should be entirely mediated through the risk factors (13).

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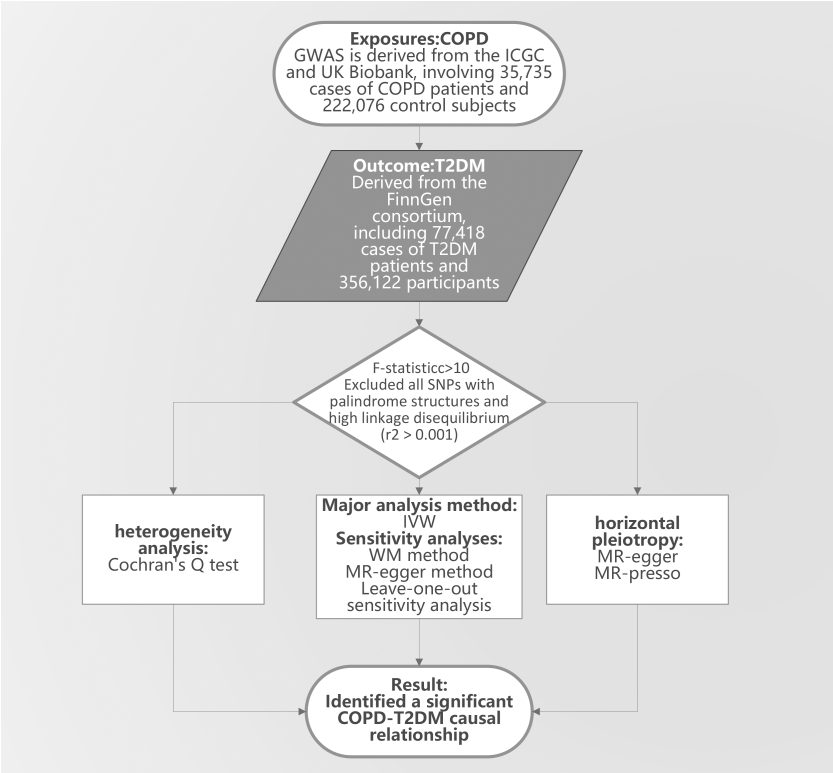

FIGURE 1
The study design. COPD, Chronic Obstructive Pulmonary Disease; T2DM, Type 2 diabetes mellitus; GWAS, genome-wide association study; IVW, Inverse Variance Weighting; MR-egger, Mendelian Randomization-Egger Regression; WM, Weighted Median; MR-presso, Medelian Randomization Pleiotropy RESIdual Sum and Outlier.

With these principles as our foundation, we cherry-picked SNPs showing a significant correlation to 'COPD' ($p < 5 \times 10^{-8}$) to serve as our IVs. We gauged the strength of the link between these IVs and exposure by computing their F-statistics (F-statistics = β_2/SE_2). SNPs presenting f-statistics <10 were discarded since larger f-statistics suggest the genetic markers cause phenotypic variations, with ensuing results diverging due to these variations (16). We then underwent LD-clumping ($r^2 > 0.001$) and sidestepped all palindromic SNPs (17–19). In our broad-spectrum ensitivity scrutiny, we vetted the remaining SNPs on the PhenoScanner portal and filtered out those linked with cardiovascular ailments, hypertension, and hyperlipidemia (20, 21). The MR-presso method facilitated our test for horizontal pleiotropy, allowing us to eject outliers (22). When MR pinpointed SNPs inherently tied to exposure in the findings, we inferred a causal influence of the exposure on the results.

Our main analytic tool was the Inverse Variance Weighting (IVW) method, which synthesized SNP causal impacts, counterbalanced by the ratio estimate variances (19, 23). The MR-egger regression's slope rendered authentic causal parameters (24). Complementarily, the Weighted Median technique, assuming the validity of 50% of the IVs, fine-tuned the reliability of causal interpretations, curbing Type I errors (25).

We employed the MR-egger intercept to gauge horizontal pleiotropy, spotting its presence if the intercept deviated from zero (26). In scenarios sans horizontal pleiotropy, the principal causal effect was drawn from the IVW method's random effects. Cochran's Q test came into play to discern heterogeneity, which, if present, contravenes the IV tenet (23). To reinforce our findings' solidity, we implemented a eave-one-out sensitivity analysis, sequentially eliminating each SNP to pinpoint anomalies.

In this study, we utilized Odds Ratios (OR) and 95% confidence intervals to elineate the causal relationship between exposure and outcome. We considered a causal relationship as established when it was consistently evidenced across both heterogeneity tests and sensitivity analyses. All statistical analyses were conducted using R version 4.3.1 in R Studio, with a primary reliance on the TwoSampleMR (version 0.5.7) and MR-PRESSO packages (version 1.0.0) for the two-sample MR analysis.

3 Results

We identified 26 independent SNPs with a robust association with T2DM, serving as instrumental variables. All exhibited an f-statistic exceeding 10, effectively ruling out weak instrument bias. Interestingly, the MR-Egger intercept closely aligned with 0 (p=0.263), suggesting no evidence of horizontal pleiotropy in our analysis (as illustrated in Figure 2). On the other hand, the initial MR-PRESSO global test returned a P-value below 0.05. Upon exclusion of three outlier SNPs — namely "rs4888379", "rs7068966", and "rs76841360" — the subsequent MR-PRESSO

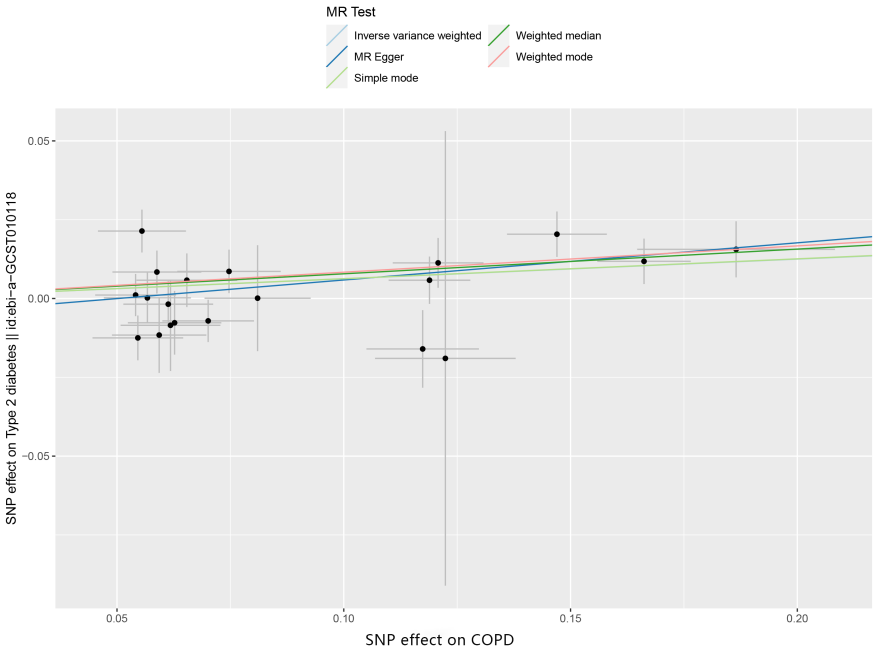

FIGURE 2
Scatter plot depicting the casual effevt of COPD on the odds ratio for T2DM.

global test yielded a p-value exceeding 0.05. This result, post the outlier exclusion, supports the absence of horizontal pleiotropy in the MR-PRESSO findings. Furthermore, Cochran's Q test detected no heterogeneity (p>0.05, Q=27.080). Given this lack of heterogeneity, there was no notable precision disparity between the random and fixed effects models, prompting our choice of the IVW random effects model for our analyses (27).

The IVW random effects model returned an OR of 1.06 (95%CI: 1.01-1.11, P=0.006), while the MR-Egger regression reported an OR of 1.13 (95%CI: 1.01-1.25, p=0.039). Additionally, the weighted median test registered an OR of 1.08 (95%CI: 1.02-1.14, p=0.005) (See Figure 3). Conclusively, the trio of IVW, MR-Egger, and weighted median methods all reinforce a causal link between COPD and T2DM, firmly positing COPD as a predisposing factor for T2DM. In particular, our IVW findings suggest that individuals with COPD are faced with a heightened risk of T2DM by approximately 6.5% in comparison to those without COPD. Importantly, the leave-one-out sensitivity analysis underscored the consistency and reliability of our findings, establishing that the omission of any single SNP failed to considerably sway our overarching results.

4 Discussion

COPD and T2DM, both chronic diseases of global concern, have been the focus of numerous studies due to their widespread prevalence. While many observational studies consistently report

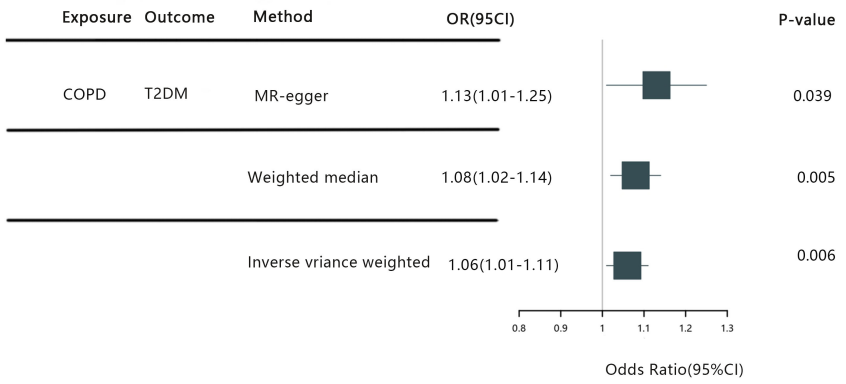

FIGURE 3
COPD, Chronic Obstructive Pulmonary Disease; T2DM, Type 2 diabetes mellitus; IVW, Inverse Variance Weighting; MR-egger, Mendelian Ra.

an elevated incidence of T2DM among COPD patients (3–6), our findings provide pivotal evidence of a causal link, positioning COPD as a significant risk factor for T2DM. Significantly, our research stands out as the inaugural MR study delving into the causal influence of COPD on T2DM. Our conclusions resonate with the outcomes of several prior studies that also hint at the possible link between COPD and the emergence and progression of T2DM. For instance, a retrospective analysis by Chao-Shsun Lin et al. from Taiwan brought to light the augmented risk of T2DM in COPD patients, even in the absence of acute exacerbations, relative to their non-COPD counterparts. In line with this, T2DM patients with antecedent COPD had heightened ICU admissions, pneumonia instances, and mortality rates (28). In another enlightening study from Taiwan, Charles T.-C. Lee et al. affirmed that, even after accounting for potential confounders like hypertension, coronary heart disease, and age among others, COPD persisted as a standalone risk factor for T2DM (4). Corroborating this trend, Birgitte F's nationwide observational research from Denmark pinpointed a risk increment of diabetes in COPD-afflicted individuals, which was approximately 20% higher than in those without COPD (3).

While some research posits a lack of significant correlation between COPD and diabetes onset, it's imperative to acknowledge the association of COPD with a heightened diabetes risk (risk ratio = 1.45, 95% CI 1.04-2.03) (29). An illustrative example comes from a population-based survey by Hyejin Joo et al. from Korea, which found no distinct association between COPD and diabetes (30). Nevertheless, a caveat remains: many such studies are region-specific cross-sectional investigations, potentially reducing their global applicability. A critical challenge in these studies lies in the ambiguous diagnosis criteria for COPD, with a heavy reliance on either self- reported data or physician diagnoses, thereby obscuring the causal nexus. The lacunae in these findings accentuate the need for more compelling evidence to establish the COPD-T2DM causality.

Mendelian randomization (MR) has emerged as a potent statistical approach, harnessing genetic variances as instrumental variables to derive causal inferences. Capitalizing on the inherent randomness of genetic allocation, MR offers more causation-aligned estimates, enhancing the evidence's robustness. A distinct edge MR holds is its ability to treat genetic variations as inherent randomized trials, side- stepping ethical or feasibility constraints typically encountered in traditional research paradigms. Amplifying its potency, MR adeptly taps into vast genetic data pools and GWAS findings, facilitating refined causal conclusions (13). Embarking on this backdrop, our investigation pioneers the MR exploration into the COPD-T2DM dynamics. Predominantly, we employed the IVW random effects model for causal delineation, unearthing a marked causal linkage between COPD and T2DM.

Complementing this, we integrated MR-Egger regression's slope estimation, the weighted median method, and a rigorous leave-one-out sensitivity assessment. Concordantly, all methodologies reinforced the IVW's conclusions. Notably, our assessment remained unmarred by pleiotropy, as evidenced by both MR-Egger intercept and MR-PRESSO global tests, and the Cochran's Q test underscored a heterogeneity-free landscape. Collectively, these rigorous assessments underpin our conviction regarding the causal interplay between COPD and T2DM presented in this study.

The association between COPD and T2DM can be understood through a multifaceted lens. It's well-documented that genetic predispositions significantly influence the susceptibility to T2DM: individuals with a T2DM-afflicted parent face a 40% lifetime risk, which amplifies to 70% when both parents are affected (31). Corroborating this genetic interplay, a comprehensive cohort study from Denmark unveiled a correlation coefficient of 0.43 between COPD and T2DM, hinting at intertwined genetic underpinnings of the two conditions (32). Such findings bolster the hypothesis that the co-occurrence of COPD and T2DM may stem from mutual genetic factors.

Inflammation, especially in the innate immune system, is a key link between COPD and T2DM (33, 34). The NLRP3 inflammasome, central to this process, releases cytokines like IL-1β and IL-18, which are important in COPD (33) and disrupt insulin signaling in T2DM. Additionally, the gut microbiota's interaction with the NLRP3 inflammasome influences insulin sensitivity and signaling (34). Oxidative stress is a key factor in both COPD and T2DM (35). In T2DM, elevated reactive oxygen species (ROS) levels decrease insulin sensitivity, leading to insulin resistance. This affects the β-cells in the islets, reducing insulin secretion. Oxidative stress impairs mitochondrial ATP production and activates stress pathways, disrupting insulin signaling (36). In COPD, patients exhibit autoantibodies against carbonyl-modified self-proteins due to oxidative stress, causing lung tissue damage. Oxidative stress also attracts immune cells, increasing IL-17 and IL-18 levels and contributing to lung injury (37). We speculate that oxidative stress may contribute to insulin resistance in patients with COPD (38).

Diving into the daily lives of COPD patients, sedentary habits, like extended, sitting or lying durations, might pave the way for muscle-atrophying obesity, a precursor for T2DM (39–41). Obesity, unequivocally, is a heavyweight risk factor for T2DM (42). On another note, the medications for COPD might also play a part. Specifically, the use of inhaled corticosteroids (ICS) — a staple in COPD management— has been tied to T2DM onset (43). Mechanistically, glucocorticoids might sabotage.β-cell function and amplify insulin resistance (44), providing a rationale for why COPD might accentuate T2DM risk.

To incorporate the research findings into public health campaigns, the focus should be on educating about the COPD-T2DM link, advocating for regular check-ups and lifestyle changes for COPD patients, and stressing the importance of early intervention for T2DM prevention and management. This approach can also inform healthcare policies for better COPD patient care, considering their increased T2DM risk.

In this pioneering study, we leveraged two extensive GWAS datasets to establish, for the first time, a causal link between COPD and T2DM. This discovery has significant implications for the treatment and prevention of T2DM. Public health initiatives should incorporate these findings, focusing on educating about the COPD-T2DM connection and advocating for regular health check-ups and lifestyle changes in COPD patients. These measures

are crucial for early T2DM intervention. Moreover, this insight can influence healthcare policies to improve care for COPD patients, given their increased risk of T2DM. Additionally, our study emphasizes the importance of a careful risk-to- benefit assessment when prescribing corticosteroids. We minimized biases by selecting European cohorts for COPD exposure and Asian cohorts for T2DM outcomes. Our methodological rigor, evident in the selection of instrumental variables with high F- statistics, strengthens the reliability of our findings. However, the study has limitations, such as unaddressed confounders like dietary habits and drug use, and it doesn't explore the specific biological mechanisms connecting COPD to T2DM. Future research should focus on these aspects, using molecular, genetic, and more detailed longitudinal studies tracking COPD medication use and diabetes onset. to further elucidate this relationship.

5 Conclusion

In conclusion, our article stands as the pioneering work utilizing the MR method to probe the causal relationship between COPD and T2DM. We not only identified but also quantified the causal effect of COPD on T2DM. Our findings offer valuable insights for clinicians, guiding the management, treatment, and prevention strategies for patients co-diagnosed with COPD and T2DM. Moreover, this research lays a foundational bedrock for further investigations into the underlying mechanisms linking COPD and T2DM.

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

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

TW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JL: Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. CH: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – review & editing. XW: Conceptualization, Methodology, Project administration, Validation, Writing – review & editing. XF: Methodology, Software, Supervision, Writing – review & editing. CY: Conceptualization, Data curation, Methodology, Supervision, Validation, Writing – review & editing. ML: Conceptualization, Data curation, Writing – review & editing. SC: Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, 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.2024.1302641/full#supplementary-material

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Differential effects of fish-oil and cocoa-butter based high-fat/high-sucrose diets on endocrine pancreas morphology and function in mice

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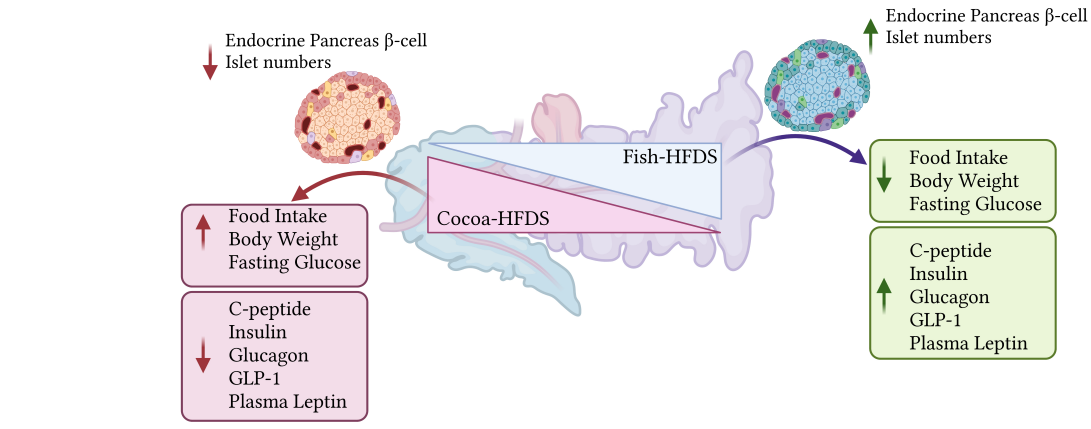
Introduction: A high-fat/high-sucrose diet leads to adverse metabolic changes that affect insulin sensitivity, function, and secretion. The source of fat in the diet might inhibit or increase this adverse effect. Fish oil and cocoa butter are a significant part of our diets. Yet comparisons of these commonly used fat sources with high sucrose on pancreas morphology and function are not made. This study investigated the comparative effects of a fish oil-based high-fat/high-sucrose diet (Fish-HFDS) versus a cocoa butter-based high-fat/high-sucrose diet (Cocoa-HFDS) on endocrine pancreas morphology and function in mice.

Methods: C57BL/6 male mice (n=12) were randomly assigned to dietary intervention either Fish-HFDS (n=6) or Cocoa-HFDS (n=6) for 22 weeks. Intraperitoneal glucose and insulin tolerance tests (IP-GTT and IP-ITT) were performed after 20-21 weeks of dietary intervention. Plasma concentrations of c-peptide, insulin, glucagon, GLP-1, and leptin were measured by Milliplex kit. Pancreatic tissues were collected for immunohistochemistry to measure islet number and composition. Tissues were multi-labelled with antibodies against insulin and glucagon, also including expression on Pdx1-positive cells.

Results and discussion: Fish-HFDS-fed mice showed significantly reduced food intake and body weight gain compared to Cocoa-HFDS-fed mice. Fish-HFDS group had lower fasting blood glucose concentration and area under the curve (AUC) for both GTT and ITT. Plasma c-peptide, insulin, glucagon, and GLP-1 concentrations were increased in the Fish-HFDS group. Interestingly, mice fed the Fish-HFDS diet displayed higher plasma leptin concentration. Histochemical analysis revealed a significant increase in endocrine pancreas β-cells and islet numbers in mice fed Fish-HFDS compared to the Cocoa-HFDS group. Taken together, these findings suggest that in a high-fat/high-sucrose dietary setting, the source of the fat, especially fish oil, can ameliorate the effect of sucrose on glucose homeostasis and endocrine pancreas morphology and function.

KEYWORDS

fish oil, cocoa butter, high-fat/sucrose diet, insulin, glucagon, α-cell, β-cell



GRAPHICAL ABSTRACT

1 Introduction

The macronutrients in the diet play an important role in developing metabolic syndrome (1). It has been found that excessive consumption of fat and sugar (a high-energetic diet) is a risk factor for metabolic diseases, and the quality and quantity of ingested dietary components are directly correlated with obesity and diabetes (2, 3). High fat and sugar diet impairs peripheral glucose transport, which is associated with obesity and insulin resistance (4). Type 2 diabetes is commonly associated with impairments in insulin sensitivity and secretion. Macronutrient composition of the diet determines the quality of insulin action (5, 6).

In vivo, dietary factors such as high-fat or high-sucrose diets impair insulin action (1, 5–7). Using a model of insulin resistance (8, 9), studies have shown that a high-fat/high-sucrose diet is associated with impaired glucose-stimulated insulin secretion (GSIS) that might affect pancreatic β-cells (10). Long-term exposure to high quantities of fat can lead to β-cell dysfunction (8). Indeed, a high-fat diet has been shown to reduce GSIS despite an absolute increase in the islet insulin content (3). Moreover, diets rich in saturated fatty acids play a role in obesity and insulin resistance (11). However, the type of dietary fat affects the endocrine pancreas function and morphology (12), as well as insulin secretion and sensitivity (7), and is associated with obesity and metabolic disease (11). Similarly, animals fed a high sucrose diet show deleterious effects on glucose homeostasis. Rats fed a high sucrose diet for an extended period developed hyperglycemia and insulin resistance (13, 14), while mice fed high sucrose diet developed glucose intolerance and impaired insulin secretion (9).

Various studies have emphasized the beneficial effects of dietary fish oil and its protective role against metabolic diseases. Dietary fish oil can improve or reverse dyslipidemia, adiposity, β-cell dysfunction, insulin secretion, and insulin action on glucose metabolism (1, 8, 14, 15). A high-fish oil diet has been shown to attenuate obesity and related systemic effects such as insulin resistance (11). In addition, supplementation of a high-fat/high-sucrose diet with fish oil restores glucose homeostasis and insulin sensitivity without changing plasma insulin concentration (1, 14, 16). Furthermore, fish oil supplementation can improve islet and β-cell hypertrophy with the amelioration of insulin resistance (17).

In the present study, we aimed to compare the effects of distinct dietary source of high fat (fish oil versus cocoa butter) in the context of a high-fat/high-sucrose diet on glucose tolerance, insulin resistance and secretion, and endocrine pancreas morphology in mice.

2 Research design and methods

2.1 Experimental design

The study was approved by the Animal Care and Ethics Committee of the Dasman Diabetes Institute and registered under the identifier RA AM 2016-007. All experiments were conducted in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals.

C57BL/6 mice were purchased from the Jackson Laboratory (Bar Harbor, Maine, USA) and housed in a temperature-controlled environment (23°C) with a relative humidity of 50–60% under 12 h/12 h light/dark cycles. Mice were provided with a standard chow diet and water *ad libitum*.

At 8–10 weeks of age, 12 male mice were randomly assigned to one of two calorie-equivalent diets containing high sucrose and 45% fat as either fish oil-based high-fat/high-sucrose diet (Fish-HFDS; D21042007i, Research Diets Inc, USA) or cocoa butter-based high-fat/high-sucrose diet (Cocoa-HFDS; D21042206i, Research Diets Inc, USA) (Table 1) (n = 6/group) and the animals were fed on these diets for 22 weeks. The body weights were measured prior to the diet intervention and weekly during the intervention, along with their food intake.

2.2 Intraperitoneal glucose tolerance test

At 20 weeks of dietary intervention, mice were fasted overnight (12 hours) with free access to water. Fasting blood glucose

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concentration was measured at 0 minutes, and then, a bolus infusion of glucose (1 g/kg body weight) was administered IP to each mouse. Blood glucose concentrations were measured at 10, 20, 30, 60, 90, and 120 minutes post-glucose infusion using a portable glucometer (Accu-chek, Roche Diagnostic, Germany).

2.3 Insulin tolerance test

At 21 weeks of dietary intervention, mice were fasted for 4 hours, and a bolus infusion of insulin (0.8 U/kg body weight) was administered IP. Blood glucose concentrations were measured at 0, 10, 20, 30, 60, 90, and 120 minutes post-insulin infusion using a portable glucometer.

2.4 Organ/tissue collection

After 22 weeks of dietary intervention, the mice were euthanized. Organs were identified, removed, weighed, and selected tissues were preserved. The pancreas were fixed in 10% neutral buffered formalin for 24 hours and then stored in 70% ethanol at 4°C until processing. Blood samples were collected from the heart, and plasma was separated and stored at -80°C for further analysis.

2.5 Plasma metabolic markers

The concentrations of plasma metabolic markers were measured using a Milliplex kit (MILLIPLEX $_{MAP}$ mouse metabolic magnetic bead panel kit, Millipore, USA), in accordance with the manufacturer's instructions.

TABLE 1 Nutritional composition of HFDs.

	Cocoa-HFDS	Fish-HFDS	Chow	HFD
Components %				
Protein	23.7	23.7	14.3	23.7
Carbohydrate	41.4	41.4	6.0	41.4
Fat	23.6	23.6	5.9	23.6
Kcal/gm	4.73	4.73	3.86	4.73
Ingredient %				
L-Cystine	3.0	3.0	0.21	3.0
Corn Starch	20.6	20.6	47.7	195.6
Sucrose	175	175	1.07	0
Cocoa Butter	202.5	0	0	0
Menhaden Oil	0	202.5	0	0
Palm Oil	0	0	0	202.5
Minerals	10	10	10	10
Vitamin Mix	10	10	10	10

2.6 Immunohistochemistry

The fixed pancreas was paraffin-embedded, and tissues were microsectioned by microtomy and labelled with multiple immunofluorescent antibodies, as previously described (18). Briefly, tissue samples on slides were deparaffinized and rehydrated, and then antigen retrieval was carried out. Samples were blocked with 10% goat serum and the following primary antibodies were used for each slide: guinea pig anti-insulin, rabbit anti-glucagon, rabbit anti-insulin and guinea pig anti-pdx1 antibodies. Secondary antibodies used were goat anti-guinea pig Alexa Flour 488 and goat anti-rabbit Alexa flour 546 antibodies (Table 2). The antibodies were visualized using an Olympus BX53 upright microscope connected to an Olympus DP73 camera (Olympus, Tokyo, Japan) and an inverted Zeiss LSM710 spectral confocal microscope (Carl Zeiss, Gottingen, Germany). Insulin- and glucagon-positive areas were digitally quantified using ImageJ (Fiji is just ImageJ version 2.9.0/1.53t, Maryland, USA).

2.7 Endocrine cell mass calculation

β-cells and α-cells were marked and calculated as areas positive for insulin and glucagon staining, respectively. The β-cell area is an area of both positive insulin area and β-cell numbers.

$$\beta - \text{cell mass(mg)} = \frac{\beta - \text{cell area per field of view}(\mu m^2) \times \text{pancreas weight(mg)}}{\text{Tissue area per field of view}(\mu m^2)}$$

The α-cell mass was measured from the above equation (18), using glucagon positive area and α-cell numbers. The total islet cell area was calculated as a sum of the β-cell and α-cell areas per field of view.

2.8 Real-time quantitative RT-PCR

Total RNA was extracted from pancreatic tissues using RNeasy Mini Kit (Qiagen, Valencia, CA, USA) as per the manufacturer's instructions. The cDNA was synthesized using 1 µg of total RNA using a high-capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, USA). Real-time PCR was performed on a QuantStudio™ 5 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) using an RT^2 SYBR Green qPCR Mastermix (Qiagen, USA). Each reaction contained 50 ng cDNA that was amplified with primers specific to genes including *Pdx1*, *Ins1*, *Mafa*, *Gcg*, *Mafb*, *and Gapdh* (Table 3), selected from PrimerBank and primer blast website. The threshold cycle (Ct) values of the *Pdx1* gene expression were normalized to the expression of housekeeping gene Gapdh and the expression of other endocrine gene markers was normalized to the expression of *Pdx1* gene. The amounts of target mRNA relative to the control were calculated using the -2ΔΔCt-method. Relative

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TABLE 2 Primary and secondary antibodies used insulin and glucagon staining.

Target/Protein	Host	Clonality	Isotype	Dilution	Supplier	Catalogue #
Insulin	Guinea pig	Polyclonal	IgG	1:150	ThermoFisher	PA1-26938
Glucagon	Rabbit	Polyclonal	IgG	1:150	Cell Signaling	2760
Insulin	Rabbit	Polyclonal	IgG	1:300	Cell Signaling	4590
PDX1	Guinea pig	Polyclonal	IgG	1:300	Abcam	AB47308
Anti-guinea pig Alex Flour 488	Goat	Polyclonal	IgG (H+L)	1:500	ThermoFisher	A11073
Anti-rabbit Alex Flour 546	Goat	Polyclonal	IgG (H+L)	1:500	ThermoFisher	A10040

mRNA expression was shown as a fold expression level over that of control expression.

2.9 Statistical analysis

Statistical analysis was conducted using JMP (version 17.0.0, SAS Institute Inc., North Carolina, USA) and GraphPad Prism (version 9.5.0, GraphPad Software, Inc., California, USA). Data were analyzed by two-way analysis of variance (ANOVA). Significant differences identified by ANOVA were followed by *post hoc* analysis student t-test. The area under the curve (AUC) for IP-GTT and ITT was calculated using the trapezoid rule. Pearson's correlation was used to examine bivariate relationships, and the correlation coefficient (r) was calculated. $P \leq 0.05$ was considered statistically significant. Results are reported as mean ± SEM values.

3 Results

3.1 Effect of fish-HFDS and cocoa-HFDS on food intake and weight gain

Bodyweight and food intake were monitored in both groups throughout the diet intervention. There was no significant difference in the starting body weight between Fish-HFDS and Cocoa-HFDS group (Figure 1A). However, after the dietary intervention, body weight of Cocoa-HFDS group was significantly ($P = 0.0001$) higher than that of Fish-HFDS group (Figure 1B). In fact, the Cocoa-HFDS group gained five times more weight than the Fish-HFDS group (Figure 1C). The Fish-HFDS group had significantly ($P = 0.003$) lower food intake compared to Cocoa-HFDS, which was consistent with the steady low increase in body weight (Figure 1D).

