ACHIEVING EFFICIENT DIABETES CARE NOW THROUGH UNDERSTANDING THE RISK FACTORS, MARKERS, AND PATIENT'S EXPERIENCES

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PUBLISHED IN: Frontiers in Endocrinology

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88974-971-3
DOI 10.3389/978-2-88974-971-3

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ACHIEVING EFFICIENT DIABETES CARE NOW THROUGH UNDERSTANDING THE RISK FACTORS, MARKERS, AND PATIENT'S EXPERIENCES

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Citation: Chew, B.-H., Vos, R., Widyahening, I. S., Khunti, K., eds. (2022). Achieving Efficient Diabetes Care Now Through Understanding the Risk Factors, Markers, and Patient's Experiences. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88974-971-3

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frontiers in Endocrinology

EDITORIAL
published: 30 March 2022
doi: 10.3389/fendo.2022.854167

Editorial: Achieving Efficient Diabetes Care Through Understanding the Risk Factors, Markers, and Patient Experiences

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Keywords: diabetes care, efficient, risk factors, biomarkers, patient's experience

Editorial on the Research Topic

Achieving Efficient Diabetes Care Now Through Understanding the Risk Factors, Markers, and Patient's Experiences

OPEN ACCESS

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

Received: *13 January 2022*
Accepted: *23 February 2022*
Published: *30 March 2022*

Citation:
Chew B-H, Vos RC, Widyahening IS and Khunti K (2022) Editorial: Achieving Efficient Diabetes Care Through Understanding the Risk Factors, Markers, and Patient Experiences. Front. Endocrinol. 13:854167. doi: 10.3389/fendo.2022.854167

Until recently, the concept of a world without diabetes mellitus (DM) was not possible. This is now foreseeable with therapeutic advancements in technology in the form of our ability to create an artificial pancreas, stem cell transplant, personalized medicine of genomic-guided treatments, metabolic surgery, lifestyle interventions (1), and nutraceutical medicine (2). The greater challenges in delivering these therapies require adaptable healthcare systems, a trained healthcare workforce, and accessible and affordable treatments for those in greatest need of it. Bridging the gap between now and a better future for diabetes management requires a collective global effort that crosses international borders and boundaries, and the need for such a development is continuously pressing and supported by all organisations and governments. This begins by achieving an understanding of the increasing burden (3) and challenges of DM and its related complications when it comes to the healthcare systems, healthcare workers, and the person-level risk factors of DM. But this is also true for the markers of diseases related to DM, such as the life experiences of the people living with DM in coping and coming to terms with the disease in the form of a therapeutic relationship with professional careers and healthy living (4). The latter also requires local studies for more direct evidence and contexts (Al-Rifai et al., Sunny et al., Bukhsh et al. and de Jong et al.). In this special Frontiers in Endocrinology Research Topic, a number of articles examine this and the biological evidence of the maternal fasting plasma glucose profile in early pregnancy and its effect on foetal growth and birth outcomes (Guo et al.), preterm birth and birth weight, and the risk of type 1 diabetes (T1D) (Huang et al.), diabetes and sarcopenic obesity (Wang et al.), sodium-glucose cotransporter-2 inhibitors on liver enzyme (Euh et al.), and abnormalities in non-coding RNA as biomarkers (Chi et al.). This collective evidence takes us a step closer to the realisation of effective diabetes care for the prevention and normalisation of DM.

Due to gestational diabetes mellitus (GDM), a new generation of human beings is set to be at higher risk of DM (Guo et al., Huang et al.). Women with GDM have almost a 10 times higher risk

for type 2 diabetes (T2D) compared to healthy women (5). Therefore, studying and reporting the prevalence and risk factors for GDM in the Middle East and North Africa (MENA) region is timely. Al-Rifai et al. have conducted a systematic review of 102 articles including 279,202 pregnant women from 16 countries in the MENA region: Algeria (1 included article), Bahrain (2), Egypt (4), Iraq (3), Iran (37), Jordan (4), Lebanon (2), Libya (1), Morocco (1), Oman (5), Qatar (6), Saudi Arabia (22), Sudan (3), Tunisia (1), United Arab Emirates (UAE) (9), and Yemen (1). This study reports a relatively high prevalence of GDM, ranging from 4.7% (95% CI, 3.0-6.7%; six studies) in Jordan to 20.7% (95% CI, 15.2-26.7%; 19 studies) in Qatar, giving an overall pooled weighted GDM prevalence in the MENA region of 13.0% (95% CI, 11.5-14.6%) in the period of 2000–2019. Pregnant women aged ≥30 years (adjusted OR 2.5, 95% CI, 1.5-4.2) and obese pregnant women (aOR 2.9, 95% CI, 1.5-5.7) were significant predictors of GDM. The wide variation in the prevalence rates in a number of published systematic reviews is due to the use of different GDM diagnostic criteria in the included studies. In another linked article, Guo et al. report data on 35,981 women (70% primigravidae); they show that a per-unit increase in the first trimester (9–14 weeks) fasting plasma glucose (FPG) levels was negatively associated with foetal growth parameters in mid pregnancy (18-24 weeks) but positively correlated with those in late pregnancy (28–34 weeks) and with birth characteristics (large-for-gestational age). The effect of first-trimester FPG levels on foetal weight (and preterm birth) was no longer of statistical significance after additional adjustment for pre-pregnancy BMI. However, this effect was present in mothers who were older (35 years), had a family history of diabetes, and had multiparity. Importantly, the study showed in the sensitivity analyses that the negative relationship between maternal FPG and foetal growth in mid pregnancy and the positive relationship in late pregnancy were essentially similar in pregnant women without GDM, and in pregnancy without common medical problems gestational hypertension, preeclampsia, placenta previa, placental abruption and cholestasis of pregnancy. Another study from China by Huang et al. suggests that T1D could be more related to preterm birth (<37 weeks) and less to birth weight, except for Chinese girls with a high birth weight (OR 3.2, 95% CI 1.3-7.5).

Efficient diabetes screening for women with a history of GDM can be hindered by inappropriate self-perceived future risk of T2D as well as many other personal, socioeconomic, and healthcare system-level barriers. These factors reported by Sunny et al. from Singapore (from both women who did and did not take up screening) are not unexpected to many, but it is remarkable how unconcerned many potential social supporters of these women and inaccessible healthcare services can be when it comes to postpartum diabetes screening for these high-risk women. There are very similar personal and psychosocial barriers to self-care among adults with T2D in Lahore, Pakistan (Bukhsh et al.). From the perspectives of human health behaviours, this shows the complexity and interplay of the (intrinsic) psychological (value system, emotion, and cognition) and the (extrinsic) sociological and environmental factors that we see in people living with DM. The intrinsic factors (knowledge, skills, and motivation) are believed to be the key strengths most worthwhile for the implementation of interventions to lower the risk of DM (6). This intrinsic and personal quality is possibly enhanced when extrinsic factors are facilitated, such as having an engaged family and members of your social circle, a healthy diet and good food quality, conducive places for activity, and the experience of readily available drugs and affordable healthcare. In terms of diabetes care specific to cardiovascular risk assessment and screening for diabetes-related complications, de Jong et al. show in their systematic review that men may be less likely to receive retinopathy screenings and women less likely to receive foot exams. This gender disparity in terms of the uptake of routine screening services is likely to be more obvious in lower economic countries, and this poses another challenge to efficient diabetes care that will require creative solutions based on a good understanding of the local context of the people, informed healthcare workers, and genuine involvement from policymakers and pertinent stakeholders.

Finally, Wang et al., Euh et al., and Chi et al. provide further interesting evidence on the clinical sciences of sarcopenic obesity, the effect of sodium-glucose cotransporter-2 inhibitors on weight and the liver, and the potential roles of non-coding RNAs (ncRNAs) in precision medicine of people with DM, respectively. Sarcopenia and obesity in diabetes and ncRNAs are emerging topics that may be worth further attention from researchers that study DM in the quest for a more efficient and effective diabetes care strategy. By bringing all these studies together in this special Research Topic, we hope the linked findings will help to develop and implement healthcare and policy strategies to reduce disparities that occur due to the wider determinants of health.

AUTHOR CONTRIBUTIONS

BC drafted the editorial. KK commented and contributed critically, RV and IW commented and further improved the editorial. All agreed to the version to be submitted.

FUNDING

KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC).

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Conflict of Interest: KK has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG/Menarini Group, Janssen, and Napp.

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

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frontiers in Endocrinology

REVIEW
published: 25 August 2020
doi: 10.3389/fendo.2020.00568

Diabetes and Sarcopenic Obesity: Pathogenesis, Diagnosis, and Treatments

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Sarcopenic obesity and diabetes are two increasing health problems worldwide, which both share many common risk factors, such as aging, and general obesity. The pathogenesis of sarcopenic obesity includes aging, physical inactivity, malnutrition, low-grade inflammation, insulin resistance, and hormonal changes. Nevertheless, there are two major reasons to cause diabetes: impaired insulin secretion and impaired insulin action. Furthermore, the individual diagnosis of obesity and sarcopenia should be combined to adequately define sarcopenic obesity. Also, the diagnosis of diabetes includes fasting plasma glucose test (FPG), 2-h oral glucose tolerance test (OGTT), glycated hemoglobin (A1C), and random plasma glucose coupled with symptoms. Healthy diet and physical activity are beneficial to both sarcopenic obesity and diabetes, but there are only recommended drugs for diabetes. This review consolidates and discusses the latest research in pathogenesis, diagnosis, and treatments of diabetes and sarcopenic obesity.

Keywords: diabetes, sarcopenic obesity, insulin resistance, aging, inflammation

OPEN ACCESS

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

Received: *18 April 2020*
Accepted: *13 July 2020*
Published: *25 August 2020*

Citation:
Wang M, Tan Y, Shi Y, Wang X, Liao Z and Wei P (2020) Diabetes and Sarcopenic Obesity: Pathogenesis, Diagnosis, and Treatments. Front. Endocrinol. 11:568. doi: 10.3389/fendo.2020.00568

INTRODUCTION

There are two greatest epidemiological trends of world—aging and obesity with the extension of average lifetime span and the changing lifestyle. The two factors dramatically affect body composition, morbidity and mortality (1). Aging is associated with the decrease in muscle mass and strength and the increase in body fat mass, which leads to frailty, falls, disability, social isolation, and hospitalization. The word sarcopenia from Greek refers to age-related loss of muscle mass. Although the impact of sarcopenia has been well-demonstrated, the effect of obesity on it emerges as a new public health problem (2). Therefore, a new term sarcopenic obesity (SO) arises to represent the coexistence of sarcopenia and obesity (3). Compared to simple sarcopenia or obesity alone, the medical sequelae related to SO are much greater, causing significantly higher healthcare costs (4). Data from Health and Nutrition Examination Survey (NHANES) noted SO rates of 12.6% in men and 33.5% in women (5). With the rapid growth of the elderly population globally, it was estimated that SO would affect 100–200 million people from 2016 to 2051 (6). Although SO is more common in older people due to the natural changes in body composition, it is estimated that younger people with class II or III obesity are vulnerable as well. A study assessed the prevalence of

SO in 120 young adults using different diagnostic criteria of SO, revealing that 23.3% female and 58.8% male suffered SO according to the definition of appendicular skeletal muscle mass (ASM) by weight × 100 % (7). Due to the chronic progress of SO, the symptoms hardly draw people's attention, resulting in poor diagnosis, which causes negative consequences of quality of life and all-cause mortality (8).

Moreover, aging and obesity are two risk factors of diabetes as well. A variety of studies have the consensus that aging as well as obesity have positive associations with diabetes. A study in America has suggested that the percentage of diabetics rises with age (9). Furthermore, a study has estimated that the number of global diabetic patients would increase from 422 million in 2014 to at least 592 million in 2,035 and it has been shown that more than 50% of the diabetics are obese (10). Hence, there is a good reason to suspect that diabetes and SO have a strong relationship (11). On the one hand, insulin loses the function to enhance cellular glucose uptake and utilization in diabetics, which is defined clinically as insulin resistance which promotes obesity. Furthermore, the increasing fat mass facilitates various cytokines which accelerate the catabolism of muscles. On the other hand, the loss of muscle mass leads to less insulin-responsive target tissue, resulting in a severe condition of insulin resistance (12, 13). Therefore, the vicious cycle continues until more negative health consequences occur (**Figure 1**). Hence, it is necessary to deduce the pathogenesis, diagnosis and treatments of both diabetes and SO in order to stop the vicious cycle and increase the quality of life. This review consolidates and discusses the latest research in pathogenesis, diagnosis and treatments of diabetes, and sarcopenic obesity.

PATHOGENESIS AND COMPLICATIONS OF SARCOPENIC OBESITY

Pathogenesis of Sarcopenic Obesity

There are multiple factors that cause sarcopenic obesity, such as aging, lack of physical activity, malnutrition low-grade inflammation, insulin resistance and hormonal changes, which leads to body composition changes (muscle mass and strength decline and fat mass increase). Moreover, each factor has independent impacts on the quality and quantity of muscle and fat, whereas, the cross-talks of them have stronger influences.

Aging

With aging, the reduction of basal metabolic rates may lead to weight gain and muscle mass decrease, which are associated with SO. Indeed, young people generally have more bone mass and muscle strength than old people. Meanwhile, studies have validated that the amount of bone mass and muscle mass peak around 30 years old, and after that, a gradual loss of muscle mass is accompanied with a parallel gain of fat mass (14). Therefore, weight generally increases in elderly people. However, it is also common that SO occurs in the old without increase of body weight, which could be due to the ectopic redistribution of fat. Studies have found that fat tends to move to viscera, muscle and abdomen with age, and the ectopic fat cause disorders of inflammatory factors, insulin and hormones, thus resulting in SO (15).

Lack of Physical Activity

Age-related SO is usually due to the lack of physical activity. In fact, old people tend to decrease physical activity, which contributes to the severe loss of muscle strength. Then atrophic muscles make even more difficult for elderly people to exercise, further aggravating the sedentary lifestyle. Numerous studies have proven that physical activity is necessary to lose weight and improve muscle strength, which is beneficial to ameliorate the state of SO (16, 17).

Imbalanced Nutrition

The imbalance of energy intake and expenditure is also linked to SO, especially for the old. On one hand, old people obtain inadequate protein in their diet. It is difficult to sustain muscle mass and strength with insufficient amount of protein intake (18). On the other hand, owing to decrease of outdoor physical activities, vitamin D produces less with scanty expose of ultraviolet radiation (19). Hence, inadequate vitamin D accelerates SO (20).

Low-Grade Inflammation

Both aging and physical inactivity have contributions on weight gain, by which an increase in adipose cell size may be determined. Specifically, adipocytes promote macrophage recruitment (21), then adipocytes and immune cells secrete more adipokines such as leptin, chemerin, resistin, and more cytokines such as tumor necrosis factor-α (TNF-α), interleukins (ILs), interferon-γ (INF-γ) (22–25), creating a circumstance of low-grade inflammation. Previous studies have indicated that an inflammatory state plays a significant role in the progression of SO as well as the morbidity and mortality driven by SO. A study conducted in Italy has verified that elevated levels of IL-6 and C-reactive protein (CRP) are related to SO, which in turn have suppressive effects on muscle strength (26). Moreover, a similar result has been shown in another cross-sectional study. The study has found the highest level of monocyte chemoattractant protein-1 (MCP-1) and the lowest level of appendicular lean mass in SO group (27), which supports the theory that low-grade inflammation is linked to SO.

Besides, the increased level of leptin contributes to leptin resistance, resulting in accumulation of free fatty acids. As less amount of fatty acid are oxidized in muscles, more fat mass deposits in visceral such as liver, heart, and spleen. Thereby, dysfunctional insulin production occurs, gradually leading to insulin resistance (28). Furthermore, the reduction of fatty acid consumption is coupled with the increase of reactive oxygen species generation. Oxidative stress is strongly associated with the expression of various inflammatory transcription factors, such as nuclear factor-kB (NF- kB) that modulates proteolytic pathways and promotes inflammation (29–31). Moreover, either low-grade inflammation or ectopic fat distribution generates myokine imbalance and mitochondrial dysfunction (32, 33). Particularly, myokines can exacerbate insulin resistance. Also, mitochondrial dysfunction causes more lipid peroxidation, which reinforces the collections of lipid intermediates and reactive oxygen

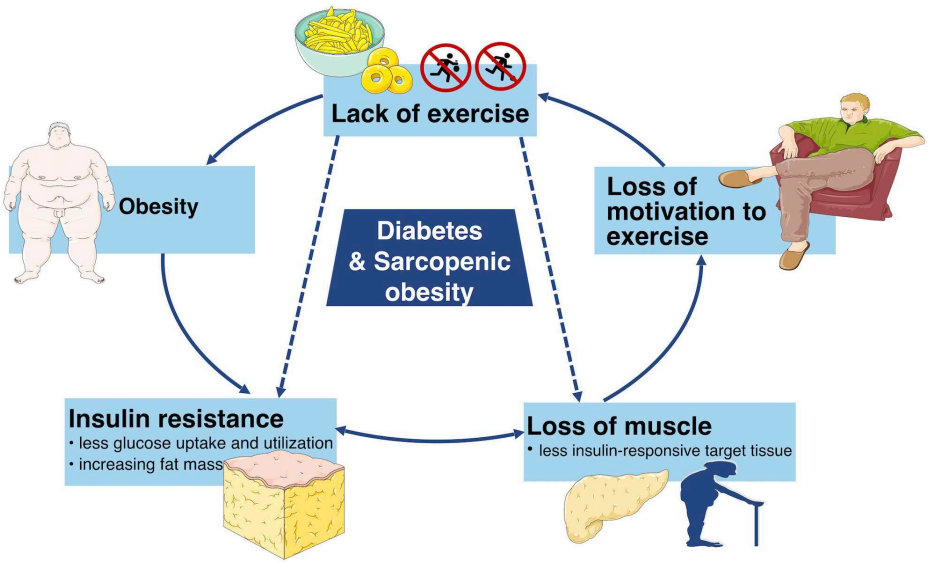

FIGURE 1 | This simplified schematic diagram depicts the vicious cycle of unhealthy lifestyle which can eventually lead to diabetes and sarcopenic obesity as well as other adverse metabolic conditions.

metabolites, accelerating inflammation, insulin resistance, and oxidative stress (33). Hence, another vicious circle leading to SO forms.