3.2 Effect of fish-HFDS and cocoa-HFDS on glucose homeostasis and islet function

To investigate the effect of Fish-HFDS and Cocoa-HFDS on glucose homeostasis, IP-GTT and ITT were performed. The fasting blood glucose concentration was significantly ($P < 0.0001$) less in Fish-HFDS group (6.6 ± 0.3 mmol.L^{-1}) compared to Cocoa-HFDS group (Figure 2A; Table 4). IP-GTT showed that clearance of plasma glucose concentration following intraperitoneal injection of glucose was significantly ($P = 0.04$) higher in mice fed Fish-HFDS compared to mice fed Cocoa-HFDS (Figure 2B). Furthermore, the improved glucose tolerance was reflected in the reduction of the AUC $_{IP\text{-}GTT}$ (462 ± 112 µg.L^{-1}.min^{-1}) (Figure 2C). Regarding ITT, the mice fed Fish-HFDS showed a greater reduction in blood glucose concentrations after intraperitoneal injection of insulin compared to mice fed Cocoa-HFDS (Figure 2D). Moreover, the increased insulin sensitivity in mice fed Fish-HFDS was displayed by the reduction of the AUC $_{ITT}$ (327 ± 35 µg.L^{-1}.min^{-1}, $P = 0.0006$) compared to mice fed Cocoa-HFDS (Figure 2E).

Next, we measured the fasting blood insulin in both groups to assess whether Fish-HFDS and Cocoa-HFDS had distinct effects on

TABLE 3 List of primers.

Target/Protein	
mPdx1-F1	CCCCAGTTTACAAGCTCGCT
mPdx1-R1	CTCGGTTCCATTCGGGAAAGG
mIns1-F1	CACTTCCTACCCCTGCTGG
mIns1-R1	ACCACAAAGATGCTGTTTGACA
mGCG-F1	TTACTTTGTGGCTGGATTGCTT
mGCG-R1	AGTGGCGTTTGTCTTCATTCA
mMAFA-F1	AGGAGGAGGTCATCCGACTG
mMAFA-R1	CTTCTCGCTCTCCAGAATGTG
mMAFB-F1	TTCGACCTTCTCAAGTTCGACG
mMAFB-R1	TCGAGATGGGTCTTCGGTTCA
mGAPDH-F1	TCGGTGTGAACGGATTTG
mGAPDH-R1	GGTCTCGCTCCTGGAAGA
mBactin-F	AAATCGTGCGTGACATCAAA
mBactin-R	AAGGAAGGCTGGAAAAGAGC
mS18-f	CAGCTCCAAGCGTTCCTGG
mS18-r	GGCCTTCAATTACAGTCGTCTTC

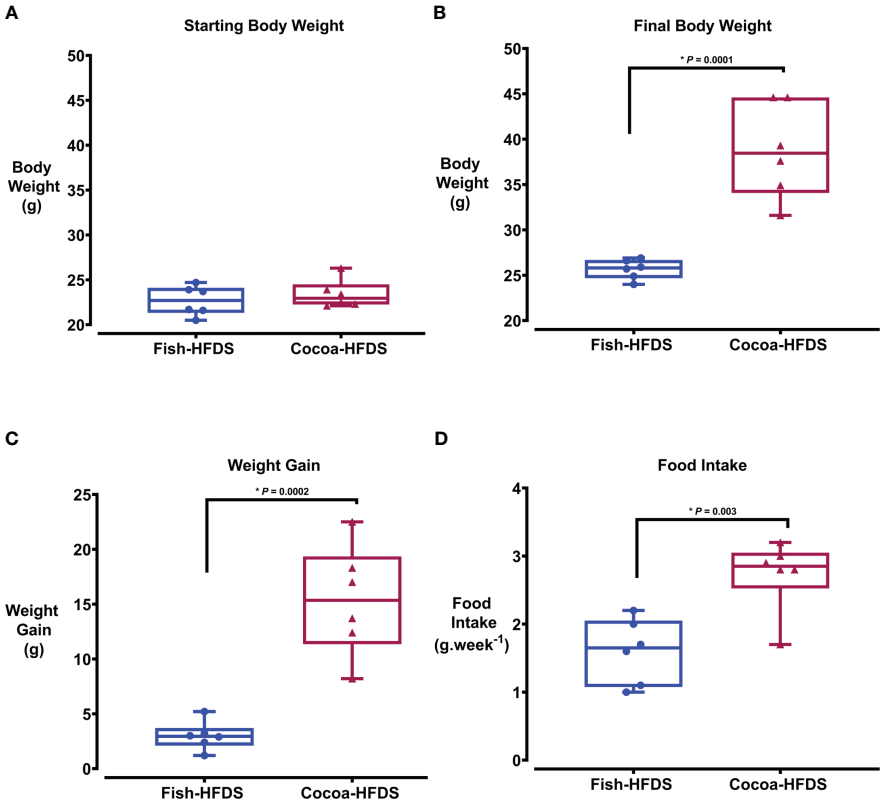

FIGURE 1
The Effect of different fat-based diets (Fish-HFDS and Cocoa-HFDS) on weight gain and food intake in mice. **(A)** The starting body weight of both groups. **(B)** The final body weight of both groups. **(C)** Weight gain after the diet intervention. **(D)** Food intake during the diet intervention. Data are mean with ± SEM. P-values for differences between groups by ANOVA and Student's t-test.

blood insulin. There was a significant difference in fasting plasma insulin concentrations between the Fish-HFDS and Cocoa-HFDS groups, with mice fed Fish-HFDS having higher concentrations (1023 ± 209 pg.mL^{-1}, P = 0.02) (Figure 2F; Table 4).

Glucagon is a peptide hormone secreted from α-cells of the pancreatic islets, and its secretion is linked to plasma insulin levels. Therefore, we wanted to see whether these different high-fat/high-sucrose diets had distinct effects also on blood glucagon concentrations. Our results showed that mice fed Fish-HFDS displayed high fasting blood glucagon concentrations compared to mice fed Cocoa-HFDS (87 ± 14 pg.mL^{-1}, P = 0.04) (Figure 2G; Table 4).

3.3 Effect of fish-HFDS and cocoa-HFDS on plasma metabolic markers

Metabolic hormones are affected by high-fat/high-sucrose diets and obesity. We wanted to see whether Fish-HFDS and Cocoa-HFDS had distinct effects on the metabolic markers. Our results showed that glucagon-like peptide (GLP-1) concentrations were significantly (108 ± 20 pg.mL^{-1}, P = 0.002) higher in Fish-HFDS group compared to Cocoa-HFDS group (Figure 3A). A negative correlation was observed between food intake and GLP-1 in both groups (Fish-HFDS group: r = -0.97, P = 0.001; Cocoa-HFDS group: r = -0.98, P = 0.005) (Figure 3B). The Fish-HFDS group had significantly (991 ± 14 pg.mL^{-1}, P = 0.0005) higher C-peptide concentrations than the Cocoa-HFDS group (Figure 3C). Plasma leptin concentrations were significantly (3752 ± 871 pg.mL^{-1}, P = 0.006) higher in Fish-HFDS group compared to Cocoa-HFDS group (Figure 3D). An inverse correlation was found between food intake and leptin levels in the Fish-HFDS group only (r = -0.94, P = 0.003) (Figure 3E). Other metabolic markers such as secretin, peptide YY, interleukin (IL)-6, pancreatic polypeptide, glucose-dependent insulinotropic polypeptide-total, and tumor necrosis factor (TNF-α) were also measured, but no significant differences were found between the two dietary groups (Table 5).

3.4 Effect of fish-HFDS and cocoa-HFDS on endocrine pancreas morphology and integrity

When pancreas sections were double stained for insulin and glucagon, the endocrine sections of the pancreas represented by the islets of Langerhans were distributed within the exocrine section of the pancreas (Figure 4). Our pancreatic histology data showed that α-cells, β-cells, and islet numbers were higher in Fish-HFDS group compared to Cocoa-HFDS group. However, only β-cells and islet numbers reached statistical significance (P = 0.025, P = 0.03,

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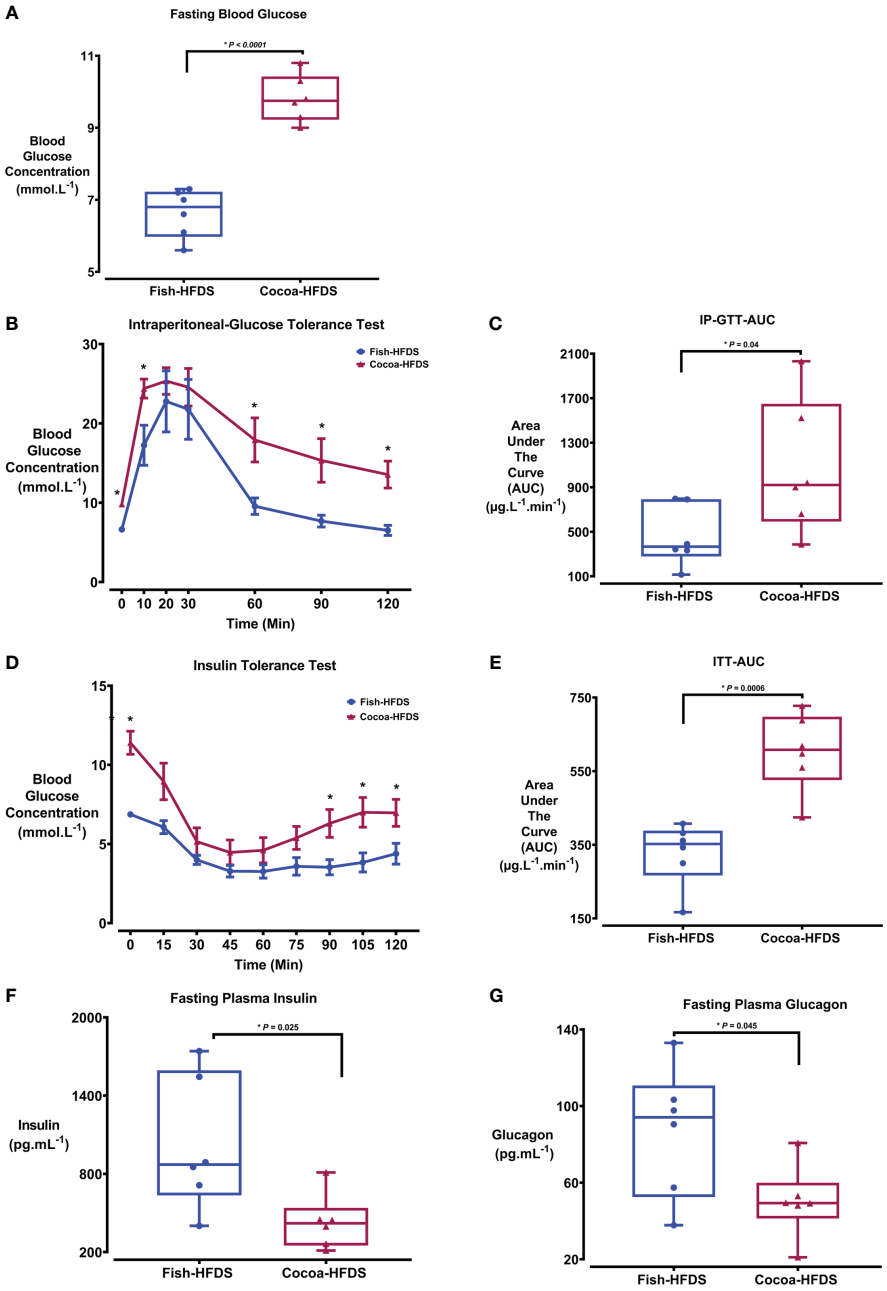

FIGURE 2
The Effect of different fat-based diets (Fish-HFDS and Cocoa-HFDS) on glucose insulin and glucagon. **(A)** Fasting blood glucose concentration of both groups. **(B)** Intraperitoneal glucose tolerance test (IPGTT). **(C)** AUC $_{IP\text{-}GTT}$. **(D)** Insulin tolerance test (ITT). **(E)** AUC $_{ITT}$. **(F)** Fasting plasma insulin concentration. **(G)** Fasting plasma glucagon concentration. Data are mean with ± SEM. *P*-values for differences between groups by ANOVA and Student's t-test. The asterisk (*) represent a P-value of ≤ 0.05.

respectively) (Figures 5A, B). Insulin and glucagon-positive areas and α-cells, β-cells, and islet mass were similar between two groups. As a key regulatory marker of endocrine pancreas function, the expression of Pdx1 was detected which differed non-significantly between two groups (Figure 6). In addition, we also compared gene expression of *Ins1*, *Gcg* and several critical transcriptional regulators of β-cell (*Pdx1*, *Mafa*) and α cell (*Pdx1*, *Mafb)* development. Except the *Ins1* gene expression ($P = 0.008$), all other markers differed non-significantly between two dietary groups (Table 6).

4 Discussion

The present study investigated and compared the effects of fish oil and cocoa butter as high-fat/high-sucrose diets on glucose tolerance, β-cell function, insulin sensitivity, and endocrine pancreas morphology and integrity in mice. This study used a mouse model to mimic a human nutritional setting of intake of high-fat diets. The components and ingredients of our diets were similar to the regular HFD, with the difference in the source of fat.

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TABLE 4 The Effect of different fat-based diets (Fish-HFDS and Cocoa-HFDS) on plasma fasting blood glucose, insulin, and glucagon.

	Group				Significance (*P*-value)
	Cocoa-HFDS	Fish-HFDS	Chow	HFD	
	N=6	N=6	N=6	N=6	
	Mean	Mean	Mean	Mean	
F.B Glucose	11.5 ± 0.7 [b]	6.5 ± 0.2 [a]	5.9 ± 0.3 [a]	10 ± 0.6 [b]	**< 0.0001**
Insulin	429 ± 86 [b]	1023 ± 209 [a]	2070 ± 216 [a]	537 ± 103 [b]	**0.02**
Glucagon	50 ± 8 [b]	87 ± 14[a]	83.5 ± 9 [a]	57 ± 14 [b]	**0.04**

Bold font indicates significance on ANOVA. Non-matching letters indicate a significant difference ($P < 0.05$) amongst groups on post hoc analysis. Cocoa-HFDS, High-fat-high-sucrose diet with Cocoa butter; Fish-HFDS, High-fat-high-sucrose diet with Fish oil; HFD, normal high-fat diet; F.B Glucose, fasting blood glucose.

High-sucrose diets are known to increase body weight (2, 6, 10); however, when supplemented with fish oil, using different models, animals either gained (8, 19, 20), lost (21, 22), or showed no change (2, 10, 14, 15, 23–25) in their body weight. Here, we show that fish oil fat source in high fat/high sucrose diet does not, in fact, increase the body weight when compared to a high-fat diet based on cocoa butter as fat source. To determine whether the increase in body weight was due to increased food intake, we assessed the dietary intake of the mice. To this end, the Fish-HFDS group showed a lower food intake compared to Cocoa-HFDS group, which was

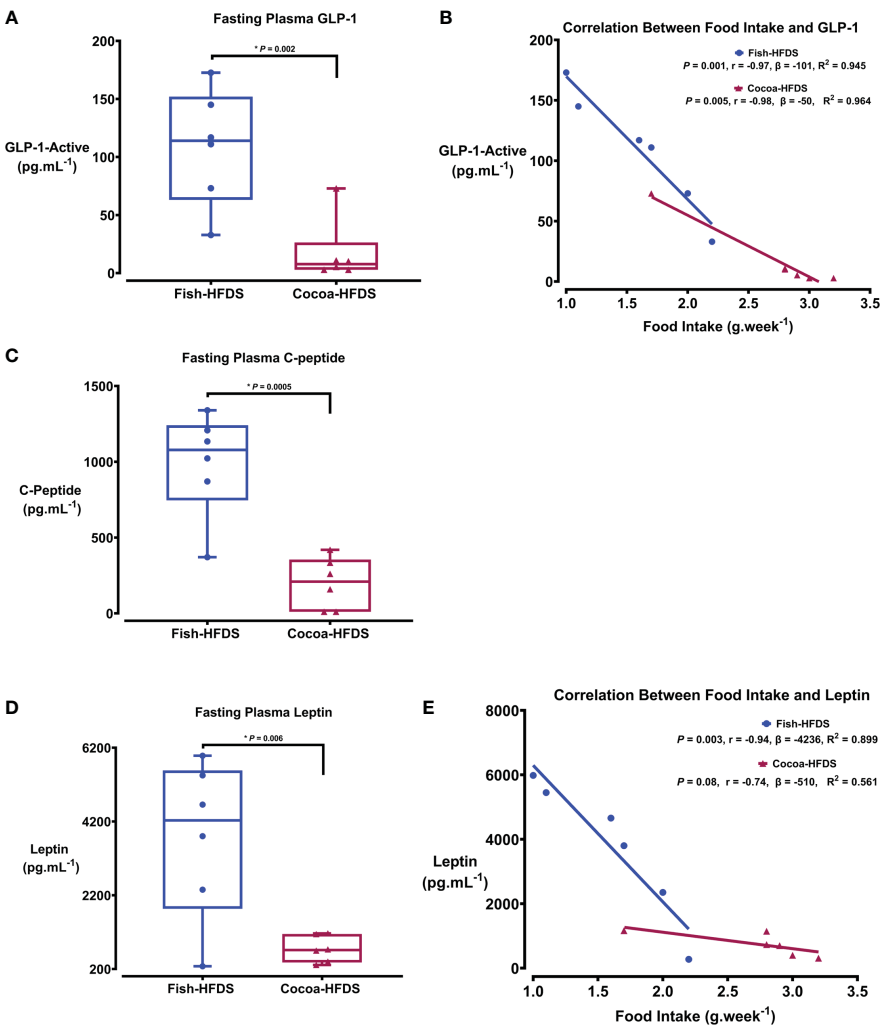

FIGURE 3
The Effect of different fat-based diets (Fish-HFDS and Cocoa-HFDS) on plasma metabolic markers. **(A)** Fasting plasma GLP-1concentration. **(B)** Correlation between food intake and GLP-1. **(C)** Fasting plasma C-peptide concentration. **(D)** Fasting plasma leptin concentration. **(E)** Correlation between food intake and leptin. Data are mean with ± SEM. *P*-values for differences between groups by ANOVA and Student's t-test.

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TABLE 5 The Effect of different fat-based diets (Fish-HFDS and Cocoa-HFDS) on plasma metabolic markers.

Plasma Metabolic Markers (pg.mL^{-1})	Group		Significance (*P*-value)
	Cocoa-HFDS	Fish-HFDS	
	N=6	N=6	
	Mean	Mean	
Secretin	94 ± 21	61 ± 17	0.25
Ghrelin-Active	130 ± 24	41 ± 13	**0.008**
Peptide YY	191 ± 25	232 ± 22	0.24
Interleukin-6	32 ± 5	32 ± 6	0.98
GLP-1	17 ± 11	108 ± 20	**0.002**
C-peptide	198 ± 69	991 ± 140	**0.0005**
Leptin	741 ± 146	3752 ± 871	**0.006**
Pancreatic Polypeptide	118 ± 35	119 ± 34	0.98
GIP	144 ± 31	241 ± 50	0.13
TNF-α	12 ± 2	14 ± 4	0.69

Bold font indicates significance in Student's t-test. Cocoa-HFDS, High-fat-high-sucrose diet with Cocoa butter; Fish-HFDS, High-fat-high-sucrose diet with Fish oil; GLP-1, Glucagon-Like Peptide-1-Active; GIP, Glucose-dependent Insulinotropic Polypeptide-Total; TNF-α, Tumour Necrosis Factor.

consistent with the steady low increase in body weight of mice in Fish-HFDS group. Comparing with other studies, mice fed with high-fat/high-sucrose diets supplemented with fish oil either showed an increase (26) or a decrease in the food intake (2). The discrepancies in results of these studies can possibly be attributed to differences with regard to mice ages, fat and sugar percentages in diets, as well as dietary components other than fat and sucrose and feeding durations.

The Cocoa-HFDS group had higher fasting blood glucose concentrations than the Fish-HFDS group, which raises the possibility of a disturbance of glucose metabolism in the Cocoa-HFDS group. It was shown previously by several studies that the presence of fish oil in the high-sucrose diet affects the fasting glucose concentration, albeit within the normal range, in comparison to other groups that had only a high-sucrose diet alone or with a different source of fat (e.g., corn oil, lard, argan oil, and krill oil) (1, 2, 8, 14, 22, 25). In our study, compared to normal (chow) diet and regular HFD, the mice fed with Fish-HFDS had similar fasting blood glucose concentrations as the mice fed with chow diet and had lower fasting blood glucose concentrations than the mice fed with regular HFD.

Insulin resistance is a condition characterized by low peripheral tissue (muscle, liver, and adipose tissues) response to insulin (27, 28). A high-fat/high-sucrose diet is commonly used as a model of diet-induced insulin resistance and impaired glucose homeostasis, shown by the increased fasting glucose concentrations and amplified glucose and insulin responses to IP-GTT (2). Of note, it has been suggested that sucrose *per se* does not affect insulin-glucose uptake (7), in spite of the fact that rats fed a high-sucrose diet showed mild hyperglycemia (8, 16). The best method, considered a gold standard, for determining insulin resistance is the hyperinsulinemic-euglycemic clamp procedure. However, since this technique cannot be implemented routinely, ITT was developed as a simple alternative technique to evaluate insulin action *in vivo* (28). Accordingly, IP-GTT and ITT tests were used in this study to measure and compare the insulin action between Fish-HFDS and Cocoa-HFDS dietary groups. Our data showed that

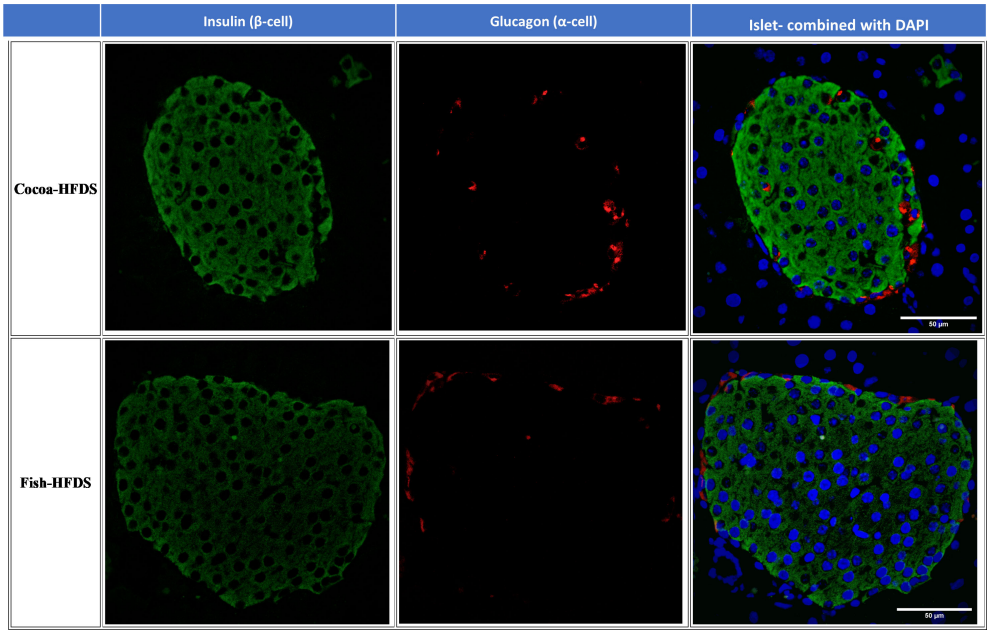

FIGURE 4
Representative photomicrographs of double staining of insulin and glucagon. Scale bar 50 μm.

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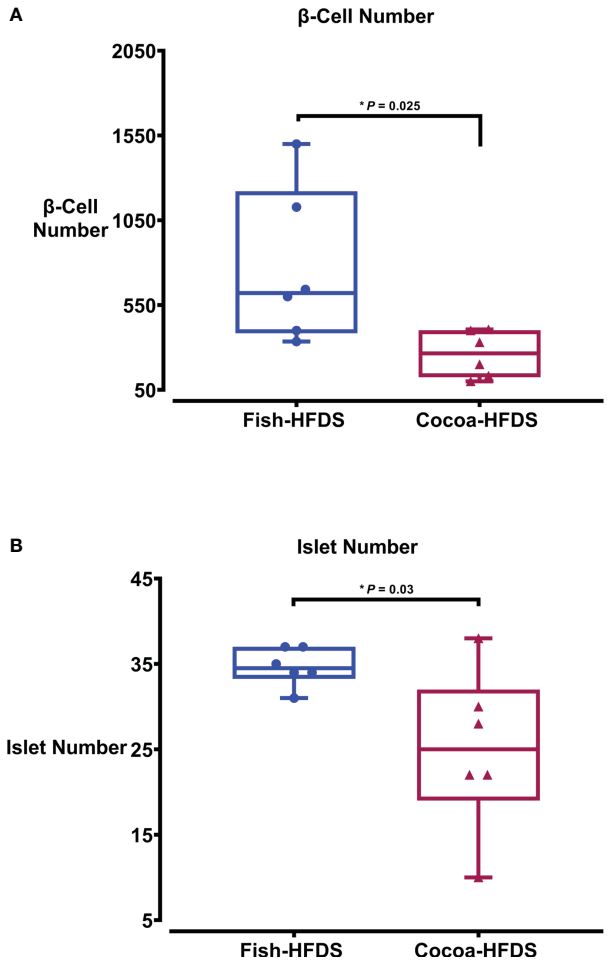

FIGURE 5
The Effect of different fat-based diets (Fish-HFDS and Cocoa-HFDS) on endocrine pancreas morphology. **(A)** Number of β-cells. **(B)** Number of islets. Data are mean with ± SEM. *P*-values for differences between groups by ANOVA and Student's t-test.

the AUC was lower in Fish-HFDS group compared to Cocoa-HFDS group, indicating a higher blood glucose clearance rate and hence a more proficient glycemic control in mice of Fish-HFDS group.

The Fish-HFDS group showed a better glucose tolerance test outcome, compared to Cocoa-HFDS group indicating that fish oil does not have harmful effects on β-cell sensitivity and may in fact have beneficial effects. This may suggest that the presence of good fat in the diet can either prevent insulin resistance or even promote insulin sensitivity, irrespective of the percentage of fat or calorie intake. The Fish-HFDS group had remarkedly lower fasting blood glucose concentrations compared to Cocoa-HFDS group, which may indicate that the Fish-HFDS group may have had more sensitive β-cells responding to glucose sensing. Moreover, the Fish-HFDS group also had higher blood insulin concentrations compared to Cocoa-HFDS group, which suggests that the fish oil may have had a positive modulatory impact on the β-cell secretory capacity, leading to an increase in insulin secretion. In support of our findings, previous studies have demonstrated that rats fed on high sucrose diet supplemented with fish oil showed normal glucose tolerance tests (1, 2, 16, 23) and did not develop insulin resistance. This indicates that the fish oil ameliorated and prevented insulin resistance (5). Of note, although previous studies have suggested that a high-fat diet impairs glucose tolerance independent of macronutrient composition (19), our study provides evidence that the type of fat does make a difference.

Moreover, it was suggested that sucrose, but not protein or fat, strongly stimulates pancreatic insulin secretion (19). In our study, the Fish-HFDS group had higher plasma insulin and glucagon concentrations compared to the Cocoa-HFDS group. However, the Fish-HFDS group had lower plasma insulin and glucagon concentrations compared to mice fed normal chow diet and higher plasma insulin and glucagon concentrations than mice fed regular HFD. Therefore, the fish oil as a source of fat in a high-sucrose high-fat diet effectively increased these hormones in mice. However, the previous studies on rats (25) and rabbits (22) fed a high-sucrose diet showed that insulin concentration was either not affected (25) or decreased (22) by fish oil supplementation. We speculate that different feeding regimens used in these dietary investigations, including ours, may be the source of differences in results regarding the circulatory insulin levels. Besides, the diets induce metabolic effects differentially across different species.

Insulin plays a vital role in glucose homeostasis; it inhibits glucose production and stimulates glucose uptake (29). During fasting, glucagon maintains glucose availability by stimulating the hepatic gluconeogenesis. Glucagon secretion is stimulated during hypoglycemia and is suppressed during hyperglycemia (30), providing the first line of defense in glucose counter-regulation (31). However, the balance between glucagon and insulin in the prandial state is responsible for normal glucose tolerance (32). Taken together, glucose homeostasis depends on the cooperation between α- and β-cells, not exclusively on the β-cells (31). Rather than having opposing roles in regulation of glucose homeostasis, α- and β-cells cooperate in the prandial state to regulate the metabolic control of nutrients (33). Besides, the role of certain enzymes such as acetylcholinesterase, α-glycosidase, butyrylcholinesterase, and carbonic anhydrase II could be considered in relation to glucose homeostasis, as some natural products studies have shown potential anti-diabetic effects by targeting these enzymes (34–36). However, glucagon measurements are still rarely reported in animal studies of glucose metabolism, which may represent an area of growing interest in metabolic research studies.

Plasma leptin concentrations were higher in Fish-HFDS group compared to Cocoa-HFDS group. Similar to our findings, previous studies showed that adipose tissue and plasma leptin concentrations were high in rats fed high sucrose, high-fat fish oil based diet (21, 26). In our study, fish oil increased plasma leptin concentrations without significant changes in body weight gains, which is consistent with what was found in previous studies (13, 26). Nonetheless, an inverse correlation was found between food intake and plasma leptin concentrations in the Fish-HFDS group, which is expected considering the metabolic role of leptin as a satiety regulatory hormone.

Our data suggest that high concentrations of GLP-1, and leptin also, could be responsible for the reduced food intake, lower blood glucose concentrations, and less weight gains in the Fish-HFDS group compared to Cocoa-HFDS group, although both groups

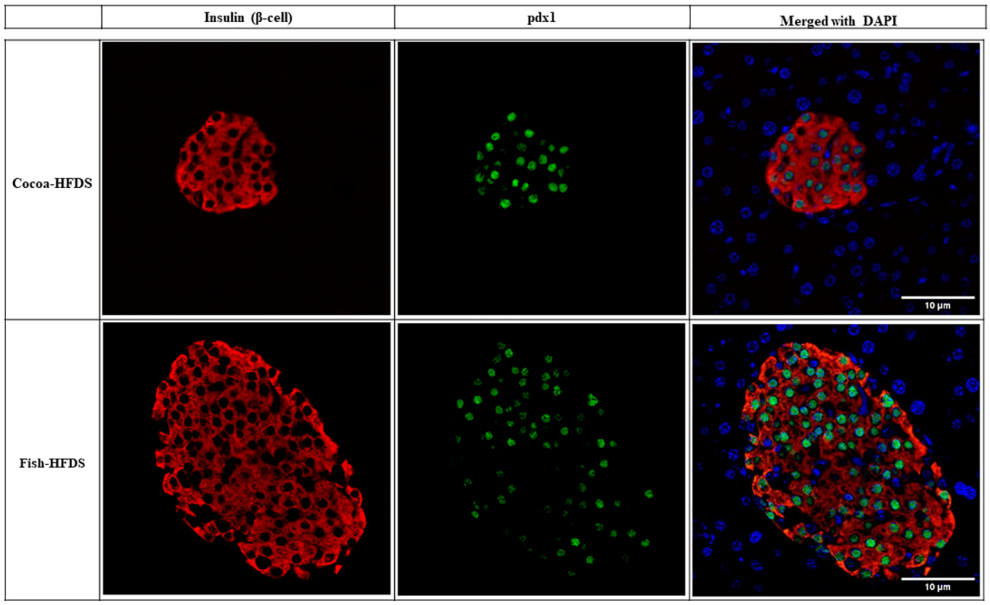

FIGURE 6
Representative photomicrographs of double staining of insulin and *pdx1*. Scale bar 10 µm.

showed a negative correlation between food intake and GLP-1. Importantly, the Fish-HFDS group had higher C-peptide concentrations than the Cocoa-HFDS group, which indicates a better β-cell function in mice fed Fish-HFDS. However, other studies reported that the C-peptide concentration was not affected by the supplementation of fish oil to a normal diet in both lean and obese rats (37). Clearly, the insulinotropic effect varied as fish oil was added as supplement to a normal diet or fed to mice concurrently as a high-fat high-sucrose diet (the regimen used in our study).