Insulin Resistance

The production and efficiency of insulin decline in elderly and obese people. Meanwhile, obesity is related to a low-grade inflammation, the increased production and secretion of multifarious inflammatory factors including TNF-α, IL-6 modulate insulin sensitivity by altering some key steps in the insulin signaling pathway, which is responsible for the subsequent insulin resistance (34–36). Studies have elucidated that insulin resistance is essential for protein anabolism, thus directly concerns muscle fiber atrophy (37). Obese individuals with insulin resistance have a higher rate of muscle catabolism, which has been evidenced in a study that leg muscle strength and quality decrease distinctly in older diabetics (38). Therefore, insulin resistance is involved in poor muscle mass and muscle strength, progressively resulting in SO. Furthermore, insulin resistance is correlated to mitochondrial dysfunction as well. A down-regulation of genes involving mitochondrial enzymes declines mitochondrial content, which has been found in insulin resistant states (39, 40), augmenting accumulation of fat in muscle and liver. Hence, the loss of muscle strength and the gain of fat which characterize SO is attributed by insulin resistance (41).

Hormonal Changes

As an endocrine organ, the muscle can produce a variety of myokines such as myostatin and irisin. It is believed that myostatin inhibits muscle cell growth and differentiation, and irisin stimulates the increase of muscle mass (42, 43). However, several studies have documented that the content of myostatin is upregulated while irisin is downregulated in sarcopenia (44). At the same time, the increase in myostatin and decrease in irisin are tightly associated with poor browning reaction of white fat, reducing energy expenditure, triggering fat gain (45). Eventually, the crosstalk between muscle and fat leads to muscle damage, eliciting SO.

Other hormones, including insulin-like growth factors-1 (IGF-1), growth hormone, testosterone, and estrogen, also regulate the anabolic and catabolic progressions in muscle (46, 47). The reduction of IGF-1 is accompanied by the downregulation of irisin (45), and high level of free fatty acids in obese people inhibits both IGF-1 and growth hormone (48), which lowers the mass and strength of muscle, leading to muscle impairment and thus to SO (49). Moreover, testosterone and estrogen are essential for muscle health (47), but the production of these hormones decline naturally with aging. Hence, the muscle mass and strength weaken with the reduced testosterone and estrogen concentrations (50). Therefore, aberrant hormonal changes with age exacerbate SO.

Complications of Sarcopenic Obesity

It is acknowledged that either low muscle mass and strength or obesity is an independent risk factor for reduced physical capacity and quality of life. Therefore, it is reasonable to speculate when muscle damage and obesity coexist, they act synergistically on the risk of mortality, metabolic disorders, and quality of life (47, 51). Firstly, SO is overtly associated with an increased risk of all-cause mortality. A meta-analysis of 12 prospective cohort studies has indicated that compare to non-SO participants, subjects with SO have a 24% increased risk of all-cause mortality, especially in men. Noteworthily, according to different definition of SO, the risk of all-cause mortality changes. Specifically, all-cause mortality is higher basing on the

criteria of mid-arm muscle circumference or muscle strength (HR 1.46, 95% CI 1.23–1.73 and 1.23, 1.09–1.38, respectively) rather than on the definition of skeletal muscle mass (pooled HR 1.24, 95% CI 1.12–1.37, $P < 0.001$) (52). Moreover, in a Japanese study, all-cause mortality increases in men with SO defined by waist circumference (HR, 1.19; 95% CI, 1.02–1.38), but not body mass index (BMI) or percent body fat (BF%) (53). Secondly, metabolic disorders including cardiometabolic syndrome (CMS), diabetes, cardiovascular disease (CVD), and cancer are common comorbidities of SO (54, 55). Several Korean studies have indicated that individuals with SO are associated with increased waist circumference, elevated fasting blood glucose, insulin resistance, higher blood pressure, and abnormal blood lipids as compared to sarcopenia or obesity alone (13, 23, 56). The cluster of abdominal obesity, hyperglycemia, hyperinsulinemia, dyslipidemia, and hypertension that composes CMS progressively leads to diabetes and CVD. A meta-analysis including 606 articles has demonstrated that SO increases the risk of T2D by almost 38% compared to individuals with excess weight or obesity alone (11). Furthermore, the characteristic may attribute to physical disability and metabolic syndromes, which has been clarified in another Korean study (57). In addition, studies have also estimated 10-years risk of CVD in SO group, non-sarcopenic group, and non-obese group, and a significant increase has been found in the SO group (58). Moreover, adverse clinical cancer outcomes reported to be relevant to SO, especially with respect to dose-limiting toxicity, surgical complications, physical disability, and shorter survival (59–61). Finally, even if there is no discrepancies between SO group and other groups of physical capacity found in a study (62), most studies support that SO causes physical disability. As the loss of muscle mass and strength makes a higher risk of osteoarthritis (63, 64), this exacerbates physical inactivity, worsening both physical and mental health. A cross-sectional study has evaluated the association between SO and cognitive function in geriatric population, and found that SO is an indicator of probable cognitive impairment (65). Therefore, these factors, which significantly affect the quality of life for elderly people, have been illustrated in another study that the highest fall risk and the lowest muscle function test results in the SO group, confirming an inverse association with health-related quality of life scores (66).

PATHOGENESIS AND COMPLICATIONS OF DIABETES

Pathogenesis of Diabetes

Diabetes mellitus is a chronic metabolic disease involving persistently elevated levels of blood glucose. Diabetes can be classified into several types: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes, maturity-onset diabetes of the youth, neonatal diabetes, and secondary diabetes resulting from endocrinopathies, steroid use. The major subtypes of diabetes are T1D and T2D (67, 68). In 1889, scientists first discovered the role of the pancreas in the pathogenesis of diabetes. There are two main subtypes of endocrine cells in the pancreatic islets: β cells and α cells. β cells are involved in the production insulin, while α cells are responsible for secreting glucagon. The function of β cells and α cells changes with the glucose environment in an individual's body (69, 70). Once the imbalance between the secretion of insulin and glucagon occurs, the levels of blood glucose skew improperly as well. In the case of diabetes, it may be linked to impaired insulin secretion (insulin deficiency), impaired insulin action (insulin resistance), or both (71).

Impaired Insulin Secretion

Impaired insulin secretion is multifactorial, the exact mechanism is still unclear, but commonly develops from glucose toxicity, lipid toxicity, immunoinflammatory response, and oxidative stress, leading to the dysfunction of islet β cells (72). Persistent elevated levels of glucose can swamp the glycolytic process and inhibit glyceraldehyde catabolism, which promotes reactive oxygen species (ROS) production and oxidative damage, inducing β cells apoptosis and inhibiting β cells secretion (73, 74).

The accumulation of free fatty acids in the islet β cells accelerates the production of NO, which causes the apoptosis of β cells. Furthermore, long chain saturated fatty acids can inhibit the expression of adenine nucleotide translocator. Thus, the inner mitochondrial membrane of islet β cells fails to protect, which increases the permeability of mitochondrial membrane, leading to β cells apoptosis (75, 76).

In fact, the chronic activation of the innate immune system, leading to intra-islet inflammation also seems to be the key part of β cells apoptosis (77). Both obesity and hyperglycemia promote the release of inflammatory mediators, like TNF-α, or IL-6, released mediators stimulate macrophages and other innate immune cells, as well as some apoptosis-related signaling pathways, such as Fas/FasL signaling pathway (78, 79). This leads to the destruction and dysfunction of certain cells, like islet β cells that produce insulin. Besides, chronic inflammatory environment is also beneficial for the formation of free radicals such as reactive oxygen species (ROS), exacerbating β cells damage and yielding a positive feedback circle with the secretion of more detrimental cytokines to trigger further damage to β cells (80).

As mentioned above, prolonged as well as elevated levels of glucose blood, high free fatty acids, and chronic inflammatory environment, all increase the levels of ROS, activating the mechanism of oxidative stress (81). Furthermore, the islet β cells are especially sensitive to ROS because of their low inherent level of antioxidant enzymes. Therefore, ROS is capable to directly damage β cells, promoting apoptosis, or it can indirectly regulate insulin signaling pathway to inhibit the function of β cells (82, 83). Moreover, chronically excessive levels of ROS can cause the loss of transcription factors PDX-1 and MsfA, disturbing the expression of insulin gene (84). With the destruction of β cells, the peak of insulin secretion will be delayed, intensifying the fluctuation of blood glucose, resulting in further severe damage of β cells (85). The general mechanism of how glucose toxicity, lipid toxicity, immunoinflammatory response, as well as oxidative stress cause β cell damage, leading to impaired insulin secretion is illustrated in **Figure 2**.

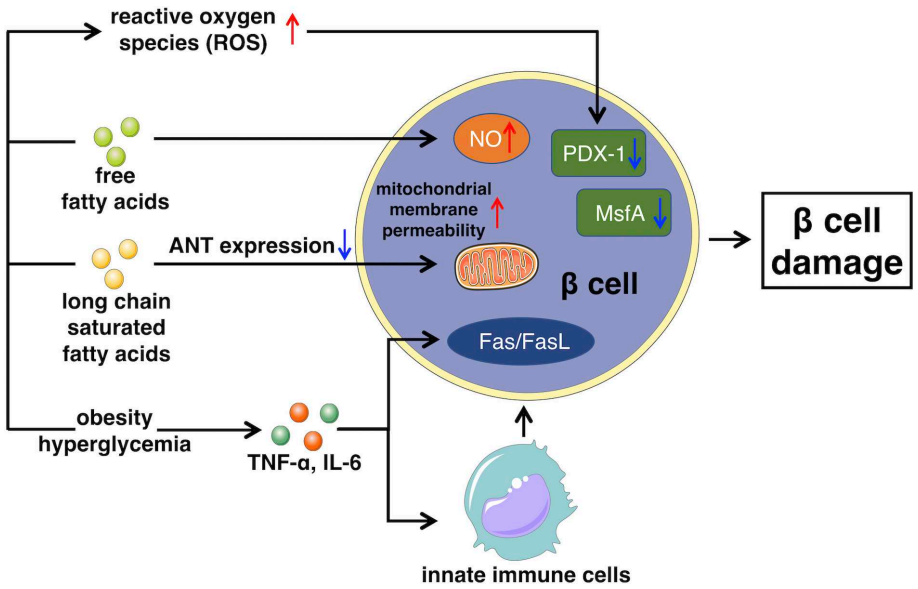

FIGURE 2 | This figure illustrates the main mechanism of impaired insulin secretion that glucose toxicity, lipid toxicity, immunoinflammatory response, and oxidative stress lead to β cell damage. ANT, Adenine nucleotide translocator.

Impaired Insulin Action

Impaired insulin action refers to the reduction of glucose uptake and utilization. In order to sustain a stable levels of blood glucose, islet β cells secret excessive insulin to compensate, leading to hyperinsulinemia (86). Increased insulin content results in less affinity of insulin receptor (IR) thus, cells (major muscle) gradually become insensitive to insulin. IR is a member of the ligand-activated receptor and tyrosine kinase family of transmembrane signaling proteins composed of two α- subunits and two β-subunits linked by disulfide bonds (87). The main function of the two α- subunits is to bind to insulin as they are located at the extracellular surface. While the two β-subunits are distributed at extracellular, transmembrane, and intracellular sites, which regulate insulin- stimulated tyrosine kinase activity. After the α- subunits bind to insulin, insulin receptor tyrosine kinase is activated by phosphorylating of the β-subunits on multiple tyrosine residues. The main physiological role of insulin receptor tyrosine kinase appears to be metabolic regulation. Therefore, any impairments occur on main phosphorylation sites will reduce insulin receptor tyrosine kinase activity, eventually affecting the insulin function (88–90).

Furthermore, there are multiple factors, particular obesity, increase the levels of adipocytes, inflammatory cytokines (IL-1, IL-6, and TNFα) (91). The elevated amount of these components stimulates several signaling pathways such as inhibitor kappa beta kinase beta (IKKβ), Jun N-terminal kinase (JNK), and NF-κB signaling pathways to induce the development of insulin resistance (92, 93). Meanwhile, the transduction of the insulin PI3K/AKT signaling pathway is weakened, which may be the major manifestation of insulin resistance, impacting the downstream mediator—glycogen synthase kinase-3β (GSK3β). GSK3β is one of the few protein kinases of which the activity can be inhibited by phosphorylation (94).

Insulin signaling pathway begins with the binding to its cell surface IR, which has a tyrosine- protein kinase activity, and regulates the insulin response (95). Then, the binding of insulin and its IR stimulates the association between the receptor and downstream mediators, such as insulin receptor substrate-1 (IRS-1) and phosphatidylinositol 3-kinase (PI3K). The insulin receptor can directly activate PI3K by binding to the p85 regulatory subunit, leading to the production of phosphatidylinositol-3,4,5-triphosphate (PIP3). Moreover, the indirect PI3K activation is associated with phosphorylation and activation of AKT, also known as protein kinase B (PKB). Afterwards, AKT inhibits GSK3β by phosphorylating at Ser9 site. When the insulin signaling pathway fails, the expression of GSK3β improves, which reduces the insulin sensitivity and increases the levels of blood glucose, thus subsequently leading to T2D (72, 96, 97). The general mechanism of how excessive insulin secretion, adipocytes, and inflammatory factors directly affect IR or indirectly interfere the insulin signaling pathway, leading to impaired insulin action is illustrated in **Figure 3**.

Complications of Diabetes

Unmanaged diabetes can cause multiple complications, most common of which are microvascular complications: nephropathy, retinopathy, and neuropathy, and macrovascular complications: cardiovascular diseases.

Renal Disease

Diabetic kidney disease is defined as persistent albuminuria, accompanied with a persistent reduction of glomerular filtration rate and an increase of arterial blood pressure, which can progress to end-stage renal disease (ESRD) (98). The prevalence of diabetic kidney disease in patients with T1D and T2D is 30 and 40%, respectively (99). A study has found that the risk of

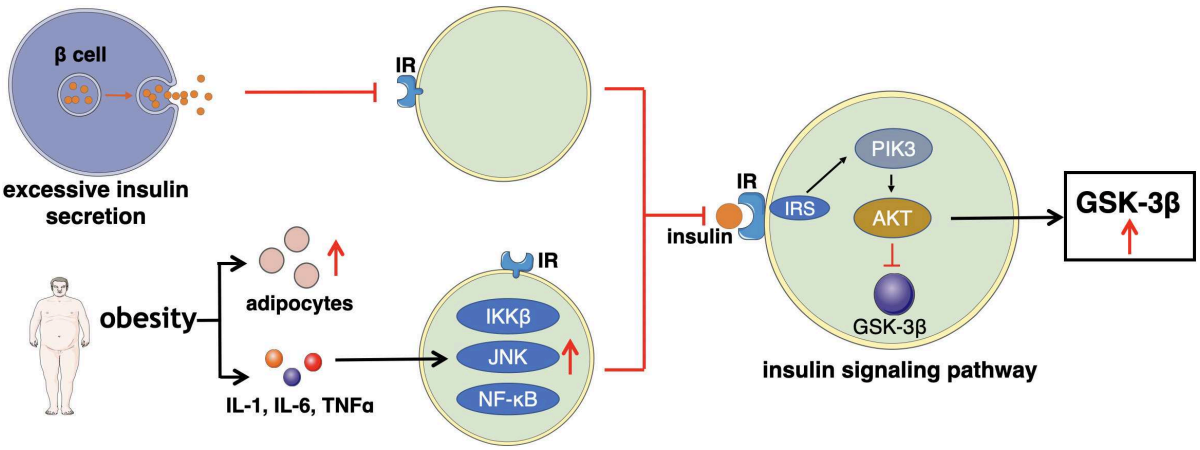

FIGURE 3 | This figure illustrates the main mechanism of impaired insulin action that excessive insulin secretion, adipocytes, and inflammatory factors directly affect IR or indirectly interfere the insulin signaling pathway.

diabetic kidney disease is much higher in Asian countries than in Western countries due to different economic outcomes (100). Furthermore, the incidence of ESRD has been estimated to be about 40%-50% in the United States (101). In fact, more than 50% of the patients in America with T1D will eventually receive renal replacement treatments (98). Besides, the prevalence of ESRD is even higher than 60% in Malaysia, Singapore, and Mexico, which may relate to genetic background, lifestyle, health awareness and economic situation (101).

Ocular Disease

There are many diabetes-related ocular diseases, such as cataract, glaucoma, ischemic optic neuropathy, cranial nerve palsies, and recurrent corneal erosion syndrome (102). However, diabetic retinopathy is the most well-known complication, and it is expected to increase from 415 million in 2015 to 642 million by 2040 (103). Moreover, World Health Organization (WHO) has estimated that diabetic retinopathy leads to blindness in 5% of blind people (104). One of the structural changes in diabetic retinopathy is widened retinal arteriolar caliber which might be an early sign of microvascular dysfunction. Also, another change is widened retinal venular caliber which might be independently related to the prevalence and progression in diabetic retinopathy, as well as an indicator of developing retinopathy (105, 106).