An optimal pancreatic endocrine cell mass is necessary for organ function, and changes in the mass lead to metabolic disorders (12). The pancreatic endocrine cell mass is calculated from the cell size; however, the mass can be increased due to proliferation and hypertrophy or decreased by apoptosis and atrophy (38, 39). Under normal conditions during adulthood, pancreatic β-cells have a steady low rate of proliferation and apoptosis (39). Maintaining β-cell mass during adulthood is vital to maintain blood glucose homeostasis and prevent diabetes (39). Cell mass, especially β-cell mass, can expand during adulthood in response to increased body weight and insulin resistance (38, 39), thereby displaying an ability to adapt to the increased insulin demand (38).

TABLE 6 The Effect of different fat-based diets (Fish-HFDS and Cocoa-HFDS) on the gene expression of Insulin, MAFA, Glucagon, MAFB and pdx1.

Genes	Group		Significance (*P*-value)
	Cocoa-HFDS	Fish-HFDS	
	N=6	N=6	
	Mean	Mean	
Insulin	0.06 ± 0.02	6.37 ± 1.98	**0.008**
MAFA	1.18 ± 0.51	1.07 ± 0.17	0.81
Glucagon	0.02 ± 0.01	15.92 ± 9.05	0.052
MAFB	0.75 ± 0.03	1.07 ± 0.17	0.13
pdx1	1.05 ± 0.09	1.01 ± 0.05	0.71

Bold font indicates significance in Student's t-test. Cocoa-HFDS, High-fat-high-sucrose diet with Cocoa butter; Fish-HFDS, High-fat-high-sucrose diet with Fish oil.

Given the critical role that the endocrine pancreas plays in maintaining blood glucose homeostasis, we assessed endocrine pancreas cell number and expression of endocrine pancreas regulatory markers. Our data showed that the α-cells, β-cells, and islet numbers were higher in Fish-HFDS group compared to Cocoa-HFDS group. However, only β-cells and islet numbers reached statistical significance. The insulin and glucagon-positive areas and α-cells, β-cells, and islet mass were similar between two groups. We observed nonsignificant differences between two dietary groups regarding gene expression of *Pdx1*, *Mafa/b* and *Gcg* while significant difference was observed regarding *Ins*. Other studies showed that when fish oil was added to a normal diet, it did not affect islet size in both obese or lean rats (37). However, a high-fat diet is known to increase pancreatic β-cell mass by both hypertrophy and hyperplasia to produce more insulin as a compensatory mechanism against insulin resistance (10, 40). β-cell hypertrophy and hyperplasia are associated with the loss of β-cell function, leading to a defect in insulin secretion (27). Prolonged insulin resistance leads to the activation of the apoptotic pathways increasing β-cell apoptosis and decreasing β-cell mass (40). β-cell function and β-cell mass are correlated, and both decrease with glucose intolerance (41). Decreased β-cell mass is associated with impaired fasting glucose and glucose tolerance (41); in our study, the Cocoa-HFDS group had high fasting blood glucose concentration and impaired glucose tolerance with no significant

difference in β-cell mass compared to the Fish-HFDS group, suggesting an impairment in glucose homeostasis. However, further studies that incorporate additional control groups (high-sucrose or/and normal diet) are needed to confirm these possibilities. Interestingly, many findings suggest that changes in α-cell mass are attributed to glucose intolerance (41). However, we measured α-cell mass and found no difference between two dietary groups. Further research measuring the β-cell apoptosis to proliferation ratios will be needed to confirm whether the increase in β-cell numbers in the Fish-HFDS group is not a compensatory mechanism against the diet-induced insulin resistance. Moreover, pre-intervention with fish oil has a favorable impact on islet morphology (42), which needs to be further evaluated in various settings.

5 Conclusion

Our findings suggest that manipulating dietary fats within a high sucrose diet may improve certain features of the metabolic syndrome improving glucose homeostasis. In this regard, replacing the fat content in the high-fat/high-sucrose diet with fish oil seems to be associated with the following: reduced food intake, reduced weight gain, reduced fasting blood glucose concentrations, improved glucose tolerance tests and insulin sensitivity, and a favorable effect on islet morphology. However, the molecular mechanisms that underlie the fish oil effects need to be further investigated.

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 and all animal experimental protocols were approved by the Dasman Diabetes Institute Animal Care and Ethics Committee (RA AM- 2016-007). All institutional and national/international guidelines for the care and use of laboratory animals were followed. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

SA: Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. AH: Formal Analysis, Writing – review & editing. HA: Writing – review & editing, Data curation, Methodology. SaS: Resources, Writing – review & editing. FA-R: Formal Analysis, Writing – review & editing. SK: Data curation, Formal Analysis, Methodology, Writing – review & editing. NA: Data curation, Methodology, Writing – review & editing. TJ: Data curation, Methodology, Writing – review & editing. StS: Data curation, Methodology, Writing – review & editing. AA: Resources, Writing – review & editing. FA-M: Formal Analysis, Resources, Writing – review & editing. RA: Conceptualization, Funding acquisition, Resources, Supervision, 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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Case report: Uncovering hidden glucose patterns in medicated versus unmedicated bipolar disorder and comorbid type 1 diabetes mellitus

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Introduction: Type 1 diabetes mellitus is characterized by an absolute insulin deficiency requiring the lifetime intensive insulin therapy accompanied by daily self-monitoring, self-management, ongoing education, and complex diabetes care. Regular patient-clinician shared therapeutic decisions based on age, sex, comorbidities, medications, predicted impact of meals, physical activity, stress, hormonal changes, insulin therapy, and patterns of glycemic changes are key for achieving glycemic targets. The impact of various phases of bipolar disorder and their treatment on continuous glucose levels remains unexplored and calls for future assessments.

Case presentation: The present case reports a 41-year-old Caucasian female with an established diagnosis of bipolar II disorder and type 1 diabetes mellitus who discontinued long-term mood-stabilizing pharmacotherapy with quetiapine. Real-time continuous glucose monitoring performed before and 6-months following the discontinuation of quetiapine revealed hidden glucose patterns in medicated versus unmedicated bipolar disorder. Despite the known adverse metabolic effects of quetiapine, the continuous glucose monitoring captured more stable and near-normal continuous glucose values during the antipsychotic treatment compared to unmedicated stages of bipolar disorder with considerably higher glucose values and glucose variability.

Conclusion: The case report highlights the importance of the ongoing psychopharmacotherapy of bipolar disorder in comorbid type 1 diabetes mellitus to reduce mood-induced reactivity, emotional urgency, and non-emotional impulsivity that may contribute to dysglycemia. If not effectively treated, the "bipolar diabetes" is likely to progress to multiple psychiatric and

somatic complications. The bidirectional links between the phases of bipolar disorder and the corresponding continuous glucose patterns can help advance clinical decision-making and yield innovative1 research that can translate into efficacious clinical practice.

KEYWORDS

bipolar disorder, type 1 diabetes mellitus, case report, continuous glucose monitoring, quetiapine

Introduction

Type 1 diabetes mellitus is predominantly an autoimmune disease (accounting for around 10% of all diabetes cases) characterized by an absolute insulin deficiency requiring the lifetime intensive insulin replacement therapy accompanied by the daily self-monitoring, self-management, ongoing education, and complex diabetes care. Without proper treatment, the condition becomes life-threatening. To achieve glycemic targets, the patient-clinician shared therapeutic decisions must be made regularly based on age, sex, comorbidities, medications, predicted impact of meals, physical activity, stress, hormonal changes, type/ways/characteristics of the administered insulin, and patterns of glycemic changes detected by self-monitoring of blood glucose and/or continuous glucose monitoring.

While type 1 diabetes mellitus is often complicated by other autoimmune disorders and somatic comorbidities, less attention is paid to an unexplored impact of comorbid psychiatric disorders on glucose levels. Specifically, the impact of various phases of bipolar disorder and their treatment on dysglycemia poses a challenge, both for persons with type 1 diabetes mellitus and for their health-care providers. Bipolar disorder is a serious lifelong affective disorder characterized by periodic mood dysregulation with elevated mood states (episodes of mania or hypomania, or episodes with mixed features) with or without depressed mood states and energy levels (1). Bipolar II disorder is one of the types of bipolar disorder (2) marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes.

Bipolar disorder symptoms and emotional urgency can potentially compromise diabetes control, particularly in brittle diabetes. Despite an evidence that stress hyperglycemia is associated with poor clinical outcomes (3), the extent to which the bipolar mood-induced reactivity may affect actual glucose levels and glucose variability in type 1 diabetes mellitus is still undetermined and calls for future assessments. The present case reports the baseline and follow-up results of continuous glucose monitoring in a middle-aged female with bipolar II disorder and type 1 diabetes mellitus who discontinued long-term mood-stabilizing antipsychotic treatment. Particularly unique about the present case is the ability to uncover the hidden glucose excursions in medicated vs. unmedicated bipolar disorder, which is relevant for clinical practice. Novel insights may help to clarify the links between mood fluctuations and associated glycemic fluctuations. The findings will thus inform clinical practice and further research to continue to investigate novel approaches to prevent adverse outcomes in bipolar disorder and comorbid type 1 diabetes mellitus.

Case presentation

Ms. K. is a 41-year-old Caucasian female teacher who has been attending mental health services for almost 6 years and has an established diagnosis of bipolar II disorder. She has previously experienced several episodes of illness and undergone one previous hospitalization with severe depression. Her illness has been stable for the past five years since commencing antipsychotic treatment. For the past four years she has been on a monotherapy with quetiapine. The participant's race, ethnicity, female sex, and female gender identity were ascertained by self-report.

Her past medical history (Table 1) included brittle type 1 diabetes mellitus (since 1996) without significant complications that was well-managed with an insulin pump therapy, Hashimoto thyroiditis (since 1996) with hypothyroidism (since 2014), arterial hypertension (since 1998), and antiphospholipid syndrome (since 2023). Owing to the presence of multiple autoimmune diseases and

TABLE 1 Past medical history and current treatment.

past medical history	year of diagnosis	current treatment
type 1 diabetes mellitus	1996	insulin pump therapy, insulin lispro
diabetic axonal polyneuropathy	2012	alpha-lipoic acid, benfotiamine
Hashimoto thyroiditis	1996	none
primary hypothyroidism	2014	levothyroxine
arterial hypertension	1998	bisoprolol
bipolar disorder	2018	quetiapine SR
antiphospholipid syndrome	2023	none

brittle type 1 diabetes, the patient has been fully assessed. An immunological examination detected negative anti-21-hydroxylase autoantibodies, negative antiparietal cell antibodies, negative antibodies against extractable nuclear antigen and positive titers of antibodies to glutamic acid decarboxylase, antithyroid peroxidase and anti-thyroglobulin in the serum. There were normal levels of vitamin B12, normal blood count results, and no symptoms of malabsorption. The results confirmed the presence of the immune-mediated diabetes mellitus with autoimmune thyroiditis (Polyglandular Autoimmune Syndrome type IIIA). The patient was single, denied recreational drug use, did not smoke, and only drank alcohol occasionally. She was highly educated. She was employed as a full-time teacher at the local university. There was a family history of type 1 diabetes mellitus, type 2 diabetes mellitus, arterial hypertension, and coronary artery disease. Family psychiatric history was positive for cyclothymic disorder, impulsive borderline personality disorder, depressive disorders, and alcohol use disorders.

Since January 2019 till January 2023, the patient's chronic medication therapy included insulin lispro 30-40 IU/day delivered via insulin pump at preset basal rates (40%) and administered in several premeal boluses (60%), levothyroxine 100-125 mcg q.d., bisoprolol 5 mg q.d., and quetiapine SR 200-400 mg q.d. (nightly) (Table 1). Until 2021 she also had aripiprazole 10-30 mg q.d. Her adherence to therapy was excellent. Her diabetes was well-controlled with glycated hemoglobin (HbA1c) values near normal range during the past five years. Her most recent laboratory NGSP HbA1c readings were 6.10% (IFCC HbA1c 43 mmol/mol) in June 2022 and 5.77% (40 mmol/mol) in November 2022. Because of the intensive insulin treatment, she self-monitored her blood glucose daily and regularly performed the real-time continuous glucose monitoring using FreeStyle Libre® system to reveal and manage even hidden glucose excursions. The system is minimally invasive and uses a disposable factory-calibrated glucose sensor inserted into the user's arm. A touchscreen device/reader is then used to scan and retrieve continuously monitored real-time glucose readings. Figure 1 depicts the summary of the continuous glucose monitoring results reflecting the period of consecutive 14 days (October 18-31, 2022) of medicated bipolar disorder. The patient met important glycemic targets, including the time within target range (83%), time above 10.0 mmol/l (7%), and time above 13.9 mmol/l (0%). The average sensor glucose was 6.6 mmol/l, glucose management indicator 6.2% (44 mmol/mol), and glucose variability was 33.8% (defined as percent coefficient of variation). Figure 1 also shows an ambulatory glucose profile, a summary of sensor glucose values from the report period, with median and other percentiles shown as if occurring in a single day. Finally, the Figure 1 provides details on daily glucose profiles with each daily profile representing a midnight-to-midnight period. During this monitoring, the patient's mood was stable, and she was on bimodal mood-stabilizing monotherapy with quetiapine SR 300 mg q.d. (nightly). Other prescribed drugs included levothyroxine 125 mcg q.d., bisoprolol 5 mg q.d., alpha-lipoic acid 600 mg q.d., and benfotiamine 300 mg q.d. On physical examination, her height was 170 cm, and her weight was 63 kg. The body mass index was 21.8 kg/m^2. Her body weight was stable over the past three years. Thyroid function tests and the baseline laboratory findings were normal.

In December 2022, her mood deteriorated with a rapid onset of severe depression requiring immediate management plan (Table 2). At the review, it emerges that the depressive episode was triggered by a newly diagnosed health problem the patient does not wish to be disclosed in this report. The patient is not keen to be admitted to hospital, and her friend volunteers to "keep an eye on her for a few days." After discussion, she agrees to have her symptoms managed as an outpatient, and she agrees to gradually increase her dose of quetiapine to a therapeutic dose. Over the coming weeks, her low mood improves, and her mental state settles with quetiapine SR 800 mg nightly.

In January 2023, she underwent a common medical procedure that required a three-day inpatient hospital stay. The procedure went uncomplicated, and the patient was discharged and returned home and back to work. Two weeks later, she had an urgent review for not sleeping at all for several nights with extremely increased goal-directed behavior, impaired judgment, increased energy, and reduced appetite. It emerges that the patient had been reducing her quetiapine dose and completely discontinued her antipsychotic medication in mid-January 2023. Upon discussion, she revealed the reason for stopping her long–term psychopharmacological treatment. She admitted she wanted to make a new distracting problem to forget about her current another health issue she is extremely worried about. When asked to rate the helpfulness of her psychiatric medication prior to attempting discontinuation, she indicated that the medication had been extremely helpful. Since she refused any psychopharmacological alternatives to quetiapine for maintenance treatment of bipolar disorder, she agreed to continue monitoring symptoms, mood and mental state, and report any signs of relapse as soon as possible (Table 2).

Over the following six months of unmedicated bipolar disorder, the patient experiences a relatively unstable period alternating between hypomania lasting for several weeks to a less expansive, irritable mood, and a low mood. During the hypomanic episodes her sleep needs decreased to 1-4 hours per night, she was overtalkative, and her workmates expressed concerns that she had been overfamiliar with students. She reported feeling "fundamentally liberated" and accepted to be a little high. She did not report any delusional ideas and denied other psychotic phenomena. Over the coming weeks, her mood gradually normalized. Regarding the somatic comorbidities, following the discontinuation of quetiapine, the patient's antihypertensive therapy was augmented by the addition of ramipril 5 mg q.d. because of the persisting significantly increased systolic and diastolic blood pressure values. The basal and total doses of insulin increased by 20%. Her follow-up labs were remarkable for significantly elevated NGSP HbA1c 7.26% (IFCC HbA1c 56 mmol/mol) in April 2023 (Table 2). Figure 2 depicts the summary of the continuous glucose monitoring results reflecting the period of unmedicated bipolar disorder (6-months following the discontinuation of quetiapine). The glycemic control was considerably deteriorated, with parameters being outside the targets. The time within target range decreased to only 59%, time above 10.0 mmol/l increased to 28%, and time above 13.9 mmol/l increased to 10%. The average sensor glucose increased to 9.3 mmol/l,

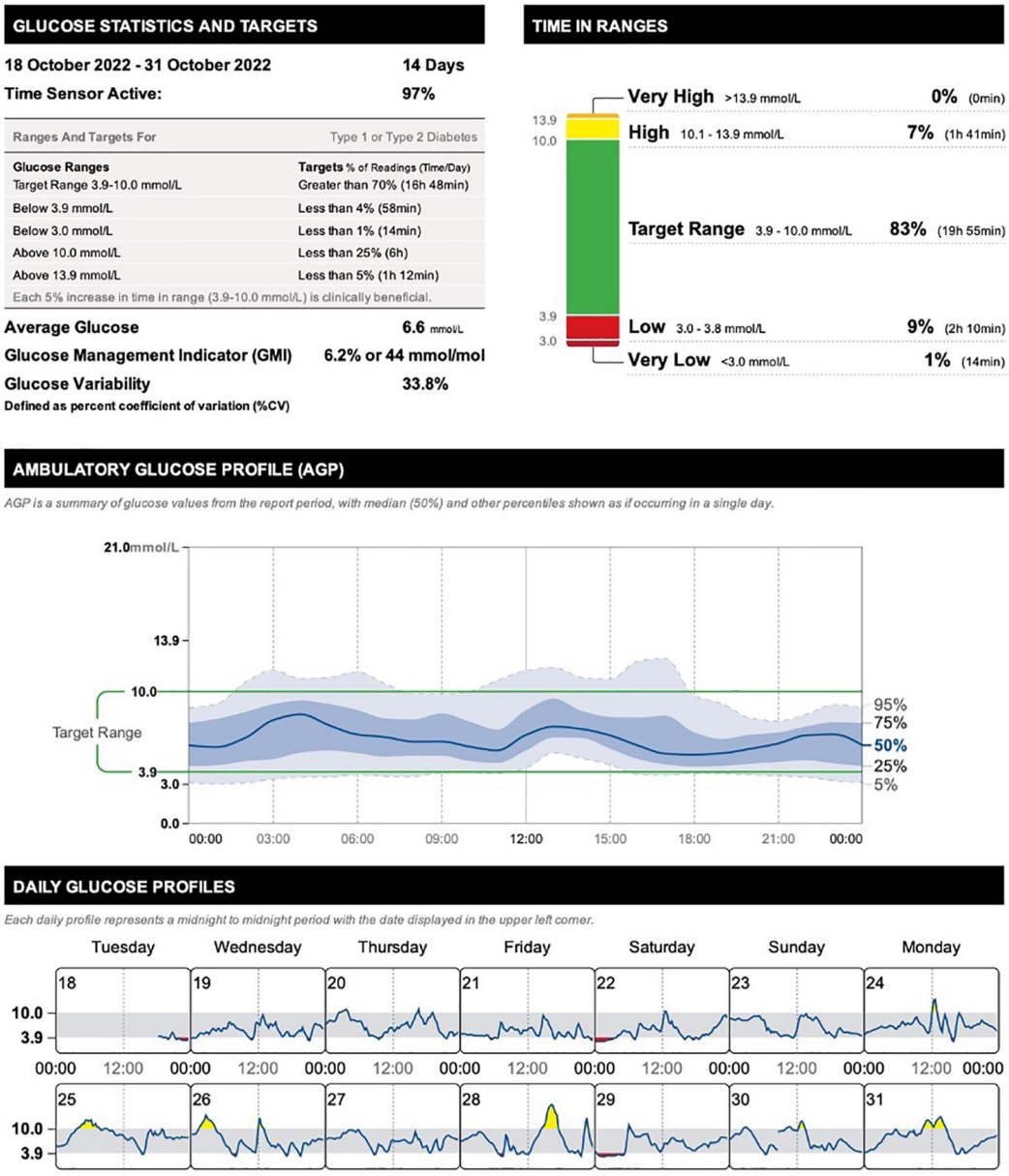

FIGURE 1
Summary of the continuous glucose monitoring results reflecting the period of medicated bipolar disorder (quetiapine SR 300 mg nightly) in a 41-year-old female with comorbid type 1 diabetes mellitus.

glucose management indicator deteriorated to 7.3% (56 mmol/mol), and glucose variability increased to 37.4%. The details of the ambulatory glucose profile and daily glucose profiles are depicted in Figure 2 as well.

In June 2023, the patient's mood worsened considerably, approaching moderate depressive episodes. In July 2023 (Table 2), the patient agreed to commence the psychopharmacotherapy with venlafaxine and quetiapine. Venlafaxine was gradually up titrated to 150 mg daily, and quetiapine SR was up titrated to 400 mg nightly to achieve its antidepressive, antimanic, stabilization, and prophylactic effects. Venlafaxine was discontinued after 23 days because of the onset of hypomanic symptoms at the end of July 2023. The patient continued monotherapy with quetiapine SR 400 mg nightly, and regular follow-up outpatient mental health appointments were scheduled. The follow-up appointments were spent on monitoring quetiapine dose and on reviewing side effects, goals, coping strategies, and progress. Support and psychoeducation were provided. The patient reported improvements in both mood and glucose control with considerably reduced fluctuations.

Discussion

To our knowledge, this is a first report of the glycemic impact of medicated and unmedicated bipolar disorder on continuously monitored glucose levels in comorbid type 1 diabetes mellitus.

TABLE 2 A timeline of relevant patient-related data from each episode of care.

January 2019 - January 2023	• insulin lispro 30-40 IU/day • levothyroxine 100-125 mcg q.d. • bisoprolol 5 mg q.d. • alpha-lipoic acid 600 mg q.d. • benfotiamine 300 mg q.d. • quetiapine SR 200-400 mg q.d. (nightly) • aripiprazole 10-30 mg q.d. (until 2021)	• excellent adherence to therapy • HbA1c 6.10% (43 mmol/mol) in June 2022 • HbA1c 5.77% (40 mmol/mol) in November 2022 • regular self-monitoring and continuous glucose monitoring (CGM) with excellent results
October 18-31, 2022	• insulin lispro 30-40 IU/day • levothyroxine 125 mcg q.d. • bisoprolol 5 mg q.d. • alpha-lipoic acid 600 mg q.d. • benfotiamine 300 mg q.d. • quetiapine SR 300 mg q.d. (nightly)	• CGM time within target range 83%, time above 10.0 mmol/l 7%, time above 13.9 mmol/l 0% • average sensor glucose 6.6 mmol/l, glucose management indicator 6.2% (44 mmol/mol), glucose variability 33.8%
December 2022	• ongoing diabetes, antihypertensive and thyroid treatment • quetiapine SR dose gradually increased to a therapeutic dose of 800 mg nightly	• severe reactive depression • mental state settles with quetiapine SR 800 mg nightly
January 2023	• ongoing diabetes, antihypertensive and thyroid treatment • quetiapine tapered and discontinued	• hyposomnia/insomnia, increased goal-directed behavior, impaired judgment, increased energy, reduced appetite • continued monitoring of mood/mental state/ symptoms/signs of relapse
February-June 2023	• unmedicated bipolar disorder • the basal and total doses of insulin increased by 20% • antihypertensive therapy augmented by addition of ramipril 5 mg q.d. • ongoing thyroid treatment	• hypomanic-mixed-depressed episode • persisting significantly increased systolic and diastolic blood pressure values • follow-up HbA1c 7.26% (56 mmol/mol) in April 2023 • CGM time within target range 59%, time above 10.0 mmol/l 28%, time above 13.9 mmol/l 10% • average sensor glucose 9.3 mmol/l, glucose management indicator 7.3% (56 mmol/mol), glucose variability 37.4%
July 2023	• ongoing diabetes, antihypertensive and thyroid treatment • commencement of venlafaxine and quetiapine treatment • venlafaxine up titrated to 150 mg daily, discontinued after 23 days • quetiapine SR up titrated to 400 mg nightly	• moderate depressive episodes • improvements in mood and glucose control with considerably reduced fluctuations
	• continued monotherapy with quetiapine SR 400 mg nightly • regular follow-up outpatient mental health appointments	

(Continued)

TABLE 2 Continued

Despite the known adverse metabolic effects of quetiapine, we observed more stable real-time continuous glucose values approaching normal glucose targets during the antipsychotic treatment with quetiapine compared to unmedicated stages of bipolar disorder that featured considerably higher glucose values and glucose variability consistent with the unstable mood.

In our previous report (4), we have demonstrated that targeting diabetes distress is critical to successful management of type 1 diabetes mellitus. Bipolar disorder as a psychiatric comorbidity represents and additional stressor through changes in mood that may precipitate dysglycemia in diabetes. The underlaying pathophysiology of mood-induced dysglycemia in diabetes remains less well understood. We have already reported the bidirectional links between bipolar disorder and type 2 diabetes mellitus (5). The information regarding associations between type 1 diabetes and bipolar disorder is scarce (6, 7). With respect to long-term glucose control, our case report shares a similarity with the previous case report by Chu and Liang (8) who reported the mood state as a blood glucose modulator in a patient with type 2 diabetes and bipolar disorder based on changes in HbA1c. Specifically, the authors report worsening of glucose control as indicated by increases in a three-month HbA1c that was related to bipolar depressive episodes, whereas improvements in HbA1c accompanied periods of hyperthymia and manic episodes (8). Associations between symptoms of depression and higher HbA1c levels have already been reported (9–11). A large Korean cohort study (12) has demonstrated that high glycemic variability and persistent hyperglycemia were associated with increased incidence of depression and anxiety disorders.

Novel glucose monitoring technologies have been developed to assist individuals with type 1 diabetes mellitus to make intensive therapeutic decisions 24/7, reduce risks, severity, and duration of hypo- and hyperglycemia, and thus help to achieve glucose targets with good precision and accuracy. With respect to the continuous glucose monitoring technology employed in the present case report, the FreeStyle Libre® system utilizes artificial intelligence-based machine learning model to predict glucose variability and risk of imminent hypoglycemia in real-time. Our findings are in line with evidence from a systematic review (13) that has demonstrated a positive impact of the real-time continuous glucose monitoring on glycemic control.

This case report highlights the importance of the ongoing psychopharmacological treatment of bipolar disorder to prevent relapses of hypomania, mixed episodes, and depression, and thus help reduce the mood-induced reactivity, emotional urgency, and stress contributing to dysglycemia in type 1 diabetes mellitus. If not effectively treated, the "bipolar diabetes" is likely to progress to multiple psychiatric and somatic complications. Information about

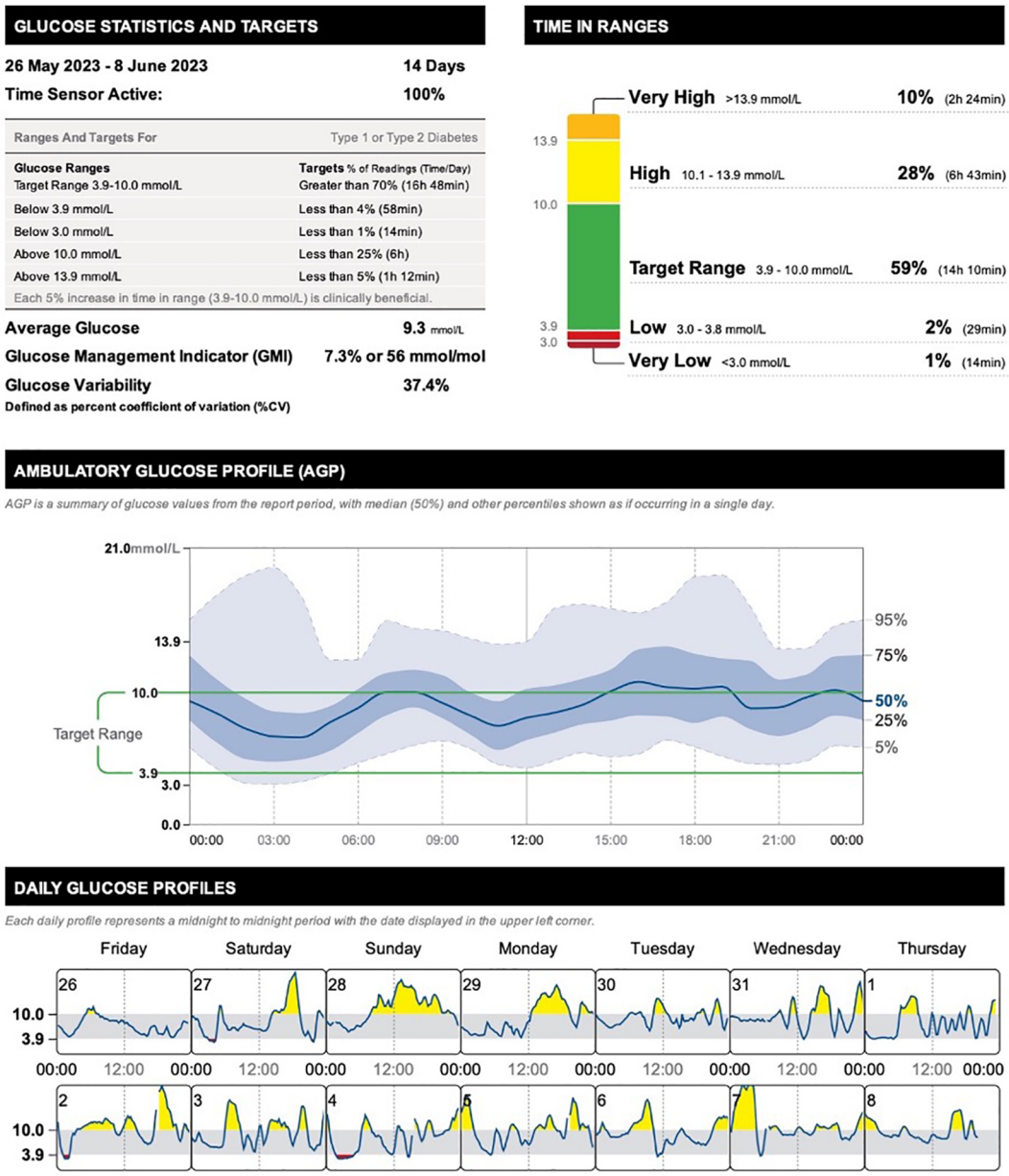

FIGURE 2
Summary of the continuous glucose monitoring results reflecting the period of unmedicated bipolar disorder (6-months following the discontinuation of quetiapine SR) in a 41-year-old female with comorbid type 1 diabetes mellitus.

the course of daytime and nighttime continuous glucose values in type 1 diabetes mellitus comorbid with bipolar disorder has not been reported so far. The associated risks of dysglycemia (hyperglycemia along with the increased glucose variability) during various stages and phases of bipolar disorder and their treatment are not quantified at all. The novel findings of potential bidirectional links between the phases of bipolar disorder and the corresponding continuous glucose patterns reported here can enhance clinical decision-making and yield future innovative clinical research into "bipolar diabetes".