Diabetic Neuropathy

Diabetic neuropathy is one of the most prominent complications of diabetes. The true prevalence is unclear but it varies from 10 to 90% in diabetics, according to the different standards and approaches used to define diabetic neuropathy (107). Diabetic neuropathy involves various syndromes, such as mono- and polyneuropathies, plexopathies, radiculopathies and autonomic neuropathy, among which distal symmetric polyneuropathy is very prevalent (108). Meanwhile, distal symmetric polyneuropathy mainly contributes to disability in diabetics, stemming from gait disturbance, fall-related injury, and foot ulceration and amputation (109). It has been reported that neuropathy is associated with a 1.7-fold increase in the risk of amputation, and even higher when coupled with other problems (107). In the UK, approximately one third amputees have a history of diabetes (110), and in Australia, about half of the amputees have diabetes (111). Therefore, diabetic neuropathy extremely influences the quality of life in diabetic people.

Cardiovascular Diseases

Cardiovascular diseases, involving coronary heart disease, peripheral vascular disease and cerebrovascular disease, are the primary contributors of death and disability in diabetic people (112). Individuals with diabetes suffer from a higher risk of cardiovascular diseases compared to those without diabetes, which is associated with a number of common risk factors such as age, obesity, smoking, hypertension, and dyslipidemia (113). Moreover, recent studies have shown that diabetes is considered as an independent risk factor for coronary heart diseases (114). Interestingly, a study has indicated that patients with T2D in Asian countries have a lower risk of coronary diseases than those from eastern Europe or Established Market Economies (100). However, Indian patients with T2D are as twice likely to develop coronary artery diseases as white Europeans who have T2D (115).

Cancer

Numerous epidemiological evidences have indicated that diabetes is considered as an independent risk factor for increased rates of various types of cancer. Cancer is a class of diseases resulted from external factors such as environment, diet and radiation as well as internal factors including obesity and diabetes (31, 116, 117). It has been proven that there is 1–2% of diabetic patients who will develop pancreatic cancer in 3 years (118). Also, diabetes serves as an independent risk factor for colorectal cancer as a study has found that there is a 49% increased risk of colorectal cancer in men with diabetes (119). Moreover, diabetes contributes a 27% increased risk of breast cancer in women and predisposes to more aggressive cancer stages (120). For endometrial cancer, the new-onset diabetics (<5 years) have a

two-fold risk compared with those with long-standing diabetes (≥5 years) (121). Besides, diabetic individuals with liver cancer and bladder cancer are associated with a poor survival compared with non-diabetic subjects (122).

Other Complications

Recent studies have regarded Alzheimer's disease as type 3 diabetes because of insulin signaling pathways damage (123). Moreover, sexual dysfunction becomes more and more popular in both men and women with diabetes (124). Besides, high prevalence of depression as one of psychological complications that result from diabetes, makes it harder for diabetics to manage blood glucose, thus leading to further complications (125).

DIAGNOSIS OF SARCOPENIC OBESITY AND DIABETES

Diagnosis of Sarcopenic Obesity

There is currently no consistent diagnosis of SO, nevertheless an adequate one should include the individual diagnosis of obesity and sarcopenia. According to the criteria of WHO, BMI $\geq$ 30 kg/m^2 or wrist circumference (men $\geq$ 102 cm and women $\geq$ 88 cm) is considered as obesity. However, whether these criteria are appropriate for each individual has been questioned. Alternatively, cutoffs of BF% (Body Fat Percentage) or other adiposity indices have been regarded as useful outcomes measure of obesity (126, 127).

European Working Group on Sarcopenia in Older People (EWGSOP) has proposed that (1) low muscle mass; (2) low muscle strength; (3) low physical performance are the three important parameters to define sarcopenia (128). Various techniques emerge for assessing muscle mass, among which, computed tomography (CT) and magnetic resonance imaging (MRI) are deemed as the gold standard to distinguish fat from other soft tissues, thereby, effectively estimating fat mass and muscle mass. However, it is hard to generalize CT and MRI due to the high cost, and the risk of radiation (for CT) (129). Therefore, another relatively inexpensive and low radiation method called dual-energy-X-ray absorptiometry (DXA) is recommended to estimate the lean and fat mass of the whole body or certain regions of body. Moreover, it also manifests strength in assessment of bone mass and density, thus simultaneously providing the conditions of bone, muscle, and fat (130, 131). In addition, as an affordable and available tool, bioelectrical impedance analysis (BIA) is used to measure muscle mass as well, whereas, the inaccuracy makes it unrecommended to diagnose sarcopenia (132). For it indirectly reflects body composition by evaluating the entire body and segmental reactance as well as resistance influenced by fluid retention and disease-related conditions. Hence, an overestimation is accompanied with a poor distinction between extracellular and intracellular fluid (133). Furthermore, air displacement plethysmography (ADP) measures body volume and body density and hence, total fat and lean tissue (134). In spite of the widespread use of anthropometric measurements, such as mid-upper arm circumference, calf circumference, and skin fold thickness, they are inaccurate (135). Muscle strength can be assessed by handgrip strength, knee flexion/extension, and peak expiratory flow. Handgrip strength is a great predictor of extremity muscle power and mobility. Furthermore, keen flexion/extension is strongly related with certain functional activities. Although peak expiratory flow manifests the strength of respiratory muscles, it is not considered as a separated method. Physical performance is defined by short physical performance battery (SPPB), usual gait speed, timed get-up-and-go test, and stair climb power test, which evaluate an individual's balance, gait, strength and endurance (136, 137).

In 1998, Baumarterner et al. (138) first defined sarcopenia as ASM divided by body height squared [ASM(kg)/height^2 (m^2)] two or more standard deviations below the mean of a young reference values measured by DXA. Later, Janssen et al. (139) proposed a definition of sarcopenia that the skeletal muscle mass index [skeletal muscle mass (kg)/weight (kg) $\times$ 100] is one or two standard deviations below the reference value of younger, healthy individuals measured by BIA. Then, Newman et al. (140) came up with a new criteria for sarcopenia according to appendiculate lean mass (ALM) adjusted for height and fat mass using residuals from linear regression models.

Based on the abovementioned assessments, the calculation of Baumarterner et al. with the addition of the BF% exceeds 60% of population of the peers is one definition of SO (141). Another definition includes that BF% exceeds 60% of population of the peers and muscle mass is inferior to 60% of population of the peers (142). However, the diagnosis of SO varies with the changes of the diagnosis of obesity and sarcopenia. After 2010, when the standard of sarcopenia was updated by EWGSOP, the diagnosis of SO should change too. The evaluation of muscle strength and physical function are supposed to be combined with the assessments mentioned above (4).

Diagnosis of Diabetes

According to American Diabetes Association (ADA), there are four approaches to diagnosis diabetes: Fasting plasma glucose test (FPG), Two-Hour Oral Glucose Tolerance Test (OGTT), Glycated Hemoglobin (A1C), and Random plasma glucose coupled with symptoms (67). **Table 1** summarizes these approaches as well as their respective diagnostic standards.

Fasting Plasma Glucose Test (FPG)

The test should be carried out after at least 8 h fast, the level of FPG more than 126 mg/dL (7.0 mm/L) is considered as diabetes (67).

Two-Hour Oral Glucose Tolerance Test (OGTT)

In this test, individuals should consume at least 150 g per day of carbohydrate for 3–5 days without taking any medications. Then, the test is carried out before and 2 h after consuming 75 g of glucose. The 2-h plasma glucose is more than 200 mg/dL (11.1 mmol/L) is consistent with the diagnosis. Although OGTT is a standard test, it is less convenient and affordable than FPG (67).

Glycated Hemoglobin (A1C)

A1C shows the average of blood glucose over last 2–3 months, and it is relative accurate since less influence by acute illness or

TABLE 1 | Four approaches to diagnose diabetes according to ADA.

Diagnostic tests	Diabetes diagnostic standards
FPG	>126 mg/dL (7.0 mm/L)
OGTT	>200 mg/dL (11.1 mmol/L)
A1C	>6.5% (48 mmol/mol)
Random plasma glucose coupled with symptoms	>200 mg/dL (11.1 mmol/L)

stress. Diabetes is diagnosed if the result of A1C is more than 6.5% (48 mmol/mol) (67).

Random Plasma Glucose Coupled With Symptoms

In patients with classic symptoms: polydipsia, polyphagia, and polyuria, random plasma glucose more than 200 mg/dL (11.1 mmol/L) is diagnosed as having diabetes (67).