Type 1 diabetes mellitus is a lifelong condition that requires an ongoing complex care addressing physical, mental, and emotional health. Specifically, it should target not only physical but also psychiatric comorbidities. Importantly, clinical management of bipolar disorder in persons with type 1 diabetes mellitus calls for balanced assessments of metabolic risks and glycemic benefits. Technology-enabled diabetes management solutions can facilitate this process. Given the risks of untreated bipolar disorder, discontinuation of psychopharmacotherapy should be discouraged. Advancing psychiatrists' and diabetologists' knowledge and skills may improve patient-clinician shared therapeutic decision making for persons with type 1 diabetes and comorbid bipolar disorder. Real-time continuous glucose monitoring can help reveal otherwise undetected glucose fluctuations related to mood changes, emotional urgency, and distress in various stages and phases of bipolar disorder. In addition, the continuous glucose profiles may serve as a

motivational tool demonstrating a more stable glucose control in medicated bipolar disorder with a stable and normalized mood, and thus help increase an adherence to psychopharmacotherapy. It is likely that community mental health care may also help to better support patient choice and self-determination regarding the use and discontinuation of psychiatric medication, especially in case of crisis.

The patient has shared her perspective on the treatment she received and stopped receiving at some point to return back to it later: "I walked through hell after discontinuing my psychiatric medication, not sleeping at all, being crazy. My mood was unstable with extreme mood and blood sugar swings, with never-ending ups and downs. I was laughing and crying spells. Later, depressions with suicidal thoughts came back to me again…. There were times I beg for psychiatric treatment and its continuation despite my unwillingness. When I had decided to stop my medication, the only reason to do so was that I really needed to stop thinking about other health issues killing me at that time. I made my choice to artificially create a new problem that would distract me from the other problems. In addition, having a short-term experience to be a medication-free, I was worried that with a psychiatric medication, I would not be myself anymore. I would not be able to fully perceive my emotions. I would not be free anymore because of the decrease in my energy levels. I would stop flying high. I would have to fight with emotional barriers posed by medication, including my intimate life. I would have to bury or at least amputate my creativity. I would be a completely different person. After stopping my bipolar medication, I admitted the medication had been extremely helpful. With the medication, I found the stability that I needed in life. As a person living 25 years with type 1 diabetes, the experience of quetiapine discontinuation has taught me a lesson: My brain and mood have a joint control over my blood sugar that is beyond my control. So, it is my choice - it is up to me: To live longer and better with a stable, normalized mood and without significant diabetes complications or to have fluctuations in mood and fluctuations in blood sugar that will result in countless and serious problems".

Conclusion

The extent of dysglycemia during various stages and phases of bipolar disorder and its treatment remains unexplored in adults with type 1 diabetes mellitus. Continuous glucose monitoring allows to uncover hidden glucose patterns and associate them with mood changes, emotional urgency, and their treatment. Unmedicated bipolar disorder is characterized by less stable and elevated continuous glucose values compared to bimodal mood-stabilizing psychopharmacotherapy with quetiapine. Findings suggest that ongoing bipolar pharmacotherapy can alleviate mood-induced dysglycemia in type 1 diabetes mellitus. Continuous glucose profiles demonstrating a link between stability of glucose control and stability of mood can help boost the motivation of the patient and increase the adherence to psychopharmacotherapy. The enhanced patient-clinician shared clinical decision-making has a potential to yield future innovative clinical research into individually tailored treatment of "bipolar diabetes". Optimal diabetes care is interdisciplinary and complex. It is to provide continuous medical care with multifactorial risk-reduction strategies to reach a goal of safe near-normal glucose levels and a good quality of life.

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 independent ethics committee of the Presov self-governing region. 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. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

DB: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. MP: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, 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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Practice effects of personalized interventions with interdisciplinary teamwork in type 2 diabetes remission: a retrospective study

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Objectives: A retrospective analysis of the clinical outcomes of personalized interventions for type 2 diabetes mellitus (T2DM) in an interdisciplinary team.

Methods: Under the guidance of an interdisciplinary team, 40 patients with T2DM underwent a systematic examination at the beginning of the intervention, 3 months after the intervention, and 3 months of follow-up at the end of the intervention (i.e., at 6 months). Key indicators such as fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), fasting insulin level (FINS), glycated hemoglobin (HbA1c), blood lipids, and body mass index (BMI) were measured.

Results: After the 3-month intervention, participants' BMI, FPG, 2hPG, FINS, and HbA1c improved significantly, with statistically significant differences ($P<0.05$).These metrics remained essentially stable at the 3-month follow-up. Of all the participants, 92.5% (37 cases in total) successfully discontinued their medication after 3 months of intervention, of which 80% (32 cases) remained stable during the 3-month follow-up after discontinuation, fulfilling the criteria for remission of T2DM; 2 cases successfully reduced the dose of their medication, and only 1 case was maintained on the original treatment.

Conclusions: Through an interdisciplinary team intervention strategy, we significantly optimized the glucose metabolism, lipid metabolism, and BMI status of patients with T2DM, making diabetes remission an achievable goal, which provides valuable experience for further optimization of diabetes prevention and control protocols.

KEYWORDS

interdisciplinary, type 2 diabetes, personalized interventions, diabetes remission, retrospective study

Introduction

Type 2 Diabetes Mellitus (T2DM) was once viewed as a progressive, lifelong disease requiring medication (1–3). However, with a better understanding of diabetes and advances in the field of treatment, through intensive lifestyle interventions, medications, and metabolic surgeries, some diabetic patients have been able to completely discontinue their medications while keeping their blood glucose levels on target or within the normal range, achieving remission of their diabetes (4–7). This transformation not only significantly improves patients' quality of life and reduces healthcare costs, but also helps to slow the progression of diabetes, which is important for preventing complications and improving disease prognosis.

The traditional management strategy for T2DM has been described as a "five-pronged chariot", covering the five key aspects of diet, exercise, medication, blood glucose monitoring and health education (8, 9). However, in actual management, medication is still dominant. Guidelines increasingly emphasize the early use of more advanced and expensive hypoglycemic (10), lipid-lowering, and antihypertensive medications to control blood glucose and reduce associated complications and cardiovascular risk (2, 11, 12). In daily life, many T2DM patients lack adequate self-management, are more bound by traditional concepts, and tend to rely on medication for a long period of time, while ignoring the importance of comprehensive management.

Related research in 2011 showed that patients with T2DM could normalize beta cell function and hepatic insulin sensitivity by restricting dietary intake, which was associated with reduced triacylglycerol storage in the pancreas and liver. Since then, researchers have begun to delve into the possibility of disease reversal or remission (13). The line between mitigation and reversal is not always clear in this area. Reversal of T2DM refers to a change in the direction of the underlying pathogenic pathway that leads to a favorable recovery of the patient's health. We believe that the term "remission" is more appropriate because it specifies that the patient's metabolic status has improved to a nondiabetic level within the consensus definition of at least 6 months after cessation of glucose-lowering medication. However, it also means that there is a possibility of recurrence of the disease, rather than indicating that the disease has been completely and permanently cured (14). T2DM remission refers to a situation where, through specific interventions, a patient's blood glucose can remain at target or normal levels without the use of glucose-lowering drugs (15). This shift not only signifies a more proactive treatment goal for patients but may also offer new strategies to alleviate pressures on the global health system. However, in the past few years, such studies have mainly focused on T2DM patients with concomitant obesity, metabolic surgery to achieve T2DM remission (16–18), or on a single area such as lifestyle (19), exercise, weight management, or insulin-intensive therapy to explore its effect on T2DM remission, which often focuses on adjusting for a specific factor and ignores the fact that T2DM is a complex metabolic disease caused by a combination of genetic and environmental factors T2DM is a complex metabolic disease with multiple risk factors resulting from a combination of long-term effects (20). Even in the United States, 15% of newly diagnosed T2DM patients have a body mass index (BMI) within the normal range, suggesting that remission of T2DM is not limited to those with a BMI of more than 25 kg/m^2 (21–23). A comprehensive strategy is necessary to achieve diabetes remission, which requires the establishment of integrated teams for the multidimensional management of patients with T2DM. To the best of our knowledge, few studies have provided personalized and comprehensive interventions for patients with T2DM within the framework of interdisciplinary integrated team collaboration. Therefore, we conducted this study to focus on the effectiveness of a personalized and integrated approach to the practice of T2DM palliation under the guidance of an interdisciplinary team, to synthesize the existing evidence, and to provide directional recommendations for future research. We expect that this study will provide new perspectives and ideas for clinical practice, thereby advancing the progress of T2DM treatment strategies in a more beneficial and humane direction.

Materials and methods

Study design and participants

Inclusion criteria: (1) meeting the 1999 WHO diagnostic criteria for diabetes mellitus; (2) aged 18 -70 years; (3) insulin levels assessed by glucose tolerance test showing good pancreatic islet function; (4) normal cardiorespiratory fitness and absence of locomotor system disorders affecting exercise workouts; and (5) complying with the trial protocol and signing the informed consent.

Exclusion criteria: (1) adults with occult immune diabetes mellitus, type 1 diabetes mellitus and other types of diabetes mellitus; (2) those with acute complications of diabetes mellitus, such as ketoacidosis, lactic acidosis, and hyperosmolar hyperglycemic state; (3) those with acute and chronic metabolic acidosis, and acute infections; (4) women in pregnancy or breastfeeding; and (5) those with malignant tumors, and abnormalities of cardiac, renal, and hepatic functions. This study was reviewed and approved by the Ethics Committee of Foshan Hospital of Traditional Chinese Medicine (Ethics Approval Number: KY【2023】345).

Between March 2022 and March 2023, we conducted a comprehensive assessment of 56 patients diagnosed with type 2 diabetes mellitus in Foshan City Hospital of Traditional Chinese Medicine. Among them, 4 patients were unable to participate in this study due to insufficient fasting insulin level, 11 patients due to insufficient postprandial insulin, and 1 patient was unable to participate in this study due to both fasting and postprandial insulin insufficiency. The final 40 patients were managed with individualized and comprehensive diabetes treatment. We recorded the participants' medication regimens in detail at the baseline assessment stage. Of these, eight patients were treated with a single hypoglycemic agent, including metformin, SGLT-2 inhibitors, and sulfonylureas. Seventeen patients were treated with a combination of two glucose-lowering agents, such as metformin with a sulfonylurea, or a sulfonylurea with a DPP-4 inhibitor or SGLT-2 inhibitor. Fifteen patients involved a combination of three

different types of hypoglycemic agents, including different combinations of metformin, sulfonylureas, alpha-glucosidase inhibitors, SGLT-2 inhibitors, and DPP-4 inhibitors. None of the participants had received insulin therapy in the past three months. Before the intervention, the health manager had educated the patients about T2DM remission. The patients who participated in the study had carefully read and fully understood the diabetes remission program before the intervention.

Type of intervention

The study's intervention program integrated dietary modifications, exercise advice, health monitoring, medication use guidance, and psychological support to achieve a personalized diabetes mitigation strategy. Participants were enrolled in a 6-month telemanagement program consisting of dietitians, kinesiologists, endocrinologists, psychologists, and health administrators who provided ongoing, systematic services through a WeChat group. The specific responsibilities of each member in this study are detailed in Table 1. In this program, participants upload their diet, exercise, weight, blood glucose, and blood pressure data via WeChat on a daily basis. The remote management team would provide personalized advice to each participant based on these data, covering nutrition, exercise, and medication (24).

TABLE 1 Responsibilities of management team members.

Team members	Roles and responsibilities
Endocrinologist	Responsible for evaluating patients' conditions, developing and adjusting medical regimens, and monitoring efficacy and safety. Introduces the process of medical program implementation and the mechanism and significance of T2DM remission to patients to ensure that they fully understand and actively cooperate with the treatment program.
Dietitian	Responsible for helping patients fully understand the medical nutrition treatment process, the division of labor of the collaborative team, and after assessment, develop a medical nutrition treatment plan for patients based on guidelines and evidence-based evidence, and continuously follow up on implementation to ensure that the treatment plan is effectively implemented.
Kinesiologist	In conjunction with the physician, provide patients with exercise prescriptions that are of interest to them, are easy to perform and can be consistently adhered to, and instruct patients in proper exercise skills and methods.
Health manager	To help patients understand disease-related knowledge, teach them self-management knowledge and skills, and enhance their implementation of and adherence to lifestyle interventions.
Counselor	Regularly communicate with patients to improve their confidence in treatment and reduce the impact of adverse emotions on treatment outcomes.

Dietary interventions

The dietary intervention consists of three main meals and three additional meals per day, taking into account adequate water intake and essential micronutrients. The three additional meals at each stage should be based on the principle of "no additional meal if they are not hungry". To provide more personal flexibility, we allow patients to readjust their diets according to their individual preferences and needs, and provide professional guidance on diet and nutrition (25). Appropriate dietary and nutritional interventions are key to alleviating T2DM (26, 27). Measures such as the use of supplemental glycemic control foods and semi-replacement meals during treatment not only help to increase satiety, but also slow the absorption of carbohydrates, which in turn effectively aids in blood glucose management.

In our palliative practice, we implement an intensive dietary nutrition intervention program over a 4-12 week period. The program combines an energy-restricted balanced diet, a low-carb diet (28), ketogenic (29), intermittent fasting approach (30) and incorporates supplementation with key nutrients such as vitamin C, B vitamins, and micronutrients such as calcium and magnesium (31). During this process, we also meticulously managed and intervened in the patient's appetite. We encourage our patients to slow down the speed of eating and increase the number of chews, chewing 20 to 40 times for each bite of food and pausing appropriately between meals. To further reduce the speed of eating, we recommend using non-dominantly hand-held chopsticks or eating with a fork, as well as decreasing the portion size of each bite of food. It is recommended to drink a moderate amount of water before meals and consume a small amount of nuts, such as 10 almonds or 20 peanuts. When it comes to the order of eating, soup is the first thing they drink at a meal to help create a feeling of fullness. Then eat vegetables and low-sugar fruits, which, because of their size and low energy, not only help to increase satiety, but also help to slow down the absorption of food. Next consume meat, which are relatively high in energy and can further increase satiety. Finally, moderate intake of staples and carbohydrates. They can be effective in stabilizing postprandial blood sugar because they are absorbed more slowly. It is also important to increase dietary fiber intake, such as by increasing the intake of foods such as oats, whole grain breads made from meal replacement flours with 80% of the starch removed, green leafy vegetables, and low-sugar fruits (32). This can significantly prolong the feeling of fullness due to its slow emptying rate in the stomach. During the fortification period, we recommend a low-carb diet ration of 25-45% carbohydrates, about 10-15% protein, and 40-60% fat intake. And in a long-term maintenance diet, the recommended percentage of carbohydrate intake is 50-55%, protein stays at 10-15%, and fat is 30-40% (33, 34).

Exercise interventions

The exercise physician will develop an exercise prescription for the patient. Exercise will be gradually increased from the first week of the intervention. The increase in exercise volume can be paused and enter a maintenance phase when the following criteria are met: a minimum of 150 minutes of moderate to high intensity aerobic exercise per week, each lasting 30 minutes, with exercise intervals of

no more than two consecutive days, and moderate to high intensity resistance training three times per week (33). Depending on the individuality of the patient, the kinesiologist will decide on the timing of the increase in the amount of exercise and the selection of the appropriate exercise modality. The development of an individualized exercise program should, in principle, follow a gradual progression to ensure that the patient adapts gradually. All exercise programs are developed after evaluation by the kinesiologist.

Lifestyle and health monitoring

Adjust their routine to ensure that they go to bed on time and wake up early, aiming for 7-8 hours of adequate sleep each night. Increase daily activity and reduce sedentary behavior. To ensure accurate diabetes management, we continue to strengthen blood glucose monitoring and advise patients to measure fasting blood glucose at least once a day using a home glucose meter or ambulatory glucose meter. Every week, we choose a fixed time to measure body weight in the morning on an empty stomach and after completing a bowel movement. To ensure the accuracy of the measurement, it is recommended to do it under clothing of similar weight. In addition, waist circumference is measured once every two weeks in the morning while fasting and relaxed, using the belly button as a reference. Monitor blood pressure 1-2 times a week and try to do it at the same time in the morning. In addition, perform tests related to pancreatic function every three months.

Psychological interventions and medication guidance

Patients will receive regular follow-up visits from a counselor through a combination of online and offline visits. After a comprehensive assessment of the patient's medical history, symptoms, FPG, 2hPG, HbA1c, pancreatic islet function, and lipids by an endocrinologist, the patient will be given the appropriate drug regimen for clinical treatment. Through dynamic observation of the above indicators, endocrine specialists will conduct one-on-one assessment of the patient to determine his/her medication strategy, including maintenance of current medication, reduction of dosage, or complete discontinuation of medication.

Discontinuation: Under expert supervision, when the patient's condition has stabilized and FPG, 2hPG, and HbA1c have reached normal or personalized target levels and have been maintained for two weeks, the dosage of the medication will begin to be gradually reduced until it is discontinued. Even after stopping the medication, the patient still needs to receive ongoing interventions, testing and guidance.

Follow-up program

We will conduct follow-up visits in the 1st, 2nd and 3rd month after the personalized intervention to ensure that patients maintain healthy lifestyle habits. If during the follow-up, we find that the patient's blood glucose reaches the diagnostic criteria for T2DM, we will promptly advise them to go to the hospital to be evaluated by a professional doctor. Based on the assessment results, the doctor will decide on the appropriate treatment plan. If necessary, we can start this intervention program again. If medication is decided, we will record the name and dosage of the medication used by the patient. In addition, we also organize regular online and offline seminars on diabetes to help patients learn how to manage themselves.

Observation indicators

The aim of this study was to assess the effectiveness of the intervention by comparing the patients' BMI as well as the differences in glycemic and lipid biochemical indices before and after the intervention. The main blood glucose biochemical indicators we focused on were: FPG, 2hPG, HbA1c and fasting insulin level (FINS). And the insulin resistance index (HOMA-IR) was derived from the insulin calculation formula. Lipid biochemical indices included triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

Criteria for remission of type 2 diabetes mellitus were defined as an HbA1c value of less than 6.5% or an FBG of less than 7.0 mmol/L after at least 3 months of discontinuation of glucose-lowering medication or lifestyle intervention alone (14). According to Chinese standards, normal weight: 18.5 ≤BMI < 24kg/m^2, overweight: 24≤ BMI < 28kg/m^2, obese: BMI ≥ 28kg/m^2.

Statistical analysis

SPSS 26.0 statistical software was used for statistics and analysis. Normally distributed measurements were expressed as mean ± standard deviation ($\bar{x} \pm s$), and comparisons were made using the paired t-test. Non-normally distributed measures were expressed as *M(Q1, Q3)*, and comparisons were made using the *Kruskal-Wallis* rank sum test. Count data were expressed as constitutive ratios or rates (%), and comparisons were made using the $\chi 2$ test. Differences were considered statistically significant at $P<0.05$.

Results

Table 2 shows the basic characteristics of the patients before the intervention, out of these 40 participants, the mean age was 56.20 years and the mean BMI was 22.29 kg/m^2, there were 24 males and 16 females. The average duration of diabetes mellitus was 3.79 years, with 5 cases having a duration of 10 years or more, up to 16 years.

Change in weight and BMI

Table 3 displays the changes in weight and BMI indices during the pre-intervention, post-intervention, and follow-up periods. One-way repeated measures a one-way repeated measures analysis of variance (ANOVA) was applied, as the weight and

TABLE 2 Baseline characteristics of participants.

Characteristics	Participants (n = 40)
Male, n (%) Female, n (%)	24 (60) 16 (40)
Age,years (SD)	56.20 ± 7.76
Duration of T2DM,years (SD)	3.79 ± 4.04
Bodyweight, kg (SD)	63.22 ± 10.87
BMI,kg/m² (SD)	23.29 ± 2.88
Systolic Blood Pressure (mmHg) (SD)	125.35 ± 14.70
Diastolic Blood Pressure (mmHg) (SD)	78.00 ± 9.29

Data are in n (%); mean (SD); n, number.

BMI data met the criteria of normal distribution and demonstrated sphericity (*Machly's* $W = 0.946$, $p = 0.349 > 0.05$; *Machly's* $W = 0.953$, $p = 0.398 > 0.05$). The analysis revealed significant differences in weight and BMI among the pre-intervention, mid-intervention, and post-intervention phases ($F(2,78) = 50.86$, $p < 0.001$; $F(2,78) = 47.70$, $p < 0.001$). Bonferroni multiple comparisons revealed that there was a significant difference in weight between post-intervention and follow-up compared to pre-intervention, with p-values < 0.05. When comparing post-intervention with follow-up, the p-value was > 0.05, indicating no statistical difference. In summary, there was a noticeable decrease in weight and BMI indices post-intervention. However, during the follow-up period, both weight and BMI remained stable, showing no further significant changes.

Changes in blood glucose control levels

Table 4 presents the changes in HbA1c, FPG, and 2-hour PG during the pre-intervention, post-intervention, and follow-up periods. Given the normal distribution of HbA1c, FPG, and 2-hour PG data, ANOVA was employed. HbA1c and FPG data satisfied the sphericity test (*Mauchly's* $W = 0.901$, $P = 0.138 > 0.05$; *Mauchly's* $W = 0.974$, $P = 0.61 > 0.05$), while 2-hour PG did not meet the assumption of sphericity (*Mauchly's* $W = 0.69$, $P = 0.01 < 0.05$), and thus, Greenhouse-Geisser correction was applied. The analysis results indicated significant differences in HbA1c, FPG, and 2-hour PG levels among the pre-intervention, mid-intervention, and post-intervention phases ($F(2,78) = 66.49$, $P < 0.001$; $F(2,78) = 32.35$, $P < 0.001$; $F(1.527, 59.55) = 22.87$, $P < 0.001$). Bonferroni multiple comparisons revealed significant differences in HbA1c, FPG, and 2-hour PG levels between post-intervention and pre-intervention ($P < 0.05$) as well as between follow-up and pre-intervention ($P < 0.05$). However, no statistical differences were observed in HbA1c, FPG, and 2-hour PG levels between post-intervention and follow-up ($P > 0.05$). In summary, there was a significant decrease in HbA1c, FPG, and 2-hour PG indices after the intervention. However, during the follow-up period, both HbA1c, FPG, and 2-hour PG levels remained stable, showing no further significant changes.

Changes in insulin resistance

Table 5 illustrates the changes in FINS and HOMA-IR levels during the pre-intervention, post-intervention, and follow-up periods. Due to the normal distribution of FINS and HOMA-IR data, one-way repeated measures analysis of variance was employed. However, both FINS and HOMA-IR data did not meet the assumption of sphericity (*Mauchly's* $W = 0.826$, $P = 0.026 < 0.05$; *Mauchly's* $W = 0.81$, $P = 0.018 < 0.05$), necessitating the use of Greenhouse-Geisser correction. The analysis results indicated significant differences in FINS and HOMA-IR levels among the pre-intervention, mid-intervention, and post-intervention phases ($F(1.70, 66.43) = 16.61$, $P < 0.001$; $F(1.68, 65.52) = 29.43$, $P < 0.001$). Bonferroni multiple comparisons revealed significant differences in FINS and HOMA-IR levels between post-intervention and pre-intervention (P <0.05) as well as between follow-up and pre-intervention ($P < 0.05$). However, no statistical differences were observed in FINS and HOMA-IR levels between post-intervention and follow-up (P >0.05). In summary, there was a notable decrease in FINS and HOMA-IR indices after the intervention, while during the follow-up period, both FINS and HOMA-IR levels remained stable, showing no further significant changes.

Lipid biochemical change

Table 6 displays the changes in blood lipid biochemistry before and after the intervention. Comparison of the changes in blood lipid biochemistry, including TG, TC, HDL-C, and LDL-C, before and after the intervention was conducted using paired samples t-test, as the data met the criteria of normal distribution. The analysis results revealed that there were statistically significant differences ($P < 0.05$) in the mean values of TG, TC, and HDL-C between pre-intervention and post-intervention. The p-value for the mean LDL-C levels between pre-intervention and post-intervention was > 0.05, indicating no statistically significant difference.

TABLE 3 Comparison of weight and BMI indicators.

	Baseline	3 months	6 months	F-value	P-value
Weight	63.22 ± 10.87	58.42 ± 10.29①	59.60 ± 10.43①	50.86	<0.001
BMI	23.29 ± 2.88	21.51 ± 2.62①	21.94 ± 2.62①	47.70	<0.001

Bonferroni post hoc tests were conducted to perform pairwise comparisons:
①indicates $P < 0.05$ compared to pre-intervention.

TABLE 4 Comparison of glucose metabolism indicators.

	Baseline	3 months	6 months	F-value	P-value
HbA1c	7.13 ± 0.74	5.93 ± 0.47①	6.15 ± 0.64①	66.49	<0.001
FPG	7.42 ± 1.17	6.29 + 1.01①	6.20 ± 0.86①	32.35	<0.001
2hPG	13.54 ± 3.81	11.07 ± 3.29①	10.41 ± 2.44①	22.87	<0.001

① indicates $P < 0.05$ compared to pre-intervention.

Comparison between remission and non-remission groups

Table 7 shows the comparison of remission rates between males and females and remission rates under different menstrual phases in females. Corrected X^2 test was used because n=40, 1≤T<5. Because $X^2 = 0.0$, $P = 1.00 > 0.05$, not significant, there was no difference in T2DM remission by gender. In the female population, we conducted a comparative analysis of the effect of different menstrual stages on T2DM remission. Given the sample size of n=16, the *Fisher* X^2 test was used in this study and the chi-square value (X^2) = 1.11 was obtained while P=1.00 > 0.05, which is not significant. The insignificance of this result may stem from the small sample size of the study, which limits the ability to detect potential associations. Future studies could enhance the accuracy and reliability of statistical tests by increasing the sample size. Table 8 shows the comparison of indicators between the remission and non-remission groups.

We studied the remission of diabetes at different age of onset. The results of the study showed that in the age group of 30 to 40 years, 4 out of 6 participants succeeded in remission with a remission rate of 66.67%. Whereas in the age group of 40 to 50 years, 5 out of 8 participants had successful remission with a remission rate of 62.5%.In the age group of 50 to 60 years, 16 out of 18 participants had successful remission with a remission rate of 88.89%. In the age group of 60 to 70 years, 7 out of 8 participants were successfully relieved with a remission rate of 87.5%.When analyzing the overall effect of age of onset on remission in a comprehensive manner, we did not find a clear pattern. This phenomenon can be caused by a number of factors, including the length of time the patient has had the disease, adherence during

TABLE 5 Changes in insulin resistance.

	Baseline	3 months	6 months	F-value	P-value
FINS	52.66 ± 21.36	40.72 ± 15.45①	40.56 ± 14.31①	16.61	<0.001
HOMA-IR	2.93 ± 1.34	1.94 ± 0.90①	1.89 ± 0.77①	29.43	<0.001

① indicates $P < 0.05$ compared to pre-intervention.
The unit of FINS is pmol/L. (Same as Table 8). HOMA-IR=[FPG(mmol/L)×FINS(μU/mL)]/22.5, Insulin conversion factor: 1μU/mL≈6pmol/L (35).

TABLE 6 Comparison of indicators of lipid metabolism levels.

	TG	TC	HDL-C	LDL-C
Baseline	1.40 ± 0.70	5.01 ± 1.20	1.29 ± 0.27	3.34 ± 1.07
3 months	0.92 ± 0.41	4.54 ± 0.88	1.76 ± 0.40	3.11 ± 0.79
t-value	5.764	2.879	-8.751	1.597
P-value	<0.05	<0.05	<0.05	>0.05

TABLE 7 Comparison of gender and rate of relief of menstrual status among women.

		Remission group	Non-remission group	χ2	P
Sex	Male	19 (79.2%)	5 (20.8%)	0.00	1.00
	Female	13 (81.3%)	3 (18.8%)		
	n	32	8		
Menstrual state	Menopausal	9 (81.8%)	2 (18.2%)	1.11	1.00
	Non-menopausal	4 (80.0%)	1 (20.0%)		
	n	13	3		

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TABLE 8 Comparison of (mean standard deviation) between remission and non-remission groups.

	Age	Duration	Baseline					3 months					6 months				
			BMI	HbA1c	FPG	2hPG	FINS	BMI	HbA1c	FPG	2hPG	FINS	BMI	HbA1c	FPG	2hPG	FINS
Remission group	56.19± 7.85	2.66± 3.05	23.26± 3.07	7.09 ± 0.69	7.28± 1.15	13.65± 4.02	51.02± 22.19	21.51± 2.72	5.92 ± 0.43	6.15± 0.87	11.18± 3.47	39.91 ± 15.54	21.88± 2.75	5.92 ± 0.46	5.92± 0.72	10.54± 2.60	39.34± 13.69
Non-remission group	56.25± 7.92	8.29± 4.56	23.42± 2.09	7.28 ± 0.94	8.00± 1.13	13.08± 3.03	59.20± 17.35	21.50± 2.36	5.93 ± 0.64	6.86± 1.40	10.59± 2.60	43.93 ± 15.66	22.18± 2.19	7.07 ± 0.38	7.32± 0.33	9.92± 1.69	45.42± 16.63

treatment, and daily lifestyle. Meanwhile, the sample size of this study is limited, which may be a non-negligible factor affecting our conclusions. In future studies, we will expand the sample size to improve the statistical credibility of the data.

Discussion

In recent years, the dramatic increase in type 2 diabetes globally has been largely attributed to environmental factors, with people's poor lifestyles playing a key role. Although each patient needs to receive a basic treatment approach, in practice we still need to develop an individualized treatment plan based on each patient's specific situation. This individualized approach takes into account the patient's genetic background, lifestyle, metabolic status and differences in response to treatment. Recognizing this, our research team adopted an innovative strategy by assembling an integrated interdisciplinary team. The objective was to employ a personalized approach in combatting T2DM and to evaluate its clinical effectiveness. The study's findings are promising. This comprehensive intervention approach not only significantly enhanced patients' blood glucose control, rejuvenated pancreatic β-cell function, and improved insulin sensitivity, but also optimized BMI and lipid metabolism profiles. More importantly, patients in T2DM remission were able to cease using glucose-lowering medications. This not only alleviated their psychological stress but also bolstered their confidence in leading a healthier life. As a result, patients experienced an improved quality of life, delayed disease progression, and a reduced risk of complications. This provides new ideas for the future prevention, control and treatment of T2DM. In a reversal of previous perceptions, T2DM is not necessarily a progressive disease. It is possible to achieve remission through personalized intervention. This brings a challenge to the long-held notion that T2DM patients need to take medication for life.