TREATMENTS FOR SARCOPENIC OBESITY AND DIABETES

Conventional Treatments for Sarcopenic Obesity and Diabetes

The most common treatments of SO and diabetes are dietary intervention and physical activity. Although there are various approved and effective drugs for diabetes, there is currently no recommended pharmacological intervention for SO, not even for diabetics with SO.

Dietary Intervention for Sarcopenic Obesity

The main dietary interventions for SO consist of caloric restriction, protein intake, and micronutrient supplementation. It is noted that lack of proper randomized clinical trials (RCTs) makes expert opinions to be the major guidelines at present of dietary interventions for SO.

Caloric restriction aims to lose weight, inducing body composition changes, and a reasonable weight loss goal should be under 5–8% of the initial body weight (1, 143). As acute caloric restriction could promote proteolysis and negatively affect muscle protein synthesis, resulting in a further reduction of muscle mass, acute caloric restriction is not recommended. In contrast, chronic caloric restriction might increase muscle protein synthesis rather than downregulate (144, 145). Major RCTs in non-sarcopenic women with obesity have suggested that caloric restriction (500 kcal deficit) with at least 0.8 g/kg of protein intake can effectively lose fat and improve physical function (146, 147). Moreover, another study has demonstrated that even caloric restriction might cause loss of muscle mass, and hence, it is still more beneficial to mobility and strength when accompanying with resistance training (148).

Increased dietary protein can prevent weight loss-induced sarcopenia. According to existing evidence, a healthy young individual should take an average daily protein intake of 1 g/kg per day. While in older people, a higher protein intake should be provided in order to promote muscle protein synthesis due to anabolic resistance. Therefore, adequate protein intake of 1–1.2 g/kg per day is recommended for geriatrics, and an even higher intake for older people suffering from SO or other similar diseases. Acceptable protein intake of 1.2–1.5 g/kg per day should be provided for individuals with acute or chronic diseases, which are related to unbalanced body composition. Furthermore, individuals with critical illness or severe malnutrition need an increased protein intake from 2 g/kg per day (149–151). Moreover, oral protein supplements should be considered when ample dietary intake is not practical. A study assessed the effect of a diet moderately rich in proteins on lean mass in SO older women, and has indicated that sufficient protein intake is able to preserve muscle mass in older women with SO (18). A similar result has been shown in another study that high-protein diet improves muscle strength in SO patients and prevent weight loss-induced sarcopenia (152).

Despite that vitamin D supplement has not been properly tested in patients with SO, several studies have suggested that vitamin D deficiency is associated with lower muscle strength, greater body instability, falls and disability in geriatric population (153). Therefore, in order to minimize the adverse effects of weight loss, it may be necessary to increase vitamin D intake (154, 155). Besides, studies have elucidated that vitamin D has the capability of regulating bioactive metabolites, and thus, improving muscle function (156). A study has verified that 25-hydroxyvitamin D3 can indirectly impact muscle function as its free metabolite is more closely related to body fat than muscle gene expression (155).

Dietary Intervention for Diabetes

Dietary intervention plays an important role in the management of diabetes and diabetes-related complications. The intake of low glycemic food including cereal fiber or a mixture of whole grain and bran can decrease 18–40% of risk for diabetics (157). Moreover, the risk of diabetes reduces by 26% due to the consumption of one sugar-containing beverage more than 1 month compared to one per day (158). Furthermore, a systemic review of randomized clinical trials has assessed the effects of low carbohydrate, macrobiotic, vegan, vegetarian, Mediterranean, and intermittent fasting diets, compared to low-fat diets on diabetes control and management. However, there were no evident differences of low carbohydrate diets and low-fat diets in glycemic control, weight and lipids. The macrobiotic and vegan diets were beneficial to glycemic control, while the vegetarian diet demonstrated better weight loss and insulin sensitivity. Besides, the Mediterranean diet showed a greater regulation of A1C levels. Therefore, the study has concluded that vegan, vegetarian and Mediterranean diets are better strategies to control glycemic marker in diabetics (159). In addition, a study has also found that the benefits of Mediterranean diets were greater than low-fat diets in diabetic retinopathy, but no significant differences were found in diabetic nephropathy (160). Furthermore, dietary intervention is an important modifiable factor to reduce the incidence of cardiovascular diseases in diabetics (161). Hence, it may be necessary to implement dietary intervention in public health managements of diabetes.

Physical Activity for Sarcopenic Obesity

A combination of physical activity and dietary intervention is a more effective strategy to treat SO. Indeed, there are multiple biological effects of physical activity: promote insulin sensitivity, improve anabolic response to endogenous amino acids, activate skeletal muscle satellites cells and trigger the proliferation and differentiation of them, amplify irisin production, adjust hormonal milieu, increase mitochondrial biogenesis, ameliorate inflammation and reduce oxidative stress (162–164). Even though various studies have confirmed that exercise has positive effects for SO patients, many professional organizations recommend that a combination of resistance training and aerobic training seems to be the most practical way to improve physical performance (165, 166). For geriatric people, the main goal of physical training is to ameliorate elasticity, strength, and physical endurance. Meanwhile, as resistance training can improve flexibility, muscle strength, and muscle hypertrophy, aerobic training focuses on increasing physical endurance of older people (166). Therefore, two non-consecutive sessions of resistance training coupled with at least 150 min per week of aerobic training is recommended for all older individuals (167, 168). A meta-analysis involving 14 RCTs and a quasi-experimental trial has clarified that exercise, particularly resistance training plays a key part in improving body composition and physical performance in patients with SO (169). Also, an RCT, allocating 60 men and women to four groups (resistance training, aerobic training, combination training, and control), has found that the skeletal muscle mass, body fat mass, ASM/weight % and visceral fat area of treatment groups exhibited better results than control group. Noteworthy, the grip strength and knee extensor performance of resistance group were superior to those of the other groups (170). Furthermore, a clinical study evaluated the effects of resistance training, aerobic training, or combination training in obese older people. It has revealed that the physical performance test score was the highest in the combination group (21% increase) compared to the resistance group (14% increase) and aerobic group (14% increase). But strength increased more in the resistance group (19% increase) than in the combination group (18% increase) and aerobic group (4% increase). While peak oxygen consumption (milliliters per kilogram of body weight per minute) increased most in the aerobic group (18% increase) compared to the combination group (17% increase) and resistance group (8% increase). Thus, resistance training combined aerobic training is the most effective way to alleviated physical disability (171).

Physical Activity for Diabetes

Several studies have demonstrated that physical activity is an effective regimen to lower the risk of developing diabetes by improving the β-cell function (172). A randomized controlled trial has evaluated the effects of moderate to intense exercise on pancreatic fat content and β cell function. The amount of pancreatic fat decreased in both healthy group (from 4.4 to 3.6%) and prediabetes/T2D group (from 8.7 to 6.7%), without significant differences observed for the improvement of β-cell function in different exercise strategies (173). Another study also has confirmed that high-intensity interval training is strongly associated with the improvement of β-cell function in patients with T2D. The total body-fat percentage was reduced, whereas lean body mass was protected. Noteworthy, high-intensity interval training was not able to regulate the levels of fasting plasma glucose, insulin, C-peptide, pro- insulin, and free fatty acids, nor did the levels of first-phase (0–30 min) and late-phase (30–180 min) plasma glucose, insulin, C-peptide, and proinsulin (174). Furthermore, as mentioned previously that the combination of resistance and aerobic training is beneficial to SO, it is a highly effective strategy for diabetes as well. A randomized controlled trial conducted in America has examined the effects of resistance training alone, aerobic training alone, and a combination of both on A1C within diabetics. Compared to control group, there were no significant mean changes of A1C in either the resistance training alone group (−0.16%; 95% CI: −0.46–0.15%; $P = 0.32$) or the aerobic training alone group (-0.24%; 95% CI: −0.55–0.07%; $P = 0.14$), however, there was a significant absolute mean change of A1C in the combination training group. Moreover, the combination training group had a maximal progression of oxygen consumption compared to other groups. All three exercise groups decreased waist circumference by 1.9–2.8 cm as compared to the control group. Therefore, in spite of the benefits of resistance training alone and aerobic training alone on diabetics, the combination of both could improve the level of A1C, which could hardly be obtained by each training exercise alone (175).

Pharmacological Intervention for Sarcopenic Obesity and Diabetes

In spite of many novel pharmacological interventions are under investigation, such as testosterone supplement, selective androgen receptor modulators, and myostatin inhibitors, there is currently no approved drugs for SO (176–178). However, there are approved and effectively drugs for diabetes. Metformin is considered as one of the most prevalent medications for diabetes management (179). Based on existing evidence, the National Institute for Health and Care Excellence (NICE) guidance for adults with type 2 diabetes recommends standard-release metformin as the initial drug treatment (180). A considerable number of studies have also found that metformin decreases fasting plasma glucose (PG) concentration and hemoglobin A1c by conserving the β-cell function or by decreasing liver glucose production (hepatic gluconeogenesis) (181–184). Also, thiazolidinediones can promote insulin sensitivity, increase glucose metabolism, and preserve the β-cell function through activating PPAR-γ (185, 186). Meanwhile, they can reduce plasma free fatty acid and intramyocellular lipid content to increase insulin sensitivity and redistribute fats from visceral to subcutaneous adipose to alleviate diabetes. Pioglitazone and troglitazone, belonging to thiazolidinediones, have the effect of controlling the progression on gestational diabetes (187, 188). Besides, α-Glucosidase Inhibitors contribute for prolonging the overall carbohydrate digestion duration and reducing the rate of glucose absorption (189). Whereas, it should be noted that they do not increase insulin sensitization (190), and a systematic review disapproves of acarbose dosages higher than 50 mg (three times a day), as there is no better effects on glycated

hemoglobin (191). Therefore, α-Glucosidase Inhibitors should not be applied as initial drugs, and it is more positive to combine them with other types of anti-diabetic drugs. Moreover, incretins can shrink appetite, thus reduce food intake, leading to weight reduction (192). Because of the impact on weight reduction, incretins may find increasing use in diabesity, which is the coexistence of diabetes and obesity (193). In addition, Sodium-Glucose Cotransporter (SGLT) 2 Inhibitors are one of the latest pharmacological interventions to decrease the reabsorption of glucose in kidney and lower FGP and A1C, which enhances urinary glucose elimination and attenuates blood glucose level. Meanwhile, they can also positively affect cardiovascular diseases due to sodium decrease, uric acid absorption, and blood pressure reduction (194).

Complementary and Alternative Treatments for Sarcopenic Obesity and Diabetes

Herbal Medicine and Derivative

With the growing of popularity of herbal medicine, many studies have indicated that herbal medicine or related derivatives may be effective methods to treat SO and diabetes. A study has reported two cases about using wild ginseng complex (WGC) on two patients who only wanted to lose abdominal fat, but not in other parts of body. After 3 weeks of WGC intervention, the two patients had an increase in muscle mass, protein content, and basal metabolic rate. Therefore, WGC intervention may be a new alternative treatment for age-related sarcopenic obesity but more studies using larger samples are required to support this (195). In another study, three major herbal medicine including Zuo Gui Wan, red raspberry leaves, and Orthosiphon stamineus were found beneficial to gestational diabetes by controlling glucose (196). Hence, effective management of diabetics with SO using herbal medicine and derivatives may be plausible but more supportive evidences are still required.

Acupuncture

Acupuncture has been used in diabetes for a long time in Asian countries and recent studies have also suggested that acupuncture may alleviate SO (197–199). A randomized controlled trial, using electrical acupuncture coupled with essential amino acid supplementation to treat SO in male older people, has indicated that both electrical acupuncture with oral essential amino acids group and oral essential amino acids alone group can decrease BF% and increase ASM/H2, with the combination group being more effective than another group. Moreover, the combination group can increase muscle mass in a shorter time (197). Besides, a meta-analysis of randomized controlled trials has confirmed that acupuncture should be recommended as a complementary treatment in T2D control, particularly with obesity or other metabolic disorders (195). Although the underlying mechanism of acupuncture on diabetes remains unclear, studies have suggested that it may be related to adjust nerve conduction, modulate signal pathways, regulate hormonal level, and ameliorate oxidative stress level (200). Further investigations are required to prove that acupuncture is indeed effective for the treatment of patients with diabetes and SO.

DISCUSSION

The occurrence of SO and diabetes has a rapid growth worldwide because of lifestyle changes and longer life expectancy. Indeed, they share many common risk factors, especially in aging and obesity. Moreover, a study has found that in the case of similar BMI, diabetics have decreased lean body mass and increased body fat mass compared with non-diabetics (57), indicating that diabetes is associated with increased risk of SO. Although the underlying mechanism of the association remains unclear, we speculate a bidirectional interplay in obesity, low-grade inflammation, insulin resistance and sarcopenia. SO combines sarcopenia and obesity, and low-grade inflammation plays a crucial role in the pathogenesis of diabetes (11). Therefore, SO may have synergistic effect with low-grade inflammation to exacerbate insulin resistance, further impairing glucose metabolism. Noteworthily, physical activity is helpful for both SO and diabetes. However, it should be treated with caution due to the degeneration of muscle mass for SO and venerable feet for diabetes. The young individuals in good metabolic control are able to do most activities, but the middle-aged and older individuals or patients with other complications are encouraged to check with the doctor to avoid injuries of intensive exercise (201). Generally, for patients with SO and diabetes, an appropriate warm-up and cool-down period should be included before and after physical activity session. A short warm-up session at a low-intensity level helps skeletal muscles, heart, lungs prepare before formal exercise. After the physical activity session, a short cool-down session should be conducted similarly as the warm-up session to gradually bring the heart rate down. Proper stretches should be structured after warm-up and cool-down period to protect muscles. Moreover, suitable footwear should be emphasized to prevent blisters and keep the feet dry because it is easy to cause trauma of the feet for diabetics. Fluid intake affects blood glucose levels and heart function, thus, during physical activity, fluid should be taken early and regularly. Finally, the diabetics should never forget to test blood glucose regularly (202, 203).

Although pharmacological intervention has been widely used in treating diabetes, doctors and patients need to be cautious of the side effects of the drugs. Metformin has been reported to cause deficiency in vitamin 12 and folic acid. Thiazolidinediones can cause bladder cancer and fractures, and combined insulin-thiazolidinediones therapy may lead to heart failure. The common adverse reactions of SGLT2 inhibitors are urinary tract infections, increase in low-density lipoprotein (LDL) cholesterol, bone fractures, and they may sometimes cause ketoacidosis. Therefore, pharmacological intervention needs to be monitored, especially in elderly patients and patients with other complications (204). Additionally, there are some limitations in the complementary and alternative treatments. Although several studies have revealed some positive results, the overall quality of the evidence is low, and the

available data are too few to adequately suggest that herbal medicine and derivative and acupuncture are useful. Thus, more large-scale, multicenter, high-quality RCTs are required in the future, which will lead to deeper understandings of complementary and alternative treatments for SO and diabetes. Furthermore, it is important to raise the awareness of the high prevalence of the sarcopenia in the obese population, which seems to be strongly associated with diabetes, and screening for SO in subjects with obesity during clinical practice may be necessary. Therapies for SO and diabetes should be treated carefully and personally in order to minimize adverse effects.

CONCLUSION

By analyzing research evidence from previous studies, this review identified possible pathogenesis of SO and diabetes, such as malnutrition, insulin resistance, low-grade inflammation, and hormonal changes. Meanwhile, the underlying mechanisms of insulin deficiency and insulin resistance have been discussed to provide a better understanding of the association between SO and diabetes. Also, complications of SO and diabetes have been explored to urge more attention on SO and diabetes. Additionally, we have consolidated the novel diagnostic methods of SO and diabetes. Furthermore, different treatment options have been exhibited that dietary intervention and physical activity are considered as prevalently effective treatments for diabetics with SO, and some complementary and alternative interventions have shown some positive effects on SO and diabetes. As a final suggestion for the prevention and treatment of diabetes and SO, we recommend dietary intervention and regular exercises, coupled with specific drugs prescribed to individuals by the clinicians.

AUTHOR CONTRIBUTIONS

ZL: conceptualization. YT and PW: resources. MW: writing—original draft preparation. YS: figure preparation. ZL, YT, XW, and PW: writing—review and editing. ZL and PW: supervision. PW: project administration. YT and PW: funding acquisition. All authors have read and agreed to the published version of the manuscript.

FUNDING

This work was funded by the "Double First-Class" Construction Funds of Discipline of Integrated Traditional Chinese and Western Medicine of Beijing University of Chinese Medicine.

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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.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 28 August 2020
doi: 10.3389/fendo.2020.00602

Facilitators and Barriers to Post-partum Diabetes Screening Among Mothers With a History of Gestational Diabetes Mellitus–A Qualitative Study From Singapore

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OPEN ACCESS

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

Received: 15 May 2020
Accepted: 23 July 2020
Published: 28 August 2020

Citation:
Sunny SH, Malhotra R, Ang SB, Lim CSD, Tan YSA, Soh YMB, Ho XYC, Gostelow M, Tsang LPM, Lock SHS, Kwek SY, Lim YTJ, Vijakumar K and Tan NC (2020) Facilitators and Barriers to Post-partum Diabetes Screening Among Mothers With a History of Gestational Diabetes Mellitus–A Qualitative Study From Singapore. Front. Endocrinol. 11:602. doi: 10.3389/fendo.2020.00602

Introduction: Gestational Diabetes Mellitus (GDM) affects one in six births worldwide. Mothers with GDM have an increased risk of developing post-partum Type-2 Diabetes Mellitus (T2DM). However, their uptake of post-partum diabetes screening is suboptimal, including those in Singapore. Literature reports that the patient-doctor relationship, mothers' concerns about diabetes, and family-related practicalities are key factors influencing the uptake of such screening. However, we postulate additional factors related to local society, healthcare system, and policies in influencing post-partum diabetes screening among mothers with GDM.