In this study, which focused on the middle-aged and elderly population, At the end of the study, 37 (92.5%) of all participants successfully discontinued their medication after the intervention; two others failed to completely discontinue the medication but succeeded in reducing the dosage, and only one continued with the original medication. Notably, 32 (80%) of the patients who successfully discontinued the drug remained in stable status 3 months after discontinuation, fulfilling the remission criteria for T2DM.For those five patients who failed to achieve sustained stabilization, there may be multiple reasons. First, older age and longer duration of diabetes were key predictors of failure to achieve remission. Patients who have had diabetes for more than 10 years have a significantly reduced chance of remission. Reduced insulin sensitivity and decreased insulin secretion with advancing age made the pre-intervention status of these patients even more unfavorable, making it predictably less likely that they would go into remission. Patients who have had diabetes for more than 10 years have a significantly reduced chance of remission. Reduced insulin sensitivity and decreased insulin secretion with age make the pre-intervention status of these patients even more unfavorable, making it predictably less likely that they will go into remission. Further,

patient compliance is extremely critical. If they don't follow their doctor's instructions to the letter after stopping their medication, or fail to adhere to recommended lifestyle and dietary habits, or don't engage in regular glucose monitoring, they may be at an increased risk of relapse. It is worth pointing out that even among patients who did not fully meet the remission criteria, they achieved significant improvements in glucose metabolism. The trends in lipid biochemistry changes before and after the intervention as a whole showed a significant improvement.

In our study, the mean value of baseline BMI was 23.29 ± 2.88. Out of 40 study subjects, 14 were categorized as overweight and 3 of them met the criteria for obesity. Surprisingly, however, despite the fact that 65% of the participants in the study were categorized as not being in the overweight or obese group, these individuals demonstrated a considerably higher rate of T2DM remission. This observation can be linked to the personal fat threshold (PFT) hypothesis. According to this hypothesis, the storage capacity of subcutaneous fat may vary from individual to individual. The theory is that each individual may have a unique PFT, a threshold that determines their susceptibility to developing T2DM (21). T2DM may develop when an individual gains enough weight to exceed their PFT, as this fat accumulation may lead to insulin resistance and metabolic problems. However, by losing weight and returning to a weight below the personal adiposity threshold, normal blood glucose levels are expected to be restored, i.e., remission of T2DM is achieved (22). This perspective is important because it suggests that the disease is not a weight-dependent manifestation of different pathogenic mechanisms, but rather that there are common physiologic mechanisms. It also provides a more personalized approach for non-overweight/obese T2DM patients in order to develop more effective strategies based on each individual's physiology.

Results from The Diabetes Remission Clinical Trial (DiRECT) showed that at 1-year follow-up, 46% of patients achieved remission of T2DM through intensive dietary and lifestyle interventions, compared with only 4.0% of patients in the control group. At the end of RCT, the 2-year intention to treat remission rate was 36.0% (15, 36). Taheri, S et al. randomly assigned T2DM patients with disease duration of up to 3 years in a 1:1 ratio to an intensive lifestyle intervention group and a control group with usual medical care. After a 1-year follow-up, the results showed that the remission rate of T2DM was as high as 61% in the intervention group, whereas in the control group, the remission rate was only 12% (37). In comparison, the intervention approach used in this study demonstrated a more significant mitigating effect. This may be attributed to our interdisciplinary synergy, personalized and comprehensive intervention strategies, well-targeted education and guidance, and comprehensive and multidimensional health management of patients. However, it is important to note that our follow-up period was relatively short. This may mean that the effectiveness and persistence of the intervention may change as time advances. The higher remission rate in this study may be related to the relatively short follow-up period, whereas longer follow-up periods have resulted in lower remission rates in other studies. This study shows data from 6 months of systemic management. Further systemic management is needed for these participants, and we will conduct a long-term follow-up study and publish long-term findings in the future.

Our treatment program does require an increased professional time commitment from participants in the short term compared to traditional clinical treatment. However, our program introduces an element of self-management and collaboration that consciously reduces the burden on patients with the help of modern technology and remote support. Patients use WeChat to clock in and out, participate in health group interactions, and follow professional advice on exercise and diet management. This flexible teletherapy approach not only reduces the amount of time patients spend traveling to the hospital, but also improves the efficiency of treatment. In the long run, we see this investment of specialized time as a great long-term investment. By engaging patients to better understand their health status and actively participate in their treatment plans, we anticipate that treatment outcomes will be improved, resulting in a reduction in the risk of complications and frequency of medical visits. On the issue of sustainability, we emphasized the need to work closely with patients to develop practical treatment plans to reduce their burden. At the same time, the support of the healthcare system and the allocation of resources are key to ensuring long-term sustainability. By continuously improving and optimizing treatment processes, we expect to achieve a sustainable balance between the time investment of patients and professionals.

There are some limitations to this study. First, there was no blank control group, which may have had some impact on the results. Second, some of the results may be biased due to the limited sample size. Third, there may be some bias in participants' self-reported data on dietary intake and exercise. In order to more accurately assess the effects of personalized comprehensive interventions in T2DM remission, we suggest future randomized controlled studies covering multiple centers with larger sample sizes, higher quality, and longer follow-up periods. This will not only help validate our findings, but also further refine and optimize treatment strategies for T2DM.

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 studies involving humans were approved by Foshan Hospital of Traditional Chinese Medicine Medical 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

XT: Conceptualization, Writing – original draft. YT: Writing – review & editing. RH: Writing – original draft, Data curation, Software. JY: Conceptualization, Writing – review & editing. HC:

Data curation, Writing – review & editing. JW: Data curation, Writing – review & editing.

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Conflict of interest

Author JW was employed by Guangzhou ShanMao Health Technology LTD.

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

Publisher's note

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Circadian dysfunction and cardio-metabolic disorders in humans

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The topic of human circadian rhythms is not only attracting the attention of clinical researchers from various fields but also sparking a growing public interest. The circadian system comprises the central clock, located in the suprachiasmatic nucleus of the hypothalamus, and the peripheral clocks in various tissues that are interconnected; together they coordinate many daily activities, including sleep and wakefulness, physical activity, food intake, glucose sensitivity and cardiovascular functions. Disruption of circadian regulation seems to be associated with metabolic disorders (particularly impaired glucose tolerance) and cardiovascular disease. Previous clinical trials revealed that disturbance of the circadian system, specifically due to shift work, is associated with an increased risk of type 2 diabetes mellitus. This review is intended to provide clinicians who wish to implement knowledge of circadian disruption in diagnosis and strategies to avoid cardio-metabolic disease with a general overview of this topic.

KEYWORDS

circadian clock, circadian rhythm disruption, cardiovascular disease risk, type 2 diabetes mellitus, insulin sensitivity, glucose tolerance, time restricted eating

1 Circadian clock and its parameters

Circadian rhythms are driven by endogenous cellular clocks that are responsible for temporal programming of physiological and behavioral processes, as well as the synchronization of these processes with changes in environmental conditions within a 24-hour cycle. These clocks generate rhythm with an approximate 24-hour period owing to a molecular transcriptional-translational feedback loop (TTFL) composed of families of clock genes (e.g. human genes PER1-3, CRY1-2, NR1D1-2, RORA-C, BMAL1-2, CLOCK, NPAS2) that are quite kept across different animal phyla (1). The encoded proteins function as transcriptional activators or repressors, controlling the expression of their

partners and downstream clock-controlled genes, which govern tissue-specific rhythmic processes. Levels of regulation in addition to TTFL such as phosphorylation of key proteins, further guarantee the stability, precision and temperature compensation of the cellular clock (2).

In humans, as in other mammals, the clocks are mutually interconnected to form a hierarchical system, which is governed centrally from a structure in the hypothalamus called the suprachiasmatic nucleus (SCN) (3). These paired nuclei are morphologically and functionally arranged as the main trigger of rhythmicity at the systemic level (Figure 1) and receive all signals directly from specific cells in the retina, which enable synchronization of the physiological biorhythm with light-dark cycles. Other internal clocks in the brain and elsewhere in the body use some of the SCN-controlled rhythmic signals, in addition to external time, to synchronize with each other. This is achieved via multiple signals which include daily changes in the tonus of autonomous nerves system, hormone levels, body temperature, metabolic state, etc. Although the SCN clock receives feedback from peripheral tissues, it is predominantly synchronized by the light/dark cycle and is highly resistant to most of the signals under standard conditions of energy balance (4).

Signals which entrain circadian clocks are called "Zeitgeber" (time giver or time cue in German), a term which was first used by Jürgen Aschoff, one of the founders of the field of human chronobiology (5). His work demonstrated the existence of endogenous (internal) biological clocks in humans maintained in time-isolation. In addition, he showed that certain exogenous (external) cues, which he called Zeitgebers, influence the phase and period of these internal clocks (5).

1.1 Sleep parameters and their evaluation

Sleep is the most important factor when setting one's circadian rhythmicity. Its timing is controlled by a complex process that requires coordination between the circadian clock in the SCN and hormonal homeostasis (6). Nevertheless, other factors such as mental and physical health can also be very important aspects for quality of sleep.

Most of the latest sleep studies have focused on basic sleep parameters that include sleep duration (e.g., insomnia, hypersomnia), sleep quality (e.g., fragmentation) and sleep timing (e.g., delayed, advanced, irregular, non-24 hour) (7). These sleep characteristics are often related to individual chronotype (6), as is discussed below.

There are multiple approaches (both subjective and objective) to evaluating sleep parameters, depending on the type of the study, experimental conditions and expected outputs (8).

A subjective evaluation of sleep quality is attained by using specialized self-reported questionnaires. The most commonly used questionnaires include, but are not limited to, the Pittsburgh Sleep Quality Index (PSQI), the Jenkins Sleep Scale (JSS), the Leeds Sleep Evaluation Questionnaire (LSEQ), the Insomnia Severity Index (ISI), and the Epworth Sleepiness Scale (ESS) (Table 1). Some questionnaires include additional questions regarding socio-economic status in order to collect information on social deprivation (EPICES) or employment conditions (KARASEK) (7).

The PSQI is a self-report questionnaire, developed by researchers at the University of Pittsburgh (8), that evaluates sleep quality over a period of 1 month. The evaluation consists of 19 individual items, which form 7 components that provide an

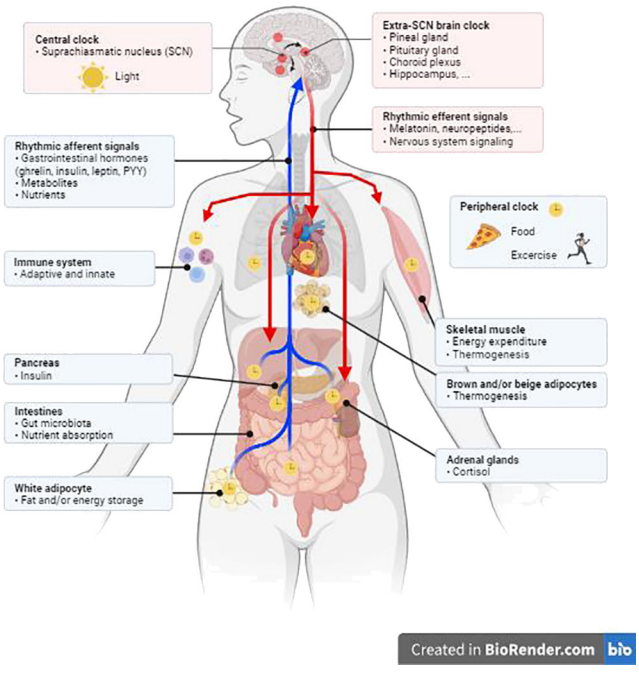

FIGURE 1
The peripheral circadian clock is regulated by the central clock in the suprachiasmatic nucleus (SCN) through responses to hormones, the neurological system, physical activity, and eating habits. Created in BioRender.

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TABLE 1 Types of questionnaires used to assess sleep quality.

Name of questionnaire	Number of questions	Result score range	Focus/output
Pittsburgh Sleep Quality Index (***PSQI***	7	0-21	7 components to asses overall sleep quality >5 considered as a significant sleep disturbance
Insomnia severity index (***ISI***)	17	0-28	evaluates symptoms of insomnia, valuation of sleep difficulty intensity >15 score indicates moderate to severe insomnia, 8- 14 subthreshold insomnia
Morningness – Eveningness Questionnaire (***MEQ***)	19	16-86	psychological behavior 5 chronotypes (extreme morning, moderate morning, intermediate, moderate evening, extreme evening)
Munich Chronotype Questionnaire (***MCTQ***)	17	Sleep time in hours	primarily focused on sleep timing relation to age, gender and self-declared body mass index MSFsc: midpoint of sleep on work-free days, corrected for sleep-debt to asses chronotype
Sleep Timing Questionnaire (***STQ***)	18	Direct responses	used to determine habitual bedtime and wake times

overall score. It is the most commonly used subjective assessment of sleep quality and is therefore utilized as a standardized sleep questionnaire for clinicians and researchers. When assessing the PSQI, seven component scores are evaluated, each receiving a score from 0 (no difficulty) to 3 (severe difficulty). The component scores are added together to give an overall score (range 0 to 21). Higher scores indicate poorer sleep quality. The PSQI is a general assessment and includes subscales that measure total sleep time, sleep onset latency, sleep efficiency (ratio of total sleep time to time spent in bed), sleep disturbances, degree of fragmentation (i.e., the number of arousals in relation to total sleep time), use of sleep medications, daytime alertness and total waking time. Little is currently known about how the various constructs, which comprise the PSQI, are individually related to diabetes control (9).

The Sleep Regularity Index (SRI) is a relatively new metric for measuring sleep regularity. The SRI evaluates the probability (presented as a percentage) of an individual being in the same state (awake or asleep) at any two time points 24 hours apart (10). Delays in circadian sleep/wake cycles and unfavorable cardiometabolic (CM) outcomes, such as an increased 10-year risk of cardiovascular disease, obesity, hypertension, T2DM markers, high fasting blood glucose levels and glycated hemoglobin (HbA1c), have been linked to lower SRI scores (11). These metrics, implemented as supplementary techniques used to characterize sleep regularity in ongoing studies, may provide a better understanding of the association between sleep and cardio-metabolic disorders.

Essentially, there are objective and subjective methods to classify sleep parameters in a patient. With regards to the objective assessment, polysomnography (PSG) is considered the gold standard when evaluating sleep physiology (12). This method implements a significant amount of complementary information that can be useful in various ways, such as in diagnosing sleep disorders (Figure 2). Polysomnography requires overnight monitoring of the patient in a specialized medical facility, and it is therefore not suitable for the assessment of sleep parameters in real life conditions. Various devices for monitoring behavioral activity (actigraphy) and other sleep parameters have been developed for this type of "field study."

Actigraphy is used to evaluate activity and rest cycles to determine sleep parameters such as timing, duration and fragmentation. Behavioral activity is monitored by a small motion sensor detector (accelerometer) worn like a watch on the non-dominant wrist (13). It enables the tracking of sleep over extended periods of time in a non-laboratory environment. These devices allow long-term non-invasive examination of circadian rhythm and sleep disruption in patients with various disorders, including neurodegenerative (14) and CM disorders (15).

The new wave of fitness trackers and other health-optimizing ('biohacking') gadgets is booming, multisensory devices are becoming popular due to the fact that they are labelled 'user-friendly' by the trade industry. These devices are capable of receiving a wide range of biosignals from their users. However, the effectiveness of these commercial devices remains controversial and their reliability has yet to be tested. In a recent study, four wearable (*Fatigue Science Readiband, Fitbit Alta HR, Garmin Fenix 5S, Garmin Vivosmart 3)* and three non-wearable (*EarlySense Live, ResMed S+, SleepScore Max)* consumer sleep-tracking devices were tested for performance in thirty-four healthy young adults (22 women; mean age 28.1 ± 3.9 years). All sleep data from these devices were compared with the data from actigraphy and PSQ. Most devices performed on par with (in some cases even outperforming) actigraphy in measuring sleep-wake performance, while the Garmin devices fared worse (16). A Korean study compared another well-known activity tracker called Fitbit

FIGURE 2
Comparison of sleep assessment methods by levels of accuracy.

Charge HR to actigraphy in 16 healthy young adults, and the results showed high accuracy of Fitbit tracker in assessing sleep and measuring circadian rest-activity rhythm (17). Ring-sized wearables are increasingly used by many consumers worldwide. One study tested the ŌURA ring and compared its performance in measuring sleep and sleep stages with that of the PSG. Sleep was monitored during a single laboratory night in 41 healthy adolescents and young adults (13 females; mean age: 17.2 ± 2.4 years) (12). In our opinion, this well-designed study provided promising results that confirm the performance of this device. The study showed that the summary variables for key sleep parameters, such as sleep onset latency, total sleep time, and waking after falling asleep, did not differ between the ŌURA ring and the PSG. The ŌURA ring was 96% in accordance with the PSG in detecting sleep, other parameters like wakefulness (48%), light sleep (65%), deep sleep (51%) and REM sleep (61%) were less in conformity. However, the ŌURA ring produced considerable variability in measuring sleep depth (underestimation) and REM sleep (overestimation) (18, 19).

These results suggest that many commercial sleep monitors show promising performance in monitoring sleep and wakefulness. In future studies, they should be tested under different conditions (different populations and environments) in order to further investigate their broader validity and applicability in medical research as an alternative tool to actigraphy for sleep assessment and circadian rest-activity rhythm measurement in a real-world environment. The increasing availability of more sophisticated devices, which go beyond mere activity recording, could provide clinicians with the opportunity to analyze diversity of sleep and physiological events during sleep in more detail.

1.2 Chronotype and its evaluation

Individuals differ greatly in their preferences for the time of day at which they perform certain activities and when they sleep. This phenomenon is called a chronotype (20) and is the natural preference of the body for wakefulness and sleep relative to solar time (and social time). Among the general population, chronotypes exhibit almost a normal Gaussian distribution (21).

It is assumed that the chronotype is determined by the central circadian clock and is also expressed via a peripheral clock within an organism (22). The exact mechanism underlying the chronotype is not yet fully understood. It is most likely related to the duration of the endogenous period of the SCN clock, since individuals with clocks that run with longer periods tend to be later chronotypes (22). However, other clock parameters may be involved, such as amplitude and its ability to entrain with actual light exposure (23). In addition, genetic, social, and environmental factors can also affect he chronotype (24). A chronotype changes considerably over the course of a lifetime, with adolescents being late chronotypes, while children and older people tend to be early chronotypes (25). A chronotype also appears to be dependent on biological sex since males tend to be late chronotypes more often than females (23), however, this difference is age-dependent (26). The factors that determine an individual's chronotype are therefore complex.

A chronotype can be determined subjectively using standardized, validated self-assessment questionnaires, as well as objectively by recording daily behavior using the methods described above or by analyzing biochemical/molecular biomarkers in non-invasively collected biological samples. The latter approach can provide precise information about the actual phase or period of the internal circadian clock.

There are 2 commonly used chronotype questionnaires for subjective assessment: the Morningness - Eveningness Questionnaire (MEQ), which assesses the preferred timing of various behaviors and the Munich Chronotype Questionnaire (MCTQ), which takes into account differences in sleeping patterns between workdays and work-free days during the week (21). The MEQ questionnaire includes 19 specific questions to determine whether a person's circadian rhythm peaks (in terms of alertness) in the morning, evening or in between these two periods. Most of the questions are preferential, e.g., the respondent is asked to indicate when they would like to wake or sleep if they had a choice (full control over their sleep/wake cycle). The MEQ questionnaire categorizes groups into morning types, evening types and intermediate types. The score ranges from 16 to 86, with lower scores indicating the evening types. The MCTQ is a useful tool in assessing chronotypes based on self-reported times of sleep or wakefulness, as well as sleep latency and inertia. The questionnaire expresses the chronotype as a midpoint of sleep on work-free days (Mid-Sleep on Free Days or MSF). The MCTQ and its significantly shortened version, μMCTQ (27), have been proven useful in assessing chronotypes in studies involving large populations, primarily through the use of an online version of the questionnaire (21). A more demanding approach is to identify a chronotype by incorporating the MCTQ into a group of questions within a population-representative sociodemographic survey. These are carried out by in-person visits to households, which provide data on chronotypes and their correlation with various social, health and life-style factors (20).

Methods used to estimate a chronotype objectively are mostly based on wrist actigraphy, i.e., the same methodology mentioned above for the assessment of sleep timing. One modification of this approach is to measure circadian rhythm parameters by monitoring wrist temperature, which is partially subject to regulation by the circadian system (28). Newer devices are equipped with a temperature sensor that is attached to the inside of the wrist with medical tape, with the sensor surface placed over the radial artery of the non-dominant hand. This temperature marker has been validated to reflect the circadian rhythm, which is related to the timing of light exposure and the amplitude of melatonin secretion.

Melatonin is produced in the pineal gland and regulated mainly by the SCN clock and light exposure (29–31). Therefore, an increase in melatonin levels exceeding the low diurnal levels found under low light conditions is used as a marker for the endogenous clock and determines the onset of subjective night, which varies according to chronotype (14).

More recently, other non-direct light-responsive markers have been introduced. They are mostly based on the molecular mechanism underlying circadian rhythmicity at the cellular level, and they have the ability to detect the phase of the molecular clock

in human samples, such as blood, skin, oral mucosa, and hair follicles (22).

1.3 A chronotype and its association with CM disorders

All the approaches mentioned above require collecting samples from subjects in short intervals around the clock. As a result, there has been an effort to introduce a technology that can reliably detect the phase of the clock from a single sample. Novel technologies suitable for rapid assessment of the phase of the circadian system and chronotype in outpatient care would provide useful diagnostic information in treating not only sleep disorders but also lifestyle-related disorders. Indeed, having an extreme chronotype is recognized as one of the risk factors or subclinical predictors of metabolic and cardiovascular disorder (CVD). Evening (late) chronotypes are generally more susceptible to CVD than are morning chronotypes (32). The pathomechanisms are unclear, but they are often explained as being related to either lifestyle factors (e.g., smoking and drinking alcohol; both more common in late chronotypes) or an increased susceptibility to disruption of rhythms (see below). For example, late chronotypes have significantly higher fasting blood glucose, HbA1c, triglycerides and low-density lipoprotein cholesterol (LDL) than their morning counterparts; however, no significant differences were found in BMI, the energy intake or blood pressure (BP) (33). When gender was involved as a variable in one study, a late chronotype correlated with a higher BMI, specifically in women (20). An extremely late chronotype, normalized for age and sex, has significantly lower HDL levels and a higher LDL/HDL ratio than those of an extremely early chronotype (20). A late chronotype is also positively correlated with levels of proteins associated with insulin resistance and cardiovascular disease, specifically retinoic acid receptor protein 2, fatty acid-binding protein adipocytes, tissue-type plasminogen activator, and plasminogen activator inhibitor (32).

Many studies have repeatedly confirmed that the risk of developing type 2 diabetes mellitus (T2DM) is higher in late chronotypes (34). Studies revealed that a chronotype could have a significant impact on insulin resistance since late chronotypes are associated with less favorable glycemic control; these studies did not take sleep duration or overall physical activity (PA) into account (35, 36).

Interestingly, recent evidence suggests that not only late chronotypes but also extremely early chronotypes may be associated with increased CVD markers such as lower HDL, higher triglycerides and an increased atherogenic plasma index (26). Due to a lack of evidence, we can currently only speculate about the underlying mechanisms. Since extreme chronotypes tend to have a larger phase angle between their endogenous clock and external time than do non-extreme chronotypes, the amplitude of their rhythms may be negatively affected. This may be further exacerbated by weak entrainment cues in modern urban settings. Instead of continually adapting to external time, extreme early chronotypes may experience sudden phase shifts when their clock runs out of sync with the light-dark cycle. This may destabilize the endogenous rhythm governing the metabolism of fatty acids and cholesterol.

Having a late chronotype is a strong predictor for a higher discrepancy between social time and endogenous (biological) time, which is referred to as social jet lag (21). This discrepancy is common in modern society and can be a result of either poor synchronization of the preferred sleep-wake cycle with social time (by choice or due to illness) or night shift work schedules. Some evidence indicates that the mismatch between preferred sleep time and long-term work schedules is associated with an increased risk of T2DM due to the disruption of glucose metabolism and a reduction in glucose tolerance (37). This mismatch could worsen disease prognosis in patients already diagnosed with T2DM (37). However, social jet lag is not only limited to shift workers since a significant portion of the population with standard work schedules experience this condition to a certain degree. In a recent population-representative study, 1957 blood samples were analyzed for 9 different biomarkers and results revealed significant associations between sleep phase preference, social jet lag and CVD biomarkers (26).

There are, however, other non-circadian factors that are linked to poor health and increased CVD risk; late chronotypes are more associated with unhealthy dietary habits (e.g., late-night eating), reduced PA and/or a low-quality social life (20). Therefore, the relation between late chronotypes, social jet lag and the risk of CVD may involve both environmental and behavioral factors.

1.4 Sex differences in sleep, chronotype and their relationship with CM disorders

Women are generally underrepresented in many research studies focusing on human physiology, with circadian and sleep research being no exception. Many human studies tend to exclude women from participation due to fluctuation in female hormone levels combined with the overall neuroendocrine system would possibly modulate circadian responses. A British study on the association between sleep and cognitive performance in men and women found that some circadian characteristics, such as the natural oscillation of the circadian clock and the amplitude of the melatonin rhythm, differ between men and women; however, no differences were observed with regards to usual amount of time spent in bed, sleep duration, or sleep quality as measured by the PSQI. Interestingly, the study revealed differences between the sexes with respect to circadian rhythmicity in cognitive skills; women experienced greater night-time impairment in cognitive performance than did men (38).

Sex-related sleep disturbances may impact CM functions via disruption of circadian regulation as well as downregulation of the metabolic pathways. The SWAN (Study of Women's Health Across the Nation) cohort study in perimenopausal women (mean age: 51 years) discovered that the greater the variability in bedtime, the higher BMI, higher body fat percentage, and lower lean mass percentage (39). As mentioned earlier, BMI is positively correlated with a late chronotype in women, but no such correlation is evident in men (21). Furthermore, social jet lag is

significantly associated with higher cholesterol levels in the younger female cohort, but not in the male cohort. Based on a composite of blood pressure, fasting blood glucose levels, lipid levels, and waist circumference measurement, another study conducted on female hospital workers revealed that women who worked rotating shift schedules had higher CM risk scores (40).

It is becoming more evident that physiological (hormonal levels), cognitive (spatial processing, emotional condition, and linguistic fluency) and social factors (family and childcare responsibilities) interact to create a landscape of different vulnerabilities to circadian disruption in men and women (41). However, in addition to the circadian phenotypes, differences between the sexes with regards to sleep and CM functions may be mediated independently of, or downstream from, circadian processes, i.e., at the level of hypothalamic-pituitary-adrenal axis function and fluctuations in reproductive hormones (38), which are linked to a range of sleep problems and particular sleep disturbances, including insomnia or breathing issues throughout the course of various phases of reproductive aging (42).

1.5 What can we learn from a UK biobank study on sleep and their connection to T2DM risk?

The majority of research focusing on the connection between circadian disruptions, sleep, and T2DM risk evaluates each sleep parameter separately rather than as a composite. To address this oversight, scientists analyzed data from a sizable biomedical database and research resource that included detailed health and genetic information from half a million UK participants between 2006 and 2010 and involved over 500 000 participants nationwide (43). After nearly nine years of follow-up, this extensive population-based cohort study on the UK Biobank was complete. A total of 6,940 case subjects with incident T2DM had been documented. The information was utilized to assess the correlation between sleep factors, genetic risk, and their combined effect on incidence of T2DM (37, 44). After an average of 8.5 years of follow-up CVD risk assessment, analysis revealed that early chronotypes were linked to a lower risk of coronary heart disease (33). High serum 25-hydroxyvitamin D concentrations are linked to a lower risk of T2DM, and these correlations are negatively influenced by sleep patterns, with daytime sleepiness (excessive sleepiness or hypersomnia) being the main contributor. To address this oversight, scientists analyzed data from a sizable biomedical database (45). The results of another large prospective population-based cohort study were published with the aim of promoting healthy sleep and circadian patterns throughout the population.

Another clinical observational study (6)used well-established sleep parameters (including long or short sleep duration, sleep scores, snoring, late chronotype, excessive daytime sleepiness and insomnia) to categorize sleep quality and circadian pattern as unfavorable, intermediate, or favorable with regards to the development of T2DM; the study involved 360 403 participants and 9 years of follow-up. Each participant was placed into a category after submitting a self-reported questionnaire. The following criteria were also established for each category in another multivariable-adjusted model: age, sex, education, socioeconomic status, PA level, smoking status, alcohol consumption, BMI, CVD, cancer, hypertension, and family history of diabetes. A genome-wide association study used genotyping to evaluate genetic data and categorize the polygenic risk score as low, intermediate, or high risk (46). The incidence of T2DM was more than twice as high (5.53%) in the group of participants with high genetic risk as it was in the group with a low genetic risk (2.01%). Even after accounting for different sleep factors, the association between genetic risk and T2DM incidence remained constant, indicating that sleep, circadian rhythms, and genetic risk were all independently linked to the incidence of T2DM. It is important to mention that this study enrolled only individuals of European ancestry; therefore, the results cannot be generalized for all ethnic groups since racial differences were not been taken into account. Another limitation of this study is its omission of other scientifically confirmed factors (e.g., shift work, late-night eating, low PA), which contribute to poor sleep patterns and, as a result, a possible increase in the risk of developing T2DM.

2 Impact of circadian disruption on cardiovascular and metabolic functions

An individual's health is dependent on the synchronization of all of the internal clocks in the body, as well as on the synchronization of said clocks with the external environment. The circadian system, which regulates metabolism and heart function, ensures that associated organs can perform at their best to meet the expected demands of the daytime and nighttime hours. Recent research on SCN-lesioned rodents revealed that the SCN clock regulates the diurnal rhythm in whole-body insulin sensitivity (IS), and a wealth of evidence suggests that the human circadian system governs the metabolism of glucose, lipids, and energy (47). The SCN clock regulates the release of hormones that impact glucose tolerance, such as cortisol, growth hormone, and melatonin (Figure 3). Muscle tissue exhibits a diurnal rhythm with higher IS in the morning than in the evening (48). However, cardio-metabolic functions are also modulated by lifestyle factors, such as PA, meal timing and sleep patterns. Food intake serves as a strong timing signal to certain peripheral clocks, while nighttime light exposure is the primary disruptor of the central clock in the SCN (49). Consequently, eating at the "wrong" time of day could disrupt the synchronization of clocks in different tissues. An imbalance between these variables and an individual's circadian rhythm may therefore increase the chance of developing metabolic and cardiovascular diseases or conditions, primarily T2DM, obesity, insulin resistance, metabolic syndrome, dyslipidemia, or high blood pressure (BP) (33). The fact that the risk of adverse CVD events varies according to the time of day, peaking at 9:00 AM and then again in the evening at 8:00 PM, suggests that circadian disruption and pathology work together (50). A recent study involving 91

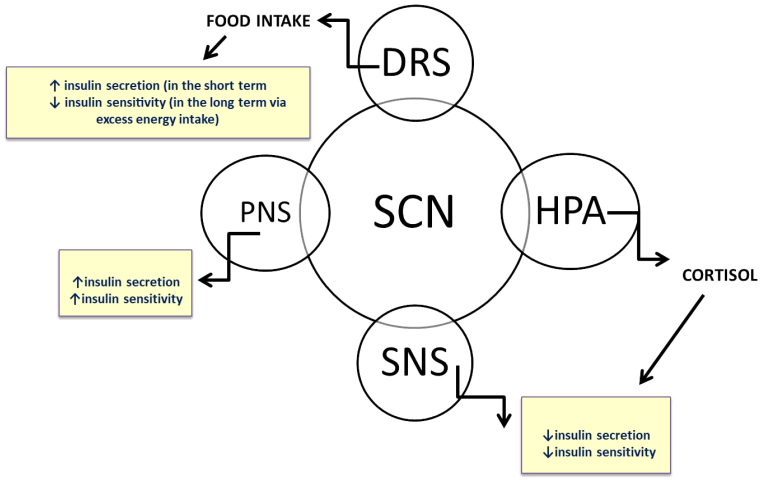

FIGURE 3
The central clock, located in the suprachiasmatic nuclei of the hypothalamus (SCN), synchronizes clocks in peripheral organs through various neuronal and humoral pathways. Glucose tolerance is directly regulated by circadian rhythm via the neuroendocrine system.

adults with obesity and prediabetes evaluated *post hoc* associations between CM risk factors, physical activity (PA), and circadian rhythm parameters (monitored by continuous wrist-temperature measurements) (51). The results showed that a more consistent circadian rhythm was associated with lower CVD risk. The relationship of PA to either cardio-metabolic risk or circadian rhythm had no effect on the incidence of CVD. Physical activity (PA) was only linked to greater circadian stability in individuals with lower systolic blood pressure (SBP). The results are extremely encouraging for future research or clinical practice in this area.

Several lines of evidence have shown that the molecular clock plays a role in lipid metabolism. Nocturnin, a gene expressed in a circadian manner and one which produces an enzyme with deadenylase activity (52, 53), is known to have a key role in the regulation of lipid metabolism. The circadian clock is also influenced by excessive fat intake and metabolic changes. Mice fed a high-fat diet exhibited symptoms of metabolic syndrome, including hyperglycemia, hyperlipidemia, and obesity, which are all likely due to widespread reprogramming of the circadian clock, as well as the transcriptome and metabolome (54). Further research is needed to understand how fat accumulation and metabolic disease can disrupt the circadian clock (55–57).

In the following text we discuss lifestyle factors, such as sleep patterns, physical activity, and food intake that lead to circadian misalignment and may increase the risk of cardiovascular and metabolic disorders.

SNS, sympathetic nervous system; PNS, parasympathetic nervous system; HPA, hypothalamic-pituitary-adrenal axis; DRS, dopaminergic reward system.

Currently, studies are on rise that aim to better characterize how certain unhealthy lifestyle factors (namely poor sleeping habits, unfavorable eating schedules and insufficient PA) can negatively influence glycemic control in patients with T2DM, obesity and an elevated risk of developing CVD (51, 58, 59).

2.1 Sleep disruption and CVD risk

Sleep duration is a significant risk factor for developing diabetes. Research has shown that people who regularly sleep for either very short or very long periods of time (based on the "optimal" sleep duration of 7 to 8 hours) are more likely to develop T2DM (48). However, other factors, such as an undiagnosed illness, may contribute to the detrimental effects that extended sleep duration has on health. One explanation for how sleep disturbance and deprivation affect IS is that they bring about a change in the sympathovagal balance (60).

In patients with diabetes mellitus, optimal blood glucose control is assessed on the basis of specific parameters like glycemic variability (GV), which refers to fluctuations in blood glucose levels over a specific time interval; these measurements are presented as time in range (TIR, glycaemia from 3.9 to 10 mmol/L), time below range (TBR) or time above range (TAR). In a recent study (61), 28 T2DM patients treated with continuous subcutaneous insulin infusion therapy had their glycemic parameters and sleep duration monitored, and results indicated that PA and longer sleep durations were positively associated with lower daily GV. It is interesting to note that sleeping for an extra hour could reduce GV by 0.72% (61). The results suggest that prolonging sleep duration in T2DM patients can significantly improve diabetes control, especially with respect to preventing peripheral neuropathy.

The effect that disruptions in sleep patterns have on glucose tolerance was previously associated with the hormone melatonin; this conclusion was reached after the discovery that genetic variations in MTNR1B – the melatonin receptor gene – correlate with impaired fasting glucose in T2DM patients (30). However, the effects of melatonin and variations in MTNR1B on metabolism are highly contradictory, and the role of melatonin in the pathophysiology of glucose tolerance remains controversial (30,

48, 59). Elucidating the benefits or detriments of melatonin is crucial for the development of melatonin agonist/antagonist drugs (30).

2.2 Timing of PA and CM risk

Physical activity is another important factor in maintaining healthy CM functions. A moderately to vigorously intense level of PA is recommended by the World Health Organization in order to prevent CVD. Between 1987 and 2012, one US research study tracked 5807 men and 7252 women aged 45 to 64 years (all participants were initially free of CVD), and the results indicated an inverse correlation between PA and CVD (58). Physical activity was the most important factor to correlate with circadian rhythm parameters in healthy young men with various BMIs (optimal, fair and poor). These men were monitored daily for changes in their wrist temperature as a measure of circadian rhythm. Other parameters were also observed, such as body composition, cardiorespiratory fitness, actigraphy, daily nutritional and sleep habits, as well as fasting lipid, insulin and glucose levels (62).

In the above-mentioned study involving T2DM patients, PA carried out at greater than 1.5 Metabolic Equivalents of Task or METs* for at least 1 hour was associated with lower GV on that given day; this was the case even though overall PA levels remained low (61). Furthermore, low bolus insulin doses were associated with higher GV, which could be due to insufficient doses of insulin at mealtimes or the absence of bolus insulin when snacking. Similarly, it is understandable that overall glucose metrics are higher during sleep than during wakefulness because of the longer intervals between meals during sleep (61). Another recent study in patients with T2DM showed that proper PA timing, based on internal time (chronotype), can help to regulate impaired glucose metabolism (63). These findings demonstrated that exercise performed at random times of the day was less effective than workouts carried out in the morning and evening for patients with early and late chronotypes, respectively. Results indicated improvement in levels of HbA1C, fasting blood glucose, triglycerides, HDL, LDL, total cholesterol, as well as an overall improvement in quality of life in people with T2DM.

There should be more widespread awareness of the importance of regular PA combined with sufficient sleep and healthy eating habits for T2DM patients. It is unclear whether developing exercise programs tailored to a specific chronotype could help people with T2DM manage their condition. Further research is necessary to determine how increasing the level and timing of PA can affect circadian system status in different populations.

The skeletal muscle circadian clock establishes strong rhythms during the oxidative metabolism in the tissue and these rhythms peak in the evening (64). It is therefore tempting to hypothesize that a decline in metabolic health is partially caused by disruptions in the muscle tissue rhythms, which are linked to circadian misalignment. Therefore, decreased oxidation in skeletal muscle may also be linked to the onset of T2DM (65).

2.3 Meal timing and CM risk

Dietary recommendations have recently focused more on meal timing rather than on mere meal quantity and quality (66). The field of chrono-nutrition is a relatively new area of study that examines the relationship between the circadian system and food intake.

Food consumption ensures that peripheral clock timing is in sync with the day/night cycle. The timing of food intake drives rhythmic processes in the metabolic organs. This is significant because some metabolic hormones exhibit daily variations due to the SCN clock, which is unaffected by food intake under energy-balanced conditions. Several hormones have been shown to have daily oscillations, the best known of which are melatonin, cortisol, gonadal steroids, prolactin, thyroid hormone, and growth hormone (GH). The so-called nutrient-sensitive hormones, which include insulin, leptin, ghrelin, and adiponectin, also oscillate on a circadian basis, and their release is influenced by environmental factors such as feeding time and light-dark cycles (31).

The hormone cortisol, which controls energy levels and primes the body for an active phase, is released in anticipation of awakening and peaks in the morning hours (7 a.m. – 9 a.m.) an individual with a well-synchronized SCN clock. Among all glucocorticoid hormones, cortisol is one of the most widely-studied from a circadian point of view (31). In one study, jet lag and sleep desynchronization were shown to increase cortisol levels in humans (67), and elevated cortisol has been associated with several pathologies, including cardiometabolic disease and sleep disorders (68, 69).

Insulin and ghrelin are two important metabolic regulators, and several circadian factors are now known to influence their secretion and activity. In another study, shift work has been shown to contribute to a rise in insulin secretion and a decrease in insulin sensitivity, potentially implying a pre-diabetic condition (31). One study revealed that circadian misalignment induced by sleep deprivation increased markers of insulin resistance and inflammation (70). The main role of the hormone ghrelin is appetite stimulation. One study involving shift workers revealed that their normal ghrelin cycle becomes disrupted, which may explain why overeating is so common among such workers (71).

On average, a person eats three meals a day (one 8am, one at 1pm, and one at 6pm), and ghrelin levels peak just before these mealtimes (72). In particular, eating breakfast on a regular basis can help regulate plasma lipid levels and glucose homeostasis, but it can also act as a morning clock synchronization cue (66). However, late-night meals are linked to inadequate glycemic control in individuals with T2DM (73). In a recent study, two separate 56-hour sessions of a random crossover design were used to monitor the metabolism of older subjects in a whole-room respiratory chamber. The findings demonstrated that maintaining lipid oxidation requires eating breakfast and avoiding late-night meals. These finding suggest that human oxidation, or storage of ingested food, is influenced by mealtimes which emphasizes the importance of optimal eating habits (74). More research is required to determine ideal meal timing and dietary habits for circadian and CM health (25).

In addition to meal timing, the importance of intervals between meals has also been widely discussed. Research data from animal studies has provided evidence that confining daily food intake to 6 to 10 hours and fasting for the remaining hours has beneficial effects on metabolism, even when consuming high-calorie food (49). This led to introduction of the "time-restricted eating (TRE)" concept into human dietary practices. It is a specific form of the more general "intermittent fasting" and involves alternating fasting and normal eating times during specific periods within a day or week (10).

When following TRE schedules, people limit their daily eating window to four to ten hours, without making any effort to limit their calorie or dietary intake.

This method has been shown to increase longevity and health in male mice without affecting the usual diet or daily calorie intake (75). A recent study (76) presented groundbreaking evidence that, in contrast to simple calorie restriction (10% life extension), the positive effects of TRE on health and longevity in mice are greatest (35% life extension) when the feeding interval coincides with the natural active phase of the animal. Time-restricted eating (TRE) has also been suggested for humans as a viable method to restore the rhythmicity of the metabolic pathways that have been disrupted by circadian misalignment.

In one study, IS was enhanced when the eating window was restricted from 7am to 3pm (77). Early TRE significantly improved body weight, waist circumference, beta cell function, and blood pressure in men with prediabetes (78).In another study, obese patients put on an isocaloric early time-restricted eating schedule (e.g., a 6-hour eating window with dinner no later than 3pm) showed decreases in insulin resistance that were much greater than those observed in participants with a 12 hour feeding window (61). Although the exact process by which TRE affects health is not fully understood, a logical explanation could be the increase in robustness of both the rhythmicity of the clock as well as the downstream pathways in metabolic tissue.

Innovative clinical trials have so far presented mixed results (79–81). Further research is required to compare different TRE schedules and their effects in humans (16:8 vs. 14:10; fasting window: eating window). Furthermore, there are few studies that focus on determining the most ideal fasting window and TRE timing (early vs. late) for improvement of health. One major drawback of these human studies is their inability to discern between the effects of TRE and calorie restriction. Although numerous TRE studies have demonstrated some benefits in people with metabolic disorders, it is crucial that further research also include participants who are healthy and do not have weight issues. Moreover, it is important to investigate additional variables, such as long-term adherence to TRE, quality of the diet while on TRE, and the social aspects of adjustment to the TRE lifestyle.

Shift work integrates most of the factors that are known to affect the circadian system (Figure 4). In night shift workers, exposure to artificial light could disrupt the central circadian clock, while late night eating disrupts certain peripheral clocks, and this may lead to internal desynchrony. There are, however, additional non-circadian mechanisms which indicate that unhealthy eating habits, insufficient sleep, and decreased PA may contribute to aspects of health problems related to shift work (82). Shift workers are therefore an ideal population to focus on when studying biological and social rhythm disturbances (i.e., the regularity with which one participates in social activities during the week). Working night shifts, particularly when they are part of a rotating shift schedule, is linked to an increased risk of developing T2DM (33). The frequency of night shifts is important because, even after controlling for risk factors and night shift length over the course of a lifetime, higher numbers of average monthly night shifts have been linked to an increase in the prevalence of diabetes (83). It is evident that shift work may lead to irregular meal schedules (i.e., random eating times) and skipping meals, which may have an impact on the hormones that regulate appetite (ghrelin, leptin, neuropeptide Y, and peptide YY) (84). Another condition commonly seen among shift workers is poor sleep, which could partially contribute to their higher risk of developing CVD. Some research has revealed that both shift work and non-shift nurses experience poor sleep quality (85).

A study involving 26 healthy adults was carried out to investigate the effects of sleep restriction on insulin resistance. IS and markers of inflammation were compared in healthy adults under conditions of circadian alignment against misalignment (determined as shift work) with daily sleep duration remaining the same (86). The participants in the above-mentioned study were subjected to either 5 h of sleep restriction with set nocturnal bedtimes (circadian alignment) or an 8.5 h bedtime delay (circadian misalignment). Both interventions comprised 3 inpatient days with a sleep duration of 10 hours, followed by 8 inpatient days with a sleep restriction to 5 hours with fixed nocturnal bedtimes (circadian adjustment) or with bedtimes delayed by 8.5 hours on 4 of the 8 days (circadian misalignment). In both the aligned and misaligned conditions, the daily total sleep time during the intervention was almost the same. After sleep restriction, IS dramatically dropped in both groups without a corresponding rise in insulin secretion, and inflammation went up. When compared to male participants who adhered to regular nocturnal bedtimes, the reduction in IS and the increase in inflammation were both doubled in those exposed to circadian misalignment. In conclusion, inadequate circadian rhythm adjustment in the context of shift work may increase the risk of diabetes and inflammation, while sleep duration is a separate, non-affecting factor in healthy subjects.

2.4 Shift work and intestinal microbiota

Over the course of a day, the intestinal microbiota in both humans and mice displays diurnal oscillations that are influenced by eating rhythms, resulting in time-specific compositional and functional profiles (87). Dysbiosis and abnormal microbiota diurnal fluctuations are caused by disruption of the host molecular clock components or induction of circadian desynchrony (jet lag), and are primarily caused by poor eating rhythmicity. When feces are transplanted into germ-free mice, the jet lag-induced dysbiosis in humans and mice leads to glucose intolerance and obesity (87). Collectively, these results demonstrate coordinated diurnal

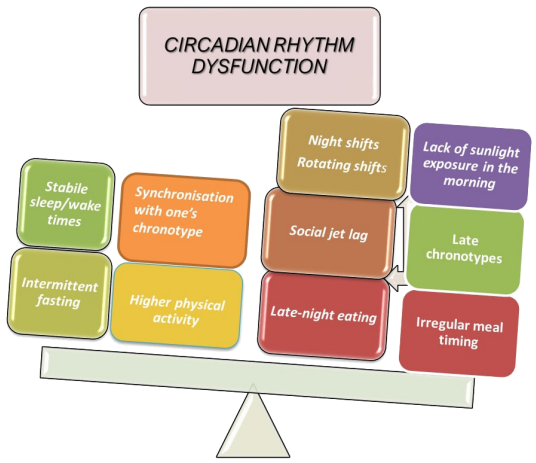

FIGURE 4
Factors contributing to circadian disruption.

rhythmicity in meta-organisms and suggest a microbiome-dependent mechanism for common metabolic disorders in people with aberrant circadian rhythms, such as those observed in frequent flyers.

A recent study on the microbiomes of ten male security workers who worked both daily and night shifts revealed that the gut microbiota of those who worked night shifts was altered in favor of "obesogenic" bacteria due to rotational day and night shift work (82). This finding raises concerns that the altered gut microbiota caused by shift work may, at minimum, partly account for the higher risk of gastrointestinal disorders and metabolic syndrome. This was corroborated by research showing that the disruption of the microbiome caused by circadian misalignment can also play a role in the development of insulin resistance. The study involved transferring feces from "jet-lagged" humans with a disturbed circadian system into the gut of germ-free mice, which decreased the mice's ability to tolerate glucose (88).

Mortas et al. found out that abundances of *Bacteroidetes* were reduced and those of *Actinobacteria* and *Firmicutes* increased when working the night compared to day shift. Faecalibacterium abundance was found to be a biomarker of the day shift work. Dorea longicatena and Dorea formicigenerans were significantly more abundant in individuals when working the night shift. Rotational day and night shift work causes circadian rhythm disturbance with an associated alteration in the abundances of gut microbiota, leading to the concern that such induced alteration of gut microbiota may at least partially contribute to an increased risk of future metabolic syndrome and gastrointestinal pathology (82).

Based on the data summarized about shift work above, there is no doubt that it represents a significant risk of developing metabolic disorders and the problem is all the more pressing in light of the rise in shift work that has followed industrialization. Given the increasing prevalence of T2DM, it is imperative to ascertain which aspects of shift work schedules may pose the greatest disruptions, and for whom. This will facilitate the development of focused primary and secondary prevention strategies, which in turn may contribute to a reduction in the societal and financial costs associated with disease. Additionally, more studies need to be done to confirm microbiome-circadian rhythm-metabolic pathology associations because the result can have outcome in targeting some compensation strategies to reverse negative impact of shift work on health.

3 Future research

The above-mentioned results suggest that researching the relationship between circadian disruption and metabolic and cardiovascular health in population-based studies is a worthwhile endeavor (26). Despite being carefully planned to test cause and effect, experimental studies are typically conducted over a brief period of time. Since humans are typically exposed to risk factors over longer periods of time in real life, more research is required to determine which factors are the strongest for developing diseases over longer time periods.

The results of studies on the effects of nocturnal night light exposure, sleep disturbance and deprivation, shift work, jet lag, late chronotype and other factors support the hypothesis that disruption of the circadian system contributes to the development of insulin resistance in humans due to impaired glucose tolerance.

The need for more tight integration of the research fields on sleep and CM functions seems obvious because their disturbances represent comorbidity of many disorders. Obstructive sleep apnea (OSA) is example of such disorder. OSA has been shown to be a separate risk factor for cardiovascular morbidity and mortality, as well as an increased risk of hypertension, stroke, acute coronary syndrome, and arrhythmias. The association between OSA and T2DM has been well characterized: on the one hand, OSA can contribute to increased insulin resistance or glucose intolerance; on the other hand, diabetes may worsen sleep-disordered breathing because of autonomic neuropathy. Insulin resistance can also be a predictor for the development of OSA. Moreover, the association between OSA and insulin resistance is probably bidirectional (89). Surprisingly, OSA can also occur in people with type 1 diabetes mellitus (T1DM) who are not obese, despite the fact that it is more commonly associated with T2DM patients (with a prevalence of up to 50%). It has been shown that during sleep, autonomic reactions to hypoglycemia are diminished, especially in individuals with T1DM. Therefore, one potential mechanism of OSA in people with T1DM is neuromuscular dysfunction of the upper airway dilator muscle, which can be impeded by upper airway neuropathy (90). Moreover, a pathological oximetry was linked to advanced age, a longer course of the illness, and a higher incidence of retinopathy (91). Nevertheless, OSA definitely needs more research in the field of CM, which could be very useful for improving the treatment methods of this diagnosis (92).

To determine the ideal meal times and dietary habits for circadian and CM health, more research is required. Timing of eating could be viewed as a novel approach for the diagnosis, prevention, and treatment of T2DM in clinical practice, particularly in vulnerable populations such as shift workers and late-night eaters, who together account for a sizable portion of our society (30). Dietary evaluation is difficult, but techniques that take

into account timing of intake—especially in relation to bed and wake times—are essential for this field. Meal and sleep timing is possible with the Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24), for instance (93).

New molecules targeting the molecular clock by modulating specific clock gene expression have been newly explored as promising targets for improving the circadian regulation such as nobiletin or REV-ERB - nuclear receptor subfamily 1 group D member 1 (NR1D1)) agonists (94). REV-ERB plays an important role in regulation of the circadian clock and it also takes part in several physiological processes, including metabolic pathways and immunity (83).

The new technologies can be employed to determine the underlying mechanism of misalignment between internal circadian rhythmicity and externally imposed behavioral schedules. For example, time-resolved metabolomics has been used as a useful tool. A study published in 2018 found that after simulated shift work, traditional markers of the circadian clock in the SCN (melatonin, cortisol, PER3 gene expression) remained relatively stable but rhythms in many plasma metabolites circulating with 24-hour rhythmicity showed complete reversal or lost rhythms (94). Detailed characterization of the rhythmic metabolite profiles may provide insight into the underlying mechanisms linking shift work and metabolic disorders and help to explore the bio-behavioral factors that orchestrate them (95–97). Additionally, the biomarkers of circadian phase can help to optimize behavioral strategies or possible pharmacological interventions to prevent metabolic disruption in humans in the future.

Finding biological markers to objectively assess the existence of circadian rhythm disruptors in clinical practice is undoubtedly one of the methodological issues that needs to be taken into account for future research. By doing this, the evidence supporting a link between circadian disruption and CM disorders would be more accurate and of higher quality.

In conclusion, it is imperative to investigate optimal compensating mechanisms for shift work, with a particular focus on ways to avoid potential metabolic complications associated with this work schedule. In the future, further clinical studies will be needed to deeply investigate the clinical utility of the current understanding of the regulation of the circadian clock of IS. There is a need to conduct research to see if any of these adjustments advanced or stabilized bedtimes, chronotype-appropriate exercise regimens, and customized meal plans—may be beneficial. This comprises studies to ascertain the efficacy of the intervention as well as implementation studies to evaluate the intervention's feasibility acceptability in real-world settings. It is crucial that these implementation studies be carried out across a range of demographic subgroups, such as ages, genders, and races and ethnicities, given the significant influence of sociocultural factors on behavior. In conclusion, these upcoming research endeavors will facilitate a more comprehension of circadian disruptors concerning cardio-metabolic disorders and facilitate the identification of efficacious strategies for intervention.

Author contributions

NM: Writing – original draft, Visualization, Validation, Resources, Methodology, Data curation, Conceptualization, Writing – review & editing. MS: Visualization, Resources, Writing – review & editing. AS: Writing – review & editing, Validation, Supervision, Resources. MD: Supervision, Project administration, Methodology, Funding acquisition, Conceptualization, 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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Elevated TyG index associated with increased prevalence of gallstones in a United States cross-sectional study

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Objective: This study aimed to investigate the correlation between the triglyceride-glucose (TyG) index and the incidence of cholelithiasis.

Research approach: In this investigation, a cross-sectional analysis was undertaken utilizing data from the US National Health and Nutrition Examination Survey (NHANES) spanning the years 2017 to 2020. The TyG index served as an independent predictor, while gallstone prevalence was considered the dependent variable of interest. We employed a multivariate logistic regression model to evaluate the interplay between these independent and dependent variables. To assess the presence of potential non-linear associations, sensitivity analysis was executed, utilizing inverse probability weighted validation, smooth curve fitting, and threshold effect analysis. In cases where non-linear relationships were observed, likelihood ratios were utilized to pinpoint potential inflection points. Ultimately, subgroup analyses were conducted to identify specific populations demonstrating heightened susceptibility to gallstone prevalence.

Results: Encompassing 838 patients who self-reported gallstones, a total of 7,794 participants were included in the analytical cohort. A statistically significant disparity in the TyG index was observed when all individuals were categorized into gallstone patients and non-patients ($p < 0.05$). Logistic regression findings indicated a positive correlation between the TyG index and gallstone disease prevalence (OR = 1.28, 95% CI: 1.12, 1.47), with a strengthening association as the TyG index increased (p trend <0.01). The results were corroborated by the use of inverse probability weighting. Additionally, a non-linear connection between the TyG index and gallstone prevalence was identified (log-likelihood ratio $p < 0.01$), with the optimal inflection point for TyG calculated at 8.96. In subgroup analysis, the positive relationship between the TyG index and gallstone prevalence was notably pronounced among black Americans under the age of 40 and female participants.

Conclusion: Alterations in the TyG index may potentially correlate with shifts in the prevalence of gallstones among adult populations in the United States. Elevated TyG index values may coincide with an augmented likelihood of gallstone occurrence.

KEYWORDS

insulin resistance, triglyceride glucose index, gallstones, cross-sectional study, NHANES

1 Introduction

Gallstones (GS) represent one of the most prevalent upper gastrointestinal disorders, manifesting with common symptoms such as abdominal discomfort, upper abdominal pain, nausea, vomiting, and diminished appetite. They affect approximately 20% of the global population (1, 2). Across the world, there are notable variations in the prevalence and formation of gallstones based on race and geographic factors. Approximately 10% of white adults in Western nations experience gallstones (2), while the prevalence stands at around 4% in India (3) and 5.13% in China (4). The incidence of gallstones rises with advancing age, reaching 57% (5). Notably, the United States witnesses over 700,000 cholecystectomies annually, incurring costs of roughly $6.5 billion (6). Extensive efforts have been devoted to unraveling the determinants that elevate the risk of gallstone formation and to develop timely and efficacious preventive strategies.

An established link has been established between gallstones and both insulin resistance and metabolic syndrome (7, 8). Although the hyperinsulinemic normoglycemic clamp (HEC) stands as the gold standard for insulin measurement, it poses practical challenges in non-study settings (9). Given the intricate nature of insulin resistance and the significant time and resource commitments it entails, simpler surrogate markers are frequently utilized for assessment. The TyG index has emerged as a dependable surrogate marker of insulin resistance (1, 10–12). Its utility has been validated across various medical conditions, including cardiovascular disease (13), hearing impairment (11), and proteinuria (10). Nonetheless, its relationship with gallstone prevalence remains unexplored. In summary, this study aimed to investigate the association between the TyG index and the incidence of gallstones within a cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) cohort.

2 Materials and methods

2.1 Study population

National Health and Nutrition Examination Survey, a recurring cross-sectional survey sponsored by the CDC, has undergone biennial updates for nearly two decades, encompassing approximately 10,000 individuals in each iteration. The NHANES database received approval from the NCHS Institutional Review Board, adhering to the updated Declaration of Helsinki. This investigation utilized data from the 2017 to 2020 timeframe, with participants under the age of 20 being excluded due to the questionnaire's exclusive administration to adults aged 20 years and older. The study cohort was carefully screened, as delineated in Figure 1, resulting in the inclusion of a total of 7,794 participants.

2.2 Data collection and definition

The triglyceride-glucose index (TyG) was formulated as the primary exposure variable. TyG = ln [fasting levels of triglycerides (mg/dL) * fasting plasma glucose (mg/dl)/2]. Triglyceride and fasting plasma glucose levels were quantified employing enzymatic techniques with an automated biochemical analyzer. Serum triglyceride concentrations were assayed utilizing a Roche Cobas 6000 chemistry analyzer in conjunction with a Roche Modular P device.

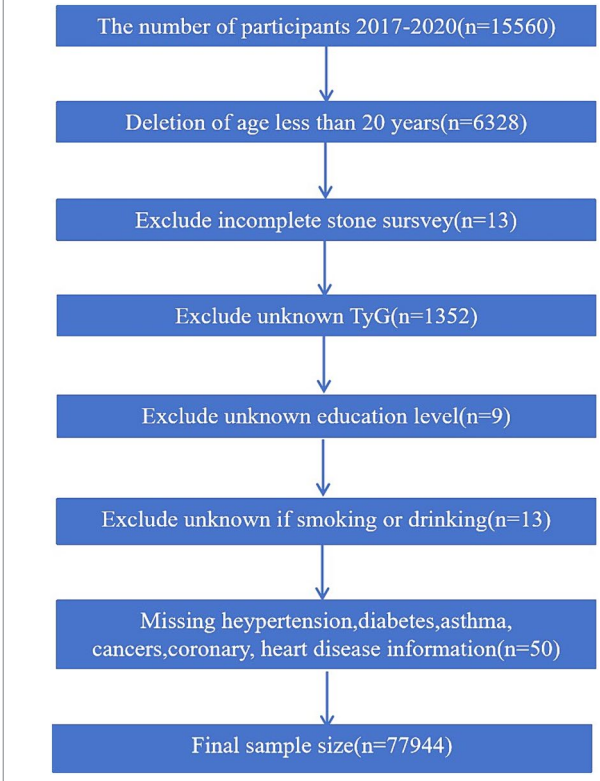

FIGURE 1
The participants selecting flow chart.

2.3 Assessing diagnosed gallstones

Gallstone status was ascertained through a questionnaire that included the following inquiries: "Have you received a diagnosis of gallstones?" Participants were provided with a choice between two response alternatives: "Affirmative" or "Negative."

2.4 Covariate assessment

Drawing from prior research (14, 15), a multivariate adjusted model was constructed to account for possible confounders. Our analysis incorporated variables such as gender, age, race, educational attainment, poverty-to-income ratio, alcohol consumption, cholesterol levels, uric acid, smoking habits, creatinine levels, history of asthma, hypertension, diabetes, coronary heart disease, and cancer as covariates.

Missing value treatment: in the current study, there were still missing values for BMI, CRP, and PIR. In order to reduce the data bias introduced by the deletion of variables and we interpolated the missing values using the Random Forest method (16), as shown in Supplementary Figure 1.

2.5 Statistical methods

Statistical significance was defined as $p < 0.05$. All analyses were performed using the Empower software (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, United States) and R version 4.0.2 (http://www.R-project.org, The R Foundation). All statistical analyses were conducted employing the NHANES sampling weights,

stratification, and clustering specifications provided in the study. To determine the appropriate weights for the variables under study within the largest population, a specific selection of variables was first defined in accordance with the Weit guidelines. In accordance with these guidelines, the study utilized fasting triglyceride data and divided the subweight associated with fasting triglycerides (WTSAF2YR) by 3.2 to derive the final weight (10). Weighted analysis was carried out using the survey design R package in the R programming language. Weighted survey means with 95% confidence intervals were reported for continuous variables, while categorical variables were presented as weighted survey proportions with 95% CIs.