Aim: The qualitative research study aimed to explore the facilitators and barriers to post-partum diabetes screening among mothers with GDM in an Asian community.

Methods: In-depth interviews were carried out on mothers with GDM at a public primary care clinic in Singapore. Mothers were recruited from those who brought their child for vaccination appointments and their informed consent was obtained. Both mothers who completed post-partum diabetes screening within 12 weeks after childbirth and those who did not were purposively recruited. The social ecological model (SEM) provides the theoretical framework to identify facilitators and barriers at the individual, interpersonal, organizational, and policy levels.

Results: Twenty multi-ethnic Asian mothers with GDM were interviewed. At the individual and interpersonal level, self-perceived risk of developing T2DM, understanding the need for screening and the benefits of early diagnosis, availability of confinement nanny in Chinese family, alternate caregivers, emotional, and peer support facilitated post-partum diabetes screening. Barriers included fear of the diagnosis and its consequences, preference for personal attention and care to child, failure to find trusted caregiver, competing priorities, and unpleasant experiences with the oral glucose tolerance test. At the organizational and public policy level, bundling of scheduled

appointments, and standardization of procedure eased screening but uptake was hindered by inconvenient testing locations, variable post-partum care practices and advice in the recommendations for diabetes screening.

Conclusion: Based on the SEM, facilitators and barriers towards post-partum diabetes screening exist at multiple levels, with some contextualized to local factors. Interventions to improve its uptake should be multi-pronged, targeting not only at personal but also familial, health system, and policy factors to ensure higher level of success.

Keywords: gestational diabetes mellitus, post-partum diabetes screening, facilitators, barriers, socio-ecological model

INTRODUCTION

According to the International Diabetes Federation, up to 20.4 million live births in 2019 were complicated by hyperglycaemia (1). Gestational Diabetes Mellitus (GDM), defined as any extent of hyperglycaemia first identified during pregnancy (2), particularly affects the South-East Asian region which has the highest prevalence of GDM in the world (3). The prevalence of GDM in Singapore, at the centre of South-East Asia, is estimated to be 18.9% (4). This is of concern as mothers with GDM are not only more likely to have hyperglycaemia in subsequent pregnancies (5) but also have a 7-fold increased risk of developing Type 2 Diabetes Mellitus (T2DM) (6). A systematic review and meta-analysis found that this risk was the highest within 3 to 6 years after the affected pregnancy (7), thus necessitating timely and appropriate screening regimens to mitigate the risk.

For early identification and management of T2DM, international and local guidelines recommend that mothers with GDM undergo screening for persistent dysglycemia at 6 to 12 weeks post-partum, with the recommended 75 g 2-h oral glucose tolerance test (OGTT) (8, 9). Whilst up to 18.2% of mothers screened are diagnosed with dysglycemia (10), the uptake of post-partum diabetes screening within the recommended window is suboptimal and varies widely across populations. A study conducted in England identified the uptake rate to be 17% (11), as compared to 81.9% in a Malaysian hospital (12). Unpublished data from a tertiary care institution in Singapore shows that just over half (54%) of mothers with GDM underwent post-partum diabetes screening within the recommended time frame. This calls for the identification of facilitators and barriers to postpartum diabetes screening among mothers with GDM.

The reasons for suboptimal uptake of post-partum diabetes screening have been assessed in Western populations (13). A systematic review in 2019, based on 16 qualitative research studies, detailed four major themes. These were broadly classified according to the health-care system and personal factors such as the mother's relationship with her physician; experience of the OGTT; mother's perceived risk of T2DM and family-related complexities (14). Singaporean mothers with GDM probably encounter similar facilitators and barriers. However, we postulate that the structure of the local health-care system and societal practices may also contribute to the suboptimal uptake of post-partum diabetes screening. In Singapore, the health-system is two-tiered, consisting of public and private health care institutions (15). Differences in demography, family structure, support, education status, social interactions, cultural, and religious background of the multi-ethnic Asian mothers may also affect the screening uptake in Singapore (16).

A framework to provide clarity to the potential interplay of personal, familial, and societal factors (17) would be ideal to understand the complex issues affecting the screening uptake. The Socio-Ecological Model (SEM) seems to be a suitable framework as it posits the role of individual, interpersonal, organisational, and public policy factors in determining health behaviour (18). It has been used widely in the study of health promotion (19). For example, the United States Department of Health and Human Services utilized the four domains of the SEM in the creation of its national objectives in 2020, thereby acknowledging its comprehensive purview in understanding the factors affecting health behaviour (20).

This qualitative research study aimed to explore the facilitators and barriers to post-partum diabetes screening among mothers with GDM in Singapore. These findings can be used to guide the development of multi-pronged strategies to improve the uptake of post-partum diabetes screening.

MATERIALS AND METHODS

Study Design

We used in-depth, semi-structured interviews to identify the facilitators and barriers to post-partum diabetes screening among mothers with GDM in Singapore. The data collected was analyzed for emerging themes, which were subsequently presented using the SEM.

Site

The study was conducted at Punggol Polyclinic, a public primary care clinic that serves an estate populated with young families in northeast Singapore. The clinic manages at least 900 patient attendances daily, with a special focus on women's and children's health.

Period of Study

The study was conducted between October 2019 and January 2020.

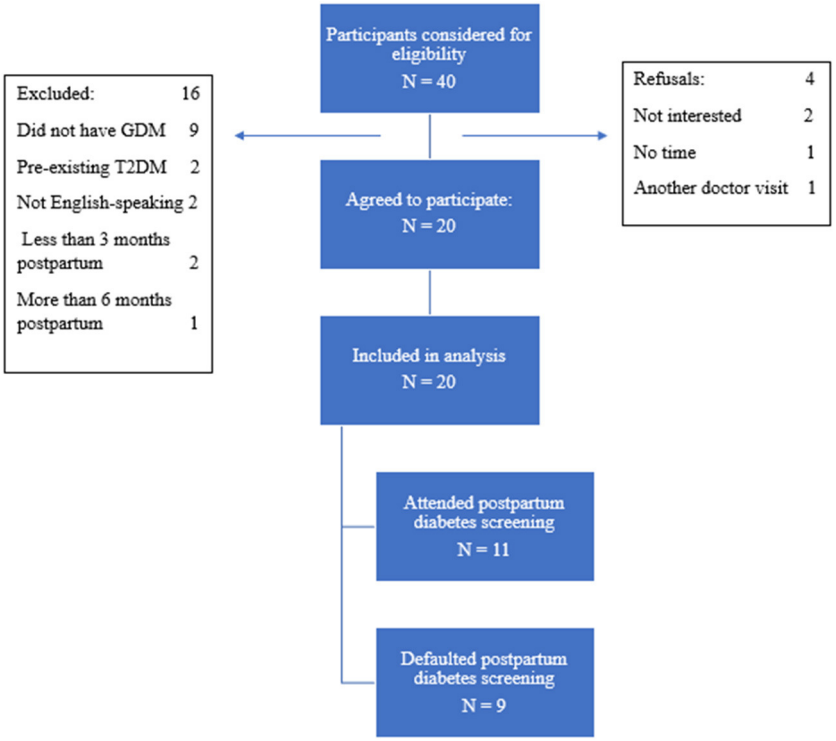

FIGURE 1 | Recruitment process of patients.

Study Population

The target participants were Singapore citizen or permanent resident mothers with a self-reported diagnosis of GDM in their most recent pregnancy, and with a child aged 3 to 6 months at the time of the interview. A lower limit of 3 months was stipulated to ensure that mothers had already attended or not attended their post-partum diabetes screening within the recommended time frame, and an upper limit of 6 months to reduce recall bias. They also had to be English-literate as the interviews were conducted in English, one of the official languages of Singapore. Those with a pre-existing diagnosis of Type 1 and Type 2 Diabetes Mellitus were excluded.

Recruitment

Potential participants brought their child to the study site for their routine childhood vaccination and developmental assessment. Mothers with GDM were directed by the nurses providing these services to the lead investigator, SHS on a consecutive case-encounter basis. SHS provided eligible participants with study-related information and clarified their doubts before obtaining their written informed consent. The recruitment process is described in **Figure 1**. Purposive sampling was intended to include women of different ethnic groups to identify specific cultural and societal practice related to ethnicity.

Conceptual Framework

The SEM was selected as the conceptual framework to identify the facilitators and barriers across the personal, interpersonal, organizational, and public policy domains. Resulting themes were subsequently organized and presented according to the SEM.

Interviews

A total of 20 mothers were recruited. They completed a demographic data questionnaire before commencing the one-to-one interview, which lasted between 20 to 30 min. Mothers were reimbursed with grocery store vouchers of SGD