Three distinct multivariate regression models were established (17–19). Model 1 remained unadjusted for covariates, Model 2 was adjusted for sex, age, race, educational attainment, and Model 3 encompassed adjustments for all variables. In the sensitivity analysis, which consists of two parts, the first is the conversion of the TyG variables from a continuous format to two categorical variables in order to assess their robustness. The linear trend was assessed by categorizing TyG into two quintiles. The precision of the outcomes was further evaluated through the utilization of inverse probability weights. Additionally, a generalized additive model (GAM) and smooth curve fitting techniques were applied to account for potential non-linearities in the TyG and gallstone association. In instances where non-linear correlations were identified, a two-segment linear regression model (segmented regression model) was employed to fit each segment and calculate the threshold effect. Second, we found that some previous reports, including METS-IR (8), WWI (20), and VAI (21) indices, were reported to be associated with the prevalence of gallstones, and we adjusted them to further clarify the effect of the TyG index on the prevalence of gallstones. In addition, subgroups were analyzed by gender, age, and ethnicity using stratified multiple regression analysis, and the results were presented using forest plots (22, 23).

3 Results

3.1 Baseline characteristics

The baseline demographic attributes of the enrolled participants are presented in Table 1. Weighted characteristics were categorized based on gallstone status. Apart from educational level, cholesterol concentrations, and the prevalence of asthma, notable disparities in baseline characteristics were observed between the two cohorts. Those with gallstones exhibited higher age, BMI, CRP levels, and TyG values, a markedly elevated proportion of females, and a greater incidence of medical conditions, including diabetes, hypertension, coronary heart disease, cancer, and asthma.

3.2 Higher prevalence of gallstones associated with higher TyG index

In the fully adjusted model, a one-unit increment in the TyG index was associated with a 28% elevated risk of gallstones (OR = 1.28, 95% CI: 1.12, 1.47). The effect of TyG index on gallbladder stones remained significant even after adjusting for the METS-IR, VAI, and WWI indices (Supplementary Table 1). Upon dichotomizing the TyG index, logistic regression revealed a noteworthy 36% escalated risk of

TABLE 1 Baselines characteristics of participants, weighted.

Characteristic	Stone formers (*n* = 838)	Non-stone formers (*n* = 6,956)	*p* value
Age (years)	58.41 (57.33,59.48)	49.96 (49.53,50.40)	<0.0001
Serum creatinine (mg/dl)	0.92 (0.88,0.97)	0.91 (0.89,0.92)	0.4622
Total bilirubin (mg/dL)	0.46 (0.44,0.48)	0.46 (0.45,0.46)	0.4851
Serum cholesterol (mg/dL)	184.10 (181.24,186.96)	186.30 (185.34,187.27)	0.151
Serum uric acid (mg/dL)	5.49 (5.38,5.59)	5.40 (5.36,5.43)	0.1049
TyG index	8.82 (8.78,8.86)	8.64 (8.63,8.66)	<0.0001
BMI (kg/m^2)	33.36 (32.77,33.94)	29.65 (29.48,29.83)	<0.0001
PIR	2.55 (2.45,2.66)	2.62 (2.58,2.65)	0.2568
CRP	5.82 (5.14,6.50)	3.99 (3.80,4.19)	<0.0001
Gender (%)			<0.0001
Male	28.53 (25.55,31.71)	50.78 (49.53,52.02)	
Female	71.47 (68.29,74.45)	49.22 (47.98,50.47)	
Race (%)			0.0129
Mexican American	13.52 (11.36,16.01)	11.88 (11.09,12.71)	
White	11.26 (9.30,13.59)	10.20 (9.49,10.96)	
Black	62.15 (58.79,65.40)	60.60 (59.38,61.81)	
Other Race	13.07 (10.95,15.53)	17.32 (16.38,18.30)	
Education level (%)			0.6604
Less than high school	18.54 (16.02,21.36)	18.69 (17.73,19.69)	
High school	25.16 (22.31,28.25)	23.75 (22.72,24.82)	
More than high school	56.29 (52.88,59.65)	57.55 (56.32,58.78)	
Alcohol (%)			<0.0001
Yes	51.73 (48.34,55.10)	40.76 (39.60,41.93)	
No	32.87 (29.78,36.12)	45.17 (43.99,46.37)	
Unclear	15.40 (13.10,18.02)	14.07 (13.26,14.92)	
High blood pressure (%)			<0.0001
Yes	54.92 (51.53,58.26)	36.42 (35.28,37.58)	
No	45.08 (41.74,48.47)	63.58 (62.42,64.72)	
Asthma (%)			0.0001
Yes	20.46 (17.86,23.34)	15.14 (14.32,16.01)	
No	79.54 (76.66,82.14)	84.86 (83.99,85.68)	
Coronary artery disease (%)			<0.0001
Yes	9.00 (7.23,11.15)	4.02 (3.58,4.51)	
No	91.00 (88.85,92.77)	95.98 (95.49,96.42)	
Cancers (%)			<0.0001
Yes	17.74 (15.29,20.50)	9.48 (8.82,10.19)	
No	82.26 (79.50,84.71)	90.52 (89.81,91.18)	
Diabetes (%)			<0.0001
Yes	26.24 (23.36,29.33)	13.91 (13.11,14.76)	
No	73.76 (70.67,76.64)	86.09 (85.24,86.89)	
Smoked (%)			0.0094
Yes	45.94 (42.57,49.35)	41.25 (40.08,42.43)	
No	54.06 (50.65,57.43)	58.75 (57.57,59.92)	

Data of continuous variables are shown as survey-weighted mean (95%CI), *p* value was calculated by survey-weighted linear regression. Data of categorical variables are shown as survey-weighted percentage (95%CI), *p* value was calculated by survey-weighted Chi-square test.

gallstones in the highest TyG index group compared to the lowest (OR = 1.36, 95% CI: 1.15, 1.61, *p* for trend <0.01). In addition, inverse probability weighted analysis results were computed based on TyG two-score. Supplementary Table 2 demonstrates that the baseline characteristics were essentially balanced between the two groups, and the results of inverse probability weighted logistic regression indicated a 36% increased risk of gallstones in the highest TyG index group compared to the lowest (OR = 1.36, 95% CI: 1.12, 1.65). Smooth curve fitting was subsequently employed to explore the association between the TyG index and gallstone prevalence. Our findings revealed a non-linear positive correlation between the TyG index and gallstone prevalence (Figure 2). A similar likelihood ratio test identified a threshold effect for the TyG index and gallstone prevalence, with the optimal inflection point determined as 8.96 (Tables 2, 3).

3.3 Subgroup analysis

Subgroup analyses were conducted to evaluate the resilience of the association between the TyG index and the prevalence of gallstones. Findings (Table 4; Figure 3): Male subgroup (OR = 1.26, 95% CI: 1.00, 1.57), Female subgroup (OR = 1.33, 95% CI: 1.11, 1.59), Age < 40 years subgroup (OR = 1.62, 95% CI: 1.12, 2.33), Age 40–59 years subgroup (OR = 1.24, 95% CI: 0.98, 1.58), Age 60 years subgroup (OR = 1.22, 95% CI: 1.00, 1.49), Mexican-American subgroup (OR = 0.99, 95% CI: 0.66, 1.50), White subgroup (OR = 1.25, 95% CI: 0.82, 1.91), Black subgroup (OR = 1.36, 95% CI: 1.13, 1.63), and Other ethnicity subgroup (OR = 1.43, 95% CI: 0.99, 2.05).

4 Discussion

Our examination demonstrated a notable and robust correlation between the TyG index and the prevalence of gallstones, even following comprehensive adjustments for pertinent confounding factors in the fully adjusted model. Additional curve fitting and assessment of threshold effects disclosed a non-linear interrelationship between the TyG index and gallstone prevalence, pinpointing a threshold at 8.96. Consequently, the monitoring of the TyG index in patients could serve as a straightforward and efficient instrument in epidemiological investigations concerning gallstones.

The global prevalence of cholelithiasis is substantial, impacting around 5–25% of adults, particularly within the Western world (24). In the United States alone, the burden of gallstone-related conditions results in approximately 1.5 million physician visits (25). Given that cholelithiasis is a chronic ailment entailing morbidity, diminishing quality of life, and considerable healthcare expenses, its prevention assumes paramount significance. The existing pressures have witnessed continued escalation across the globe. Effective strategies for gallstone prevention can be enhanced by identifying an appropriate population for the TyG index. Therefore, we conducted a subgroup analysis, revealing that within the age-stratified analysis, the TyG index exerted its most pronounced influence on gallstone prevalence in the age group under 40 years. The role of age as a risk factor for cholelithiasis remains a subject of debate. An Italian study identified advancing age as a risk factor for gallstone incidence (26), whereas a Taiwanese study associated age with gallbladder and fatty liver disease risk (27). Conversely, some investigations have posited that metabolic syndrome and obesity have a more substantial impact on gallstones in younger individuals (28), and a separate NHANES study by Wang et al. concurs with our findings (8). Concerning gender, the data suggest that female patients may bear a higher risk of gallstones (2, 29), a conclusion supported by our results as well. In the United States,

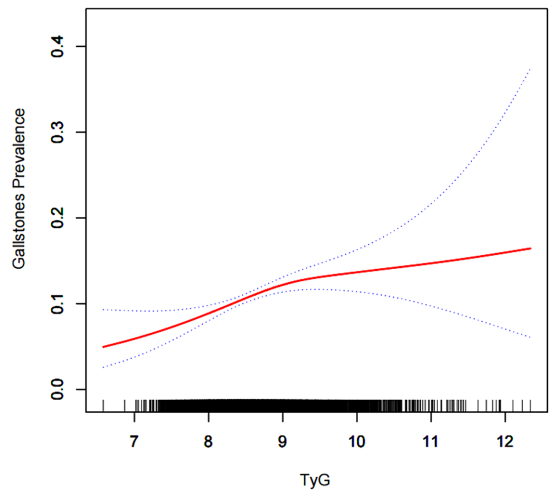

FIGURE 2
Density dose–response relationship between TyG index with gallstone prevalence. The area between the upper and lower dashed lines is represented as 95% CI. Each point shows the magnitude of the TyG index and is connected to form a continuous line. Adjusted for all covariates except effect modifier.

TABLE 2 Logistic regression analysis between TyG index with gallstones prevalence.

Characteristic	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)
TyG	1.48 (1.33, 1.64)	1.47 (1.31, 1.65)	1.28 (1.12, 1.47)	-
Categories				
Lower (6.58–8.60)	1	1	1	1
Higher (8.60–12.34)	1.73 (1.49, 2.01)	1.60 (1.37, 1.87)	1.36 (1.15, 1.61)	1.36 (1.12, 1.65)★
p for trend	<0.01	<0.01	<0.01	<0.01

Model 1 was adjusted for no covariates; Model 2 was adjusted for age, gender, race, and education; Model 3 was adjusted for covariates in Model 2 + diabetes, blood pressure, PIR, smoked, physical activity, alcohol use, serum cholesterol, TBIL,CRP, uric acid serum creatinine, coronary artery disease, asthma, and cancers were adjusted. Model 4 adjusts the same covariates as model 3; ★IPTW analysis only in model 4.

TABLE 3 Two-piecewise linear regression and logarithmic likelihood ratio test explained the threshold effect analysis of TyG index with gallstones prevalence.

TyG index	ULR test	PLR test	LRT test
	OR (95%CI)	OR (95%CI)	*p* value
<8.96	1.28 (1.12, 1.47)	1.65 (1.30, 2.11)	<0.0001
≥8.96		0.99 (0.77, 1.27)	

ULR, Univariate linear regression; PLR, Piecewise linear regression; LRT, Logarithmic likelihood ratio test, statistically significant: $p < 0.05$.

black Americans exhibit the highest prevalence of cholelithiasis, which could be linked to dietary and lifestyle disparities among various ethnic groups. A significant majority of black Americans are employed for fewer hours compared to their white counterparts, often leading to high-calorie dietary choices, identified as a risk factor for gallstones (6). This is a plausible explanation for the elevated incidence of gallstones observed in this demographic.

TABLE 4 Subgroup regression analysis between TyG index with gallstones prevalence.

Characteristic	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
Stratified by gender			
Male	1.38 (1.16, 1.65)	1.32 (1.09, 1.60)	1.26 (1.00, 1.57)
Female	1.88 (1.64, 2.16)	1.62 (1.39, 1.88)	1.33 (1.11, 1.59)
Stratified by race			
Mexican American	1.06 (0.80, 1.40)	1.05 (0.75, 1.48)	0.99 (0.66, 1.50)
White people	1.30 (0.97, 1.75)	1.24 (0.88, 1.74)	1.25 (0.82, 1.91)
Black people	1.64 (1.43, 1.88)	1.62 (1.40, 1.89)	1.36 (1.13, 1.63)
Other Race	1.63 (1.23, 2.14)	1.55 (1.15, 2.10)	1.43 (0.99, 2.05)
Stratified by age(years)			
20–39	1.53 (1.19, 1.97)	2.25 (1.69, 2.99)	1.62 (1.12, 2.33)
40–59	1.31 (1.10, 1.57)	1.53 (1.27, 1.86)	1.24 (0.98, 1.58)
60–85	1.29 (1.10, 1.52)	1.33 (1.12, 1.57)	1.22 (1.00, 1.49)

Model 1 was adjusted for no covariates. Model 2 was adjusted for age, gender, race, and education; Mode3 = adjusted for all covariates except effect modifier.

In our investigation, we employed a comprehensive regression model to mitigate the impact of potential confounding factors, enhance result stability, and elucidate the relationship between the TyG index and gallstone prevalence. We implemented inverse probability weighting (IPTW) to harmonize patient characteristics across both groups (30). IPTW has been explored using a progressively escalating approach (31). Equilibrating baseline data differences permits a more effective reduction of confounding influences on the findings. In our research, as variable disparities gradually diminished post-IPTW, the influence of the TyG index on gallstone prevalence remained consistent, further substantiating result stability. In addition, to illustrate the independent effect of TyG on the prevalence of gallstones, we included the insulin resistance index METS-IR, and we also included the visceral obesity indices WWI and VAI for adjustment, and then excluded the effects of abdominal obesity and insulin resistance, the effect of TyG index on the prevalence of gallstones still existed, which indirectly suggests that an increase in the TyG index is closely related to an increase in the prevalence of gallstones and can be used as a predictor of the prevalence of gallstones. However, due to the drawbacks of cross-sectional studies, a multicenter prospective cohort study is necessary.

The precise mechanism linking the heightened TyG index and the increased prevalence of gallstones remains uncertain, yet previous research offers insights into potential mechanisms. Investigations have demonstrated that insulin resistance in high-risk Hispanic individuals can result in cholesterol-saturated bile, disrupting gallbladder function and precipitating gallstone formation (7). Animal studies have indicated

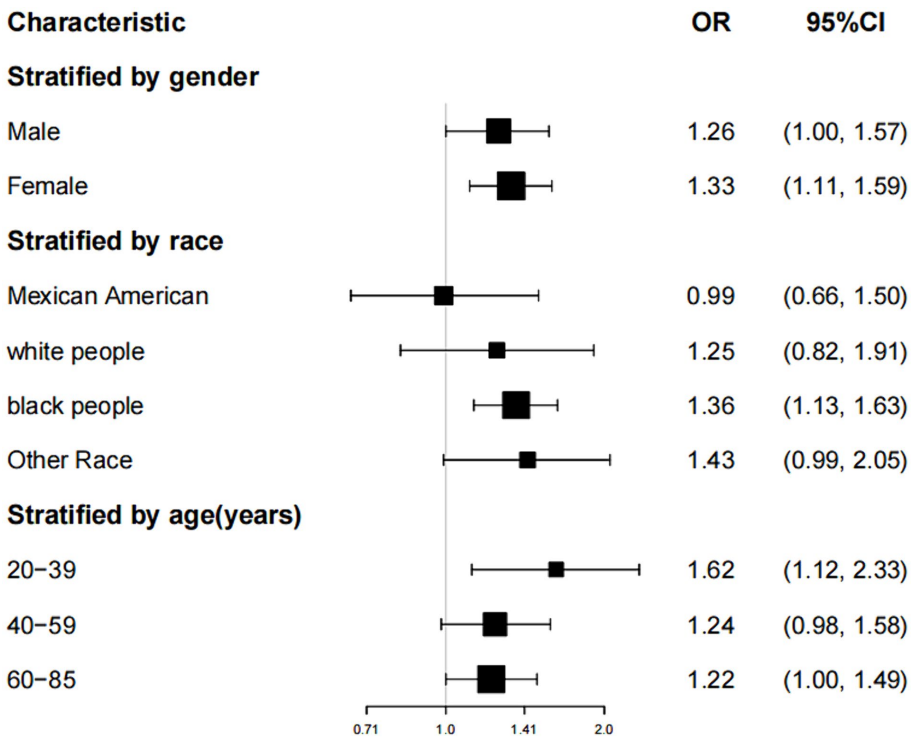

FIGURE 3
Forest plot of subgroup analysis between TyG index and gallstone prevalence in model 3.

that mice with isolated hepatic insulin resistance (LIRKO mice) have an increased propensity to develop cholesterol gallstones (32). Additionally, in mouse models, a high-protein, high-quality diet has been associated with accelerated bile acid and gallstone formation (33). Another contributory factor in gallstone pathogenesis is leptin, often linked to hyperleptinemia in cases of insulin resistance (34). *In vivo* experiments have verified that prolonged intraperitoneal administration of high-dose leptin (10 μg/g per day) induces weight loss and cholesterol gallstone formation in C57BL/6J ob/ob mice (35). Furthermore, *in vitro* experiments have demonstrated that leptin impacts gallstone formation by regulating bile acid metabolism (36).

Our study possesses several key strengths. Firstly, NHANES, with its representative United States sample, enforced strict adherence to a meticulously crafted study protocol, including robust quality control and assurance measures, thus underpinning the reliability of our findings. Secondly, NHANES contributed a wealth of demographic and metabolic data, complemented by an extensive follow-up spanning more than 20 years. This enabled comprehensive adjustments for the primary confounding factors within our multivariate model. We further mitigated the influence of confounding variables and broadened the applicability of our results through subgroup analyses. Nevertheless, our study does present certain limitations. Initially, it was a cross-sectional investigation, precluding the establishment of causal relationships between TyG and gallstones. Additionally, the reliance on questionnaire-based survey data in NHANES introduces the potential for recall bias. Despite these constraints, our study represents the first exploration of the association between TyG and gallstone prevalence and provides compelling evidence for the utility of TyG as a gallstone development predictor.

5 Summary

This investigation indicates a connection between increased TyG levels and an elevated risk of gallstone prevalence, with notable advantages potentially more pronounced in younger adults. Nonetheless, the confirmation of our results warrants further examination through additional research.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

The studies involving humans were approved by the NCHS Research Ethics Review Committee approved the NHANES survey protocol (https://www.cdc.gov/nchs/nhanes/irba98.htm), and all participants of the study provided informed written consent. The NHANES database is open to the public and therefore the ethical review of this study was exempt. 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. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XF: Conceptualization, Data curation, Investigation, Writing – original draft. SW: Methodology, Software, Writing – original draft. BK: Formal analysis, Visualization, Writing – original draft. YL: 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/fpubh.2024.1351884/full#supplementary-material

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A narrative review of the measurement methods for biomechanical properties of plantar soft tissue in patients with diabetic foot

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This article provides an overview of the development history and advantages and disadvantages of measurement methods for soft tissue properties of the plantar foot. The measurement of soft tissue properties is essential for understanding the biomechanical characteristics and function of the foot, as well as for designing and evaluating orthotic devices and footwear. Various methods have been developed to measure the properties of plantar soft tissues, including ultrasound imaging, indentation testing, magnetic resonance elastography, and shear wave elastography. Each method has its own strengths and limitations, and choosing the most appropriate method depends on the specific research or clinical objectives. This review aims to assist researchers and clinicians in selecting the most suitable measurement method for their specific needs.

KEYWORDS

diabetic foot, biomechanical properties, plantar soft tissue, shear force, measurement method

1 Introduction

Diabetes has become one of the most serious health threats in today's era. It has been reported that if the current trend of diabetes prevalence continues, it is estimated that by 2050, 21–33% of the US population will suffer from diabetes (1). China has the largest diabetic population in the world, with an estimated 116 million adults affected, accounting for about 25% of global diabetes cases (2). Diabetes is associated with complications affecting multiple systems in the body, such as retinopathy, kidney disease, diabetic foot ulceration (DFU), and autonomic neuropathy. Foot-related diseases, including infections, ulcers, and gangrene, are common symptoms among hospitalized diabetes patients. Among them, DFU is one of the most common complications of diabetes, with approximately

15–25% of diabetes patients experiencing DFU in their lifetime, and 5–24% of patients requiring amputation within 6–18 months after the first DFU assessment (3–5). According to the International Diabetes Federation, globally, approximately 9.1–26.1 million diabetes patients develop DFU each year (6). DFU imposes a significant burden on society, including limb disabilities in diabetic patients and the associated substantial hospitalization and healthcare costs. In the United States, the average cost of treating a DFU patient is around $13,179, totaling up to $58 billion annually (7, 8).

DFU is primarily developed based on three key pathological factors: neuropathy, trauma with secondary infection, and peripheral arterial disease (9). Peripheral neuropathy leads to intrinsic muscle atrophy in the feet, resulting in hammer toes and the creation of "high-pressure" areas beneath the metatarsal heads. In the presence of impaired skin sensation and proprioception, decreased feedback and adaptive adjustments to pain or pressure in the feet can lead to repeated micro-trauma even during normal walking, causing the protective plantar fat pad to atrophy and dislocate, ultimately leading to foot ulceration and infection (10). Diabetes-induced neuropathy is a symmetrical polyneuropathy affecting motor, sensory, and autonomic nerve functions to varying degrees. These factors contribute to abnormal gait, altered plantar pressure and shear forces, increased risk of infection, decreased injury threshold, and reduced skin healing capacity, collectively leading to DFU development. Hyperglycemia and its related metabolic changes can cause endothelial damage, elevated blood lipids, increased platelet adhesion and activation, and, over time, the development of atherosclerosis. With the progression of diffuse tibial arterial occlusion or more proximal arterial occlusion, inadequate microcirculation in the feet to maintain skin integrity can lead to ischemic ulcers and gangrene, and reduced self-healing ability for minor tissue injuries further exacerbates soft tissue damage (9). Therefore, DFU occurs and progresses as a result of the combined effects of multiple biological and mechanical mechanisms.

The foot is the first point of contact with the ground during human locomotion and bears several times the body weight as a reactive force. The plantar soft tissues serve as the primary cushioning structure that maximally reduces the transmission of impact stress to the skeletal system (11–13). In diabetic patients, a prolonged hyperglycemic environment leads to a series of chemical reactions between reducing sugars and cellular proteins, resulting in the formation of advanced glycation end products (AGEs) (14, 15). The accumulation of AGEs is a major cause of diabetic tissue pathology and physiological changes (16, 17). The buffering capacity of the plantar soft tissues depends largely on their viscoelastic properties. Therefore, if the tissues lose their viscoelasticity due to continuous AGE accumulation, their ability to absorb impact and evenly distribute loads during weight-bearing activities will be reduced (18). Increased stiffness, decreased damping effects, and lower tissue damage thresholds in the heel pad of diabetic patients have been confirmed by numerous studies. Thus, accurate measurement of the structural and biomechanical parameters of the plantar soft tissues is crucial for DFU prevention and early risk classification (19). Although the heel region is not the highest occurrence area for DFU and other pathological conditions on the sole, the heel pad (HP) has always been a more focused site among scholars when studying the material properties of the plantar soft tissues. Possible reasons include: (1) although DFU and other pathological conditions in the heel region are not the most common, once they occur in this area, they are difficult to heal and greatly affect the patient's mobility, resulting in high treatment costs (20); (2) the unique structure of the heel pad makes it an ideal subject for biomechanical research. Compared to the forefoot fat pad, the heel pad has a more specialized structure, comprised of differentiated adipocytes surrounded by fibro-septal compartments that form a honeycomb-like pattern (20). Additionally, the heel pad has a relatively thick and large volume, making it easier to observe and capture morphological changes during gait. The exploration of testing methods for the biomechanical properties of the plantar soft tissues has been ongoing, and significant progress has been made as advancements in available tools and measurement techniques have emerged. This paper provides a comprehensive review of the development process of testing methods for the biomechanical properties of plantar soft tissues in diabetic patients. It aims to guide the establishment of novel measurement tools for assessing the biomechanical properties of plantar soft tissues, provide references for selecting more accurate and convenient testing methods in clinical practice, and assist in the prevention and early risk classification of DFU.

2 Structural and biological characteristics of plantar soft tissues

During the gait cycle, the foot plays a crucial role in force transmission as it first contacts the ground. The plantar fat pad serves as a natural "shock absorber" with energy dissipation properties, providing cushioning and damping effects. The internal structure of plantar soft tissues consists of numerous highly differentiated compartments, as illustrated in Figure 1. These compartments are composed of adipocytes surrounded by fibrous septa, forming closed structures that do not communicate with each other (21). Within the plantar region, from the skin layer to the bone surface, the soft tissues differentiate into shallow smaller compartments and deeper larger compartments. The smaller compartments undergo minimal deformation and exhibit approximately ten times the stiffness of the larger compartments, which mainly deform under load and significantly contribute to the viscoelastic properties of the plantar soft tissues (21).

The intact structure of plantar soft tissues is crucial for buffering external stresses imposed on them, functioning similarly to a damper that attenuates peak forces and dampens vibrations (22). During walking, a portion of the compressive or shear energy applied to the plantar soft tissues dissipates as heat, while another portion is released through elastic rebound (23). The complex differentiated structure of healthy plantar soft tissues enables them to withstand stress impacts during daily activities without sustaining damage. However, conditions such as aging, diabetes, plantar fasciitis, peripheral neuropathy, foot vascular diseases, cavus foot, rheumatoid arthritis, hormonal use, and trauma can lead to degeneration of the plantar fat pad, resulting in reduced damping

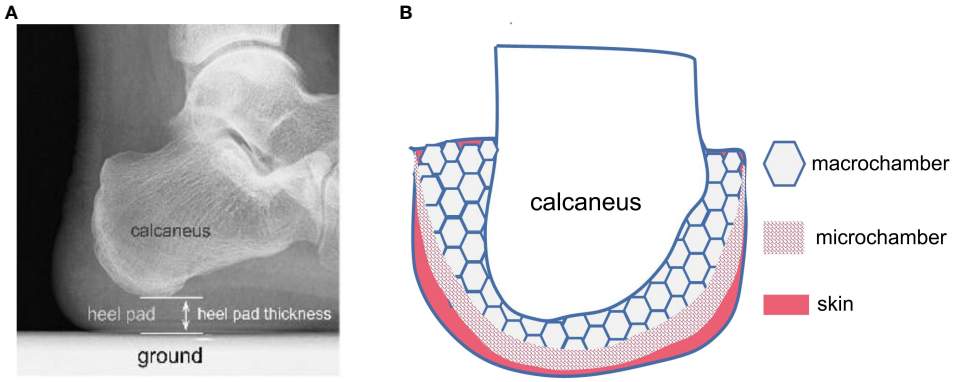

FIGURE 1
Schematic diagram of the internal structure of the heel pad (HP). **(A)** HP is a soft tissue fat pad located under the human heel, with an average thickness of 18mm. It is the first point of contact between the human body and the ground during walking. **(B)** HP exhibits a specialized honeycomb-like structure, composed of dense fibrous septa that encapsulate the fatty tissue. The main components of the fibrous septa are collagen fibers and elastic fibers, originating from the plantar fascia and terminating in the dermis, forming a completely closed cavity structure. Numerous fat cells are filled in the closed cavity formed by the fibrous septa. HP consists of an outer small compartment layer and an inner large compartment layer, exhibiting different biomechanical properties. The outer compartment layer is approximately 10 times stiffer than the inner compartment layer and undergoes minimal deformation under normal loads, while the large compartment layer is the primary structure responsible for compression deformation.

effects and lowered damage thresholds. Diabetes introduces complex biochemical changes in the body, and persistent hyperglycemia and accelerated accumulation of AGEs are major factors underlying detrimental pathological changes in diabetic plantar soft tissues (24).

Morphological studies have demonstrated tissue morphological changes in the plantar fat pad of diabetic patients, including decreased volumes of adipocytes, increased thickening and fragmentation of fibrous septa, and relative decrease in fat content with increased fibrous septa content (25–30). Wang et al. (25) compared the morphological differences in the plantar fat pads beneath the first metatarsal head and heel between diabetic and non-diabetic cadaveric specimens and found that fibrous septa and dermal layers were significantly thicker in the plantar fat pads of diabetic patients, while fusion degree between dermis and epidermis and the size of adipocytes showed no significant differences. In another study by Wang et al. (26), histological and biochemical composition analyses were performed on six different regions of the plantar fat pad (big toe area, first metatarsal head area, third metatarsal head area, fifth metatarsal head area, lateral arch area, and heel area) from elderly diabetic and non-diabetic cadavers. The authors found that the most significant changes in diabetic patients, compared to the healthy population, were increased thickness of fibrous septa and increased elastic fiber content, while no significant difference was observed in fibrous septa thickness between the heel area and other regions, but elastic fiber content was markedly reduced. Waldecker and Lehr (27) conducted biopsies on the subcalcaneal fat pad tissue, but their research did not find any differences in adipocyte size between diabetic and non-diabetic individuals. Others have reported that the skin thickness (both on the foot dorsum and at other locations) is greater in diabetic patients (28, 29), and impaired gene expression related to extracellular matrix remodeling leads to decreased mechanical performance (30). Kuhns et al. (31) reported twisted and fractured collagen fiber bundles in the fibrous septa and fat cell extravasation in degenerated heel pads of elderly individuals. The most notable changes in degenerated plantar fat pads were the relative increase in the amount, thickness, and fragmentation of elastic fibers (12). These changes result in decreased damping performance, reduced energy dissipation capacity, and consequently, more energy acting on the plantar soft tissues during gait, leading to further tissue damage.

Plantar soft tissues exhibit typical viscoelastic properties and can be simplified according to the Kelvin-Voigt viscoelastic material model, composed of parallel linear elastic elements and nonlinear viscous elements (Figure 2). The normal damping and stress-buffering capabilities of plantar soft tissues depend largely on their viscoelasticity. During the gait cycle, the plantar soft tissues experience repeated cycles of stress loading and unloading. Due to the viscoelastic properties of the plantar soft tissues, the energy generated during impact between the foot and the ground is partially dissipated as heat during the tissues' rebound, thereby attenuating the energy transmitted to the skeletal system. Stress-strain curves during loading and unloading cycles form characteristic hysteresis loops, with the size of the area reflecting the energy dissipation performance of plantar soft tissues. When biochemical composition and tissue morphology of plantar soft tissues change due to prolonged hyperglycemia, their viscoelastic properties are affected, further reducing their ability to absorb shock and evenly distribute loads during weight-bearing activities (18). Therefore, testing the viscoelastic properties of plantar soft tissues in diabetic foot conditions is an important approach for evaluating the progression of diabetic foot. However, existing research has primarily focused on testing the elastic properties of plantar soft tissues, often neglecting the exploration of their viscous properties. The time-dependent viscous properties of plantar soft tissues play a significant role in stress buffering and energy dissipation (32). Studies have shown that the viscous properties of plantar soft tissues are more sensitive in assessing the diabetic condition compared to other commonly used parameters such as tissue stiffness (33).

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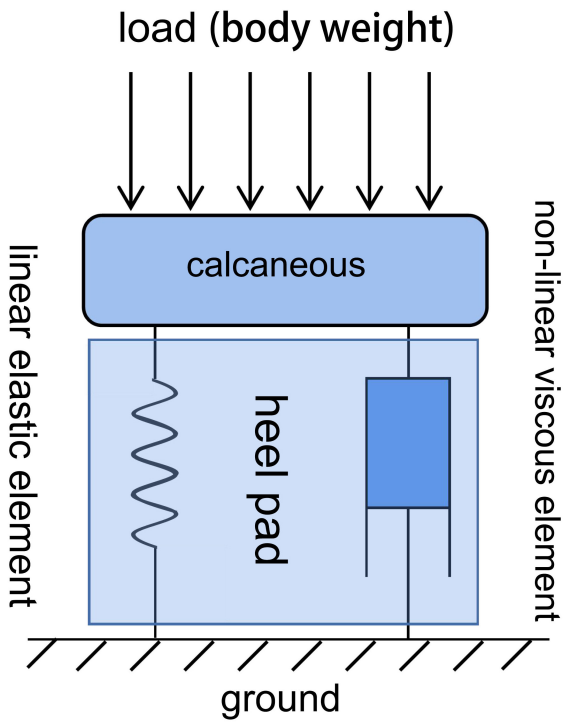

FIGURE 2
Kelvin-Voigt viscoelastic material model of the soft tissue beneath the heel, which undergoes corresponding deformation when subjected to mechanical loading. This model consists of two elements (a linear elastic element and a nonlinear viscous element) connected in parallel.

3 Advancements in biomechanical testing of plantar soft tissues

Accurate and convenient testing of the biomechanical properties of plantar soft tissues plays a crucial role in the prevention and risk stratification of DFUs. As reported by Naemi et al. (34), the mechanical properties of plantar soft tissue measured using ultrasound elastography technique can be used to improve the predictability of DFU in moderate/high risk diabetic patients. In Morrison et al. (35), the authors aimed to ascertain if B-mode ultrasound could be clinically applied to identify structural change in the diabetic foot and be utilised as an early predictor of ulceration risk. However, they found that no direct evidence was found to indicate B-mode ultrasound measures can predict soft tissue changes in the plantar foot in diabetes. With an increasing understanding of the tissue morphology and biomechanical properties of plantar soft tissues, as well as advancements in testing equipment and analysis methods, numerous methods have emerged to evaluate the material properties of plantar soft tissues. Overall, the development of these techniques has transitioned from *ex vivo* studies to *in vivo* research and from quasi-static conditions to dynamic loading. The developmental history and respective advantages and disadvantages of measurement methods for plantar soft tissue material properties are shown in Figure 3.

Initially, researchers primarily created standardized test specimens from excised plantar soft tissue and subjected them to compression testing using universal material testing machines to observe the compressive material properties of plantar soft tissues. Subsequently, some *in vivo* quasi-static testing methods were introduced, including ultrasound indentation, air-jet indentation based on optical coherence tomography (OCT), dynamic spherical indentation systems, and tissue ultrasound palpation systems. These methods yielded more reliable and repeatable results but were unable to replicate the dynamic loading-unloading process experienced by plantar soft tissues throughout a complete gait cycle.

In recent years, some scholars have attempted to dynamically observe the strain of plantar soft tissues during the gait cycle using X-ray imaging techniques. Concurrently, they recorded stress information using plantar pressure plates and solved for the material properties through fitting calculations. This method enabled dynamic assessment of plantar soft tissues during a gait cycle, providing results that are more representative of the true properties of the plantar fat pad. However, current research has predominantly focused on testing the vertical compressive properties of plantar soft tissues, while exploring the horizontal

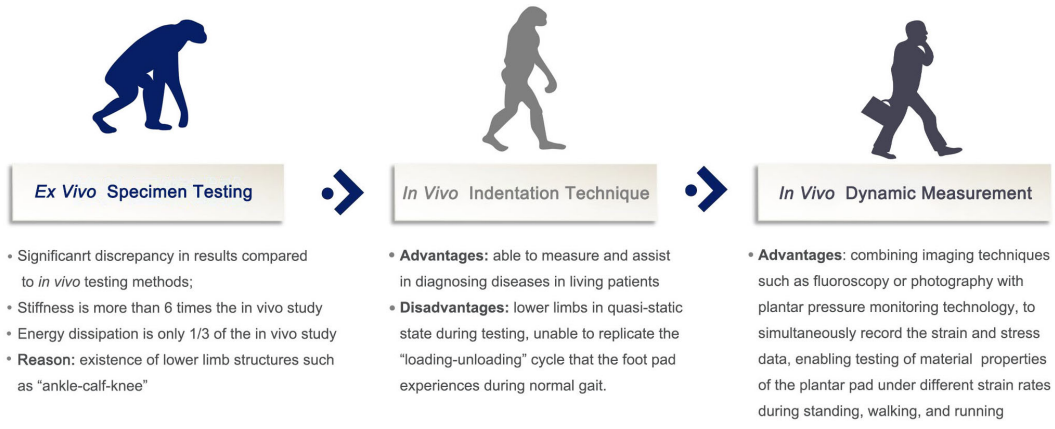

FIGURE 3
Development and pros and cons of measurement methods for soft tissue biomechanical properties of the plantar foot.

shear properties of these tissues still poses significant technical challenges. As a result, relevant evidence in this regard is difficult to obtain. This may be due to past neglect of shear forces and the technical difficulties associated with measuring shear force and shear strain.

3.1 *Ex vivo* specimen testing for biomechanical properties

Due to the limitations of early testing tools, researchers initially explored the material properties of plantar soft tissues using *ex vivo* specimens and uniaxial compression tests on universal material testing machines to measure stress relaxation and compression properties of plantar soft tissues (36–39). Alexander et al. (38) conducted initial dynamic compression testing on ex vivo specimens of foot fat pads (metatarsal pad and heel pad) from various mammals. Bennett et al. (23) performed uniaxial compression loading-unloading tests on the heel region (calcaneus + HP) of 11 cadaveric feet, observing nonlinear stiffness in all samples, with stiffness increasing as the load increased. The average stiffness measured when the load was equivalent to body weight was 1160 ± 170 kN/m, with an average compression deformation of 2.07 ± 0.29 mm. The mean energy dissipation rate (EDR) was 28.6 ± 6.9% before decalcification and 32.3 ± 5.4% after decalcification of the calcaneus. In Miller-Young et al.'s study (39), the authors prepared 8 mm diameter standard specimens of the HP from 20 cadaveric feet and subjected them to a series of unconstrained loading tests (quasi-static, 175 mm/s, 350 mm/s, and stress relaxation tests) using a material testing machine to observe the viscoelastic properties of HP and obtain constitutive equations for modeling plantar soft tissues. The results showed nonlinear viscoelastic behavior of the HP, and the experiments yielded a series of parameters suitable for finite element simulation. Ledoux et al. (36) obtained specimens of the soft tissues in six regions of the plantar surface (under the big toe, under the second metatarsal head, under the third metatarsal head, under the fifth metatarsal head, lateral arch, and heel region) from 11 cadaveric foot specimens. Compressive and stress relaxation experiments were conducted using a material testing machine on standardized 2x2 cm test specimens, and the maximum stress, elastic modulus, and EDR of the soft tissues were compared among different regions and under different strain rates. Significant differences were found in the maximum stress, elastic modulus, and EDR among the six plantar regions, with the heel region exhibiting the highest maximum stress and elastic modulus and the lowest EDR. Additionally, as the strain rate increased, the maximum stress, elastic modulus, and EDR of the plantar soft tissues also significantly increased. Pai et al. (37) used the same method to measure the force-dependent mechanical properties of the plantar soft tissues in four diabetic and age-matched non-diabetic cadaveric foot specimens. The results showed that the diabetic foot specimens exhibited higher elastic moduli than the non-diabetic foot specimens in various plantar regions and at different strain rates (average 1146.7 vs. 593.0 kPa). The material properties of the specimens demonstrated clear strain rate dependency. While *ex vivo* specimens provide convenient testing of the mechanical properties of plantar soft tissues, evidence suggests significant differences between the material properties of the heel pad measured through *ex vivo* mechanical tests compared to *in vivo* experiments, with increased stiffness and decreased EDR observed in *ex vivo* tests (23, 40–42). This difference is believed to be due to the effects of other structures of the lower limb during *in vivo* measurements (42). Therefore, *ex vivo* measurements cannot fully reflect the biomechanical properties of plantar soft tissues in physiological conditions, and *ex vivo* methods cannot provide real-time *in vivo* measurements of patients.

Furthermore, a limited number of studies have tested the shear mechanical properties of plantar soft tissues using *ex vivo* specimens (43–45). Ledoux et al. (43), Pai et al. (44), and Brady et al. (45) prepared *ex vivo* specimens of plantar soft tissues from cadaveric feet and used a material testing machine to measure the shear mechanical properties of different regions of the plantar surface. The obtained shear elastic modulus was significantly smaller than the compressive elastic modulus in the vertical direction, measuring only around 50 kPa.

3.2 *In vivo* testing for biomechanical properties

While the use of *ex vivo* specimens for testing the material properties of plantar soft tissues offers a straightforward and data-processing-friendly approach, it is limited to experiments conducted on cadaveric samples and cannot be performed in living subjects. As a result, direct data cannot be obtained for assessing the status of plantar soft tissues in diabetic patients and evaluating the risk of DFUs. Furthermore, *ex vivo* specimens lack the presence of other parts of the lower limb ("ankle-calf-knee") and the internal structures of the remaining foot, leading to complete unconstrained conditions around the plantar soft tissues after detachment. These factors contribute to a significant disparity between the biomechanical properties measured in *ex vivo* testing and those observed in *in vivo* testing. This issue is commonly referred to as the "heel pad paradox" (42, 46, 47), and was initially proposed by Aerts et al. in 1995 (42). The authors conducted pendulum impact tests on live subjects and compression loading tests using universal material testing machines on *ex vivo* specimens, revealing a substantial discrepancy in stiffness (*in vivo*: 150 kN/m vs. *ex vivo*: 900 kN/m) and EDR. Additionally, Pain et al. (46) created a two-dimensional model of the lower leg and heel pad using DADS software and compared the heel pad properties with and without the involvement of the lower limb through pendulum impact tests, further confirming the existence of the "heel pad paradox" and the impact of lower limb soft tissues on heel pad property testing results.

To address this issue, *in vivo* testing of the biomechanical properties has become increasingly prevalent, with various researchers designing numerous testing methods. Most of these methods involve maintaining the subject's foot in a quasi-static state during testing and applying different forms of loading to assess the mechanical properties of plantar soft tissues. Some researchers have

also developed dynamic testing methods that involve assessing plantar soft tissues during gait cycles under X-ray fluoroscopy, allowing for the complete reproduction of the mechanical loading process experienced by the subject's plantar soft tissues during normal walking.

In summary, attempts at *in vivo* testing of the biomechanical properties of plantar soft tissues have gained popularity, and researchers have devised various testing methods. Most of these methods involve quasi-static testing with the subject's foot in a stationary state, applying different loading units to test the mechanical properties of plantar soft tissues. A smaller number of researchers have designed dynamic testing methods that evaluate plantar soft tissues under X-ray fluoroscopy during gait cycles, allowing for the replication of the mechanical loading experienced by the subject's plantar soft tissues during normal walking.

3.2.1 *In vivo* quasi-static measurements for mechanical properties

3.2.1.1 Pendulum impact test

The pendulum impact test involves using a rod-shaped pendulum with a known mass and an accelerometer. The pendulum is suspended by a cord and swung to impact the desired area of the plantar soft tissues. The accelerometer records the acceleration data during the entire swinging process, and combined with the mass of the pendulum, it allows for the calculation of continuous displacement and force information during the impact process, which can be used to estimate the material properties of the plantar soft tissues (42, 46–48). Throughout the testing process, the subject's foot remains fixed on the testing platform in a stationary position. Weijers et al. (47) conducted a study with 11 subjects to investigate the damping characteristics of the plantar tissues in the heel region during heel strike while controlling the venous congestion of the lower limb using a blood pressure cuff. They used the pendulum test at swinging speeds of 0.2, 0.4, and 0.6 m/s to assess the mechanical properties of the plantar soft tissues and found that the venous congestion affected the damping effect of the plantar soft tissues to some extent. As previously mentioned, Aerts et al. (42) and Pain et al. (46) also employed *in vivo* pendulum impact tests to compare the results with those obtained from *ex vivo* specimen testing in order to verify the "heel pad paradox". In another study, Aerts et al. (48) performed pendulum impact tests on the heel regions of nine subjects and compared the mechanical characteristics between soft-soled shoes and hard-soled shoes based on the deformation and load data calculated from the pendulum mass and the negative acceleration recorded by the accelerometer. This measurement method provides a better simulation of the impact between the heel region and the ground during motion and offers advantages such as easy experimental setup, inexpensive equipment, and straightforward data processing.

3.2.1.2 Dynamic spherical indentation system

In vivo spherical indentation tests primarily rely on stress relaxation tests to measure the viscoelastic properties of the live heel pad (HP) (19, 49, 50). Negishi et al. (19) conducted stress relaxation tests on the soft tissues of the heel region in three healthy subjects using a self-designed spherical indentation system to investigate the influence of different strain rates on the stress relaxation curves. They found significant differences in the stress relaxation curves of the plantar soft tissues under different strain rates, indicating a notable effect of strain rate on the viscoelastic properties of the plantar soft tissues. Suzuki et al. (49) determined the viscoelastic and hyperelastic material properties of the plantar soft tissues through spherical indentation tests and an analytical contact model. They obtained the stress relaxation curve of the HP through the indentation experiment and fitted the curve into the contact model of the Maxwell model to calculate the viscosity material parameter. In another study by Suzuki et al. (50), the authors derived an analytical contact model for spherical indentation tests to directly estimate the material properties of the plantar soft tissues. Through indentation experiments, they obtained the force-displacement curve of the HP. By fitting the experimental data to the stress-strain analytical solution of the spherical indentation, they successfully calculated the nonlinear material properties of the HP using the spherical indentation method.

3.2.1.3 Ultrasound/MR elastography

Ultrasound elastography is another widely used approach for assessing the mechanical properties of plantar soft tissues (51–60). Based on the different elastic moduli of human soft tissues, their deformation under external compression varies. Ultrasound elastography converts the real-time changes in echo signal displacement before and after compression into color images. Tissues with lower elastic moduli appear red, indicating higher strains after compression, while tissues with higher elastic moduli appear blue, indicating lower strains. Tissues with intermediate elastic moduli appear green on the image. Naemi et al. (52) employed ultrasound shear wave elastography to test the elastic moduli of the soft tissues below the first metatarsal head, third metatarsal head, and heel region in 51 subjects with diabetes or prediabetes. They found a significant correlation between fasting blood glucose levels and plantar tissue stiffness. Lin et al. (54) utilized ultrasound elastography to examine the elastic modulus of the HP in 20 healthy subjects and 16 patients with unilateral heel pain. The results showed significantly higher elastic moduli in the affected compartmental layers (superficial, intermediate, and full layer) of the HP in patients with heel pain compared to the healthy side. Additionally, the elastic moduli of the compartments (superficial, intermediate, and full layer) were significantly elevated in heel pain patients compared to healthy subjects.

Magnetic resonance elastography (MRE) is an emerging imaging technique that can estimate the inherent elastic properties of tissues (61, 62). Information obtained from MRE can be displayed as tissue stiffness maps and provide valuable information for manual palpation. It is commonly used as a clinical tool for diagnosing breast diseases (61, 62). Weaver et al. (61) conducted *in vivo* testing of the shear modulus of the HP using MRE and found that the shear modulus of the soft tissues beneath the heel gradually increased from 8 kPa to 12 kPa as pressure was applied, while the soft tissues surrounding the heel remained

around 8 kPa. The obtained shear modulus results were similar to those measured using the same method for breast adipose tissue. Cheung et al. (62) performed elastic modulus testing of the plantar soft tissues in 12 non-diabetic subjects and 4 subjects with diabetic neuropathy using MRE. The elastic modulus values for the two groups were 4.85 kPa and 5.26 kPa, respectively. MRE can detect early mechanical property changes in diabetic feet and provide a non-invasive means to monitor the progression of diabetic foot disease. Using MRE technology to monitor patients can lead to earlier detection of foot disorders, prompting proactive measures by clinicians to prevent callus formation, skin breakdown, ulcers, and eventual amputation. MRE maps can also help orthopedic surgeons and engineers identify areas with the most significant changes in plantar tissue mechanical properties and design personalized cushioning footwear/insoles to control ulcer development.

3.2.1.4 Ultrasound/MR indentation technique

Ultrasound/MR indentation technique combines an ultrasound/MR probe with an indentation/compression device. The ultrasound/MR probe records the deformation and strain of the plantar soft tissues, while the loading unit on the indentation device, equipped with digital mechanical sensors, captures real-time mechanical information. By integrating these two components, the mechanical properties of the plantar soft tissues can be calculated. In recent years, numerous researchers have designed this type of measurement device and successfully applied it to test plantar soft tissues (63–73).

Chatzistergos et al. (63) designed a measurement device consisting of an ultrasound probe, a force sensor, and a manually operated ball screw loading unit to investigate the correlation between the mechanical performance of the HP in type-2 diabetes patients and clinical characteristics. They tested 35 type-2 diabetes volunteers and found a significant positive correlation between triglyceride levels and HP stiffness ($r = 0.675$, $p<0.001$), as well as a significant negative correlation between fasting blood glucose and energy absorption of the HP ($r = -0.598$, $p = 0.002$). Hsu et al. (71) developed an ultrasound transducer based on a 7.5MHz linear array and a combination of loading devices weighing 0.5→3.0→0.5kg. They conducted structural and mechanical property tests on the HP of 20 young subjects and 13 elderly subjects. The results showed that the initial thickness (2.01 ± 0.24 cm vs. 1.76 ± 0.20cm), peak strain (61.3 ± 5.5% vs. 53.3 ± 7.7%), and EDR (35.3 ± 10.0% vs. 23.7 ± 6.9%) of the HP were significantly higher in the elderly group compared to the young group. Stiffness was higher in the elderly group, although the difference was not statistically significant ($p = 0.098$). In another study by Hsu et al. (72), they used a linear array ultrasound transducer with a frequency range of 5–12MHz and a self-designed device capable of different loading and unloading speeds (fast loading: 10 cm/s; medium loading: 2.0 cm/s; slow loading: 2.5 cm/s) to compare the material properties beneath the metatarsal heads of the left foot between 10 middle-aged and elderly subjects (age range: 42–72) and 9 young subjects (age range: 19–35). They found that as the loading speed increased, the elastic modulus of the young subjects gradually increased from 300 kPa to around 500 kPa, while the middle-aged and elderly group did not show a significant trend, remaining around 500 kPa to 550 kPa. The EDR increased from 30% to approximately 60% in the young group and from 40% to around 70% in the middle-aged group. Overall, in most metatarsal heads, the elastic modulus of the middle-aged group was significantly higher than that of the young group. Trebbi et al. (73) established a measuring method using MR imaging and a mechanical loading plate to assess the internal compression and shear strain of soft tissues (HP, sacral soft tissues, etc.), providing guidance for risk assessment of DFUs or pressure ulcers.

3.2.1.5 Other quasi-static indentation techniques

In the study by Chao et al. (74), the authors designed a jet-indentation system based on OCT and a tissue ultrasound palpation system. These two systems were used to test and compare the mechanical properties of the plantar soft tissue in the forefoot of 30 young and elderly individuals. The results revealed a strong positive correlation ($r = 0.88$, $p<0.001$) between the data obtained from the two methods. The stiffness of the first metatarsal bone was significantly higher in the elderly group compared to the young participants, while the soft tissue thickness of the first/second metatarsal bone was significantly lower in the elderly group. Kwan et al. (75) also employed a tissue ultrasound palpation system to test the soft tissue thickness and stiffness of the toes, first/third/fifth metatarsal bones, and heel region in 60 participants aged between 41 and 83 years. The results showed a significant increase in the soft tissue stiffness ($p<0.001$) in all five tested locations with increasing age. There was no significant correlation between age and plantar soft tissue thickness.

3.2.2 *In vivo* dynamic measurement of mechanical properties

Although the methods mentioned above can achieve *in vivo* measurement of plantar soft tissue, the subjects are all in a quasi-static state, with their lower limbs fixed on the measuring device, unable to complete the gait cycle and reproduce the loading-unloading process of the plantar soft tissue during daily activity. In order to overcome this limitation, De Clercq et al. (18), Gefen et al. (76), and Wearing et al. (77) combined imaging techniques such as X-rays and plantar pressure testing plates to measure the *in vivo* biomechanical properties of the plantar soft tissue in dynamic gait. This method can monitor the strain and stress changes of the plantar soft tissue in real-time during the gait cycle and calculate the material properties of the tissue at different time phases. However, the studies by De Clercq et al. (18), Gefen et al. (76), and Wearing et al. (77) only used two-dimensional perspective photos to measure the vertical strain of the plantar soft tissue, and the accuracy of the measurement may be influenced by factors such as the shooting angle. To avoid this issue, Teng et al. (78) and Yang et al. (79) used double-plane X-ray perspective technology to continuously shoot perspective films of the plantar soft tissue from two intersecting vertical angles, and then reconstructed a three-dimensional structure of the heel in order to observe the deformation of the plantar soft tissue during the gait cycle in a three-dimensional manner. The real-time strain data was calculated, and the authors combined this with real-time stress data collected from the plantar

pressure plate to fit the stress-strain data and solve for the material properties of the plantar soft tissue. This improvement in measurement equipment further improves the accuracy of the test. However, using these methods may inevitably increase additional radiation exposure risks for the subjects and experimenters, which is an important factor that researches need to consider.

3.3 Comparison between the described methods

When comparing the various methods for measuring the biomechanical properties of plantar soft tissue in diabetic patients, it is essential to consider their specific advantages and limitations in different scenarios. Each technique offers unique insights, but the choice depends on the research question, available resources, and the level of detail required.

3.3.1 *Ex vivo* vs. *in vivo* testing

Ex vivo methods, such as uniaxial compression tests on universal material testing machines, are more straightforward and data-driven. However, they lack the physiological context and dynamic loading experienced *in vivo*. In contrast, *in vivo* techniques like pendulum impact tests and ultrasound elastography provide real-time data, but they may be more complex and require specialized equipment. For instance, if the focus is on understanding the impact of diabetes on tissue properties under natural loading conditions, *in vivo* methods would be more appropriate.

3.3.2 Quasi-static vs. dynamic loading

Quasi-static methods like indentation testing and ultrasound elastography yield static stress-strain curves, which are useful for understanding the material properties at a specific point in time. Dynamic testing, such as X-ray fluoroscopy during gait, captures the full loading-unloading cycle, providing a more comprehensive understanding of the tissue's behavior during functional activities. If the goal is to assess the risk of DFU development under realistic loading conditions, dynamic testing would be preferred.

3.3.3 Factors influencing the choice of methods

The choice of method depends on the research objective, the need for real-time data, and the level of detail required. A combination of techniques may be necessary to obtain a comprehensive understanding of the biomechanical properties of plantar soft tissue in diabetic patients.

Additionally, socioeconomic factors, such as income levels and educational background, can influence the type of technology available to researchers and clinicians. In regions with higher levels of poverty or lower educational attainment, it may be more challenging to obtain access to advanced imaging technologies like MRI or CT, which can be expensive and require specialized training to operate. This may limit the choice of measurement methods to more traditional and affordable options, such as manual palpation or basic imaging techniques.

Access to technology can also vary between different institutions, such as academic research centers, community hospitals, and private clinics. Academic centers and larger hospitals may have more resources to invest in new technologies and equipment, while smaller or rural institutions may have limited access to these resources. This can create disparities in the quality of care and research opportunities available to patients and researchers in different regions.

Health policy and research funding play a crucial role in shaping the direction of scientific research and the implementation of new technologies in clinical practice. Changes in these areas can have a significant impact on the adoption of advanced methods for measuring the biomechanical properties of the foot, particularly in the field of diabetes-related foot complications. For instance, government policies that prioritize the prevention and management of chronic diseases like diabetes may lead to increased funding for research in this area. This could create opportunities for the development and validation of new technologies for measuring plantar soft tissue biomechanics, which could ultimately lead to improved diagnosis and treatment of diabetic foot complications. On the other hand, budget cuts or changes in research funding priorities could limit the availability of resources for new technology development and implementation. This could make it difficult for researchers to obtain the necessary equipment and expertise to conduct cutting-edge research in this area. Moreover, policies that promote interdisciplinary collaboration and knowledge translation between academia and industry could facilitate the development and commercialization of new technologies for measuring plantar soft tissue biomechanics. This could lead to faster adoption of these technologies in clinical practice and improved patient care.

4 Summary and future directions

Accurate and convenient testing of the biomechanical properties of the plantar soft tissue has an important role in the prevention and risk grading of DFU. With the increasing understanding of the morphology and biomechanical properties of plantar soft tissue in the academic community, as well as the continuous updates of detection equipment and analysis tools, there are various methods for evaluating the material properties of plantar soft tissue. Overall, the development of these techniques has transitioned from *in vitro* research to *in vivo* research and from quasi-static states to dynamic loading states. However, current research almost entirely focuses on testing the vertical compression properties of plantar soft tissue, and there are still significant technical difficulties in exploring the material properties of plantar soft tissue in the horizontal shear direction. Therefore, there are very few related studies reported in literature.

Secondly, at present, all the testing methods on biomechanical properties of the plantar heel pad are carried out as macroscopic biomechanical measurements of the whole structure. However, the plantar heel pad is not a completely homogeneous structure, but a specialized honeycomb structure composed of fiber elastic intervals and adipocytes, which may display differences in biomechanical

properties when subjected to compression or shear stress. Currently, no study has explored the microstructures of the internal fiber intervals and adipocytes and how they affect the biomechanical properties of the heel pad when subjected to compression or shear stress. In addition, there are significant differences in the biomechanical properties between the plantar superficial layer and deep intermuscular compartment layer. The analysis of the differences in tissue structural deformation between diabetic and normal plantar soft tissues when subjected to the same level of compression or shear force has significant implications for studying the biomechanical mechanisms of DFU formation and improving DFU prevention measures. Stereology is a newly emerging interdisciplinary field that was first proposed by German biologists and mathematicians in 1961. Its core content is the quantitative study of three-dimensional structures. In recent years, with the development of modern quantitative stereology technology, its application scope has been continuously expanded, and it has now been widely used in the biomedical field. Biomedical stereology refers to the quantitative measurement of two-dimensional data obtained by measuring the geometrical information of organs, tissues, or cells using three basic geometric elements (measurable geometric information includes area, perimeter, length, width, diameter, point density, angle, etc.) and the inference of three-dimensional structural quantitative information. In recent years, some scholars have attempted to combine biomechanics with biomedical stereology and explored new methods for analyzing micro and submicroscopic biomechanical properties of soft tissues (80, 81). Eskandari et al. (80) observed the microstructural morphological changes of bovine brain white matter at different strain states under tensile and compressive mechanical loads and quantitatively analyzed the deformation of the microstructure in the tissue. Chen et al. (81) used a similar method to analyze the geometric parameters related to liver tissue injury by applying compression, tensile, and shear forces to pig liver tissue. However, there are no scholars who have applied stereological techniques to study the micro and submicroscopic biomechanics of the plantar soft tissue. Furthermore, atomic force microscope (AFM) is a more precise instrument for scanning and detecting the ultra-microscopic biomechanical properties of the sample surface, with a resolution of up to nanometer level. Therefore, future research needs to combine tissue morphological/stereological research methods with AFM and other tools to deeply explore the micro and submicroscopic biomechanical properties of the plantar soft tissue *in vitro* and compare the differences between diabetic and normal plantar soft tissues, revealing the deep impact of changes in the micro-mechanical properties on the occurrence and development of DFU.

In recent years, the integration of emerging technologies has significantly advanced the field of plantar soft tissue biomechanics research. These advancements have not only improved the accuracy and precision of measurements but also opened up new avenues for non-invasive and real-time monitoring. Wearable devices, such as smart shoes and insoles, equipped with sensors and microelectronics, can track plantar pressure distribution, gait patterns, and even detect subtle changes in tissue properties during daily activities. These devices can provide continuous, real-time data, enabling researchers to study the biomechanics of plantar soft tissue under more natural conditions. Artificial intelligence (AI) and machine learning can analyze large datasets generated by these technologies, identifying patterns and correlations that may not be apparent to the human eye. This can lead to more accurate predictions of tissue health and risk stratification for DFU. In future research, it is essential to continue exploring the potential of these emerging technologies to improve the accuracy, sensitivity, and non-invasiveness of plantar soft tissue biomechanical measurements. This includes developing novel data processing methods, integrating multiple sensing modalities, and validating these techniques in larger and more diverse patient populations. By doing so, researchers can better understand the complex interplay between diabetes and plantar soft tissue mechanics, ultimately leading to more effective prevention and management strategies for diabetic foot complications.

Author contributions

XY: Project administration, Writing – original draft, Writing – review & editing. ZP: Writing – original draft, Supervision. XL: Writing – review & editing, Validation. XL: Writing – review & editing. SL: 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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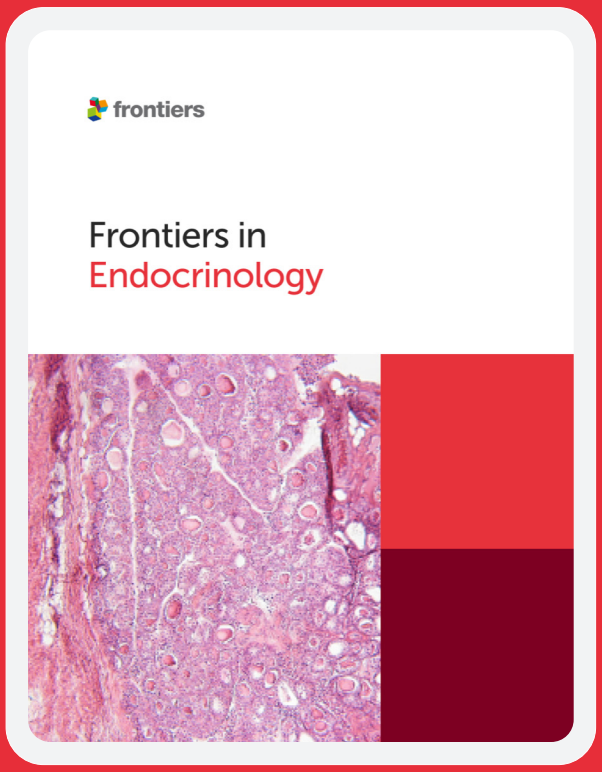

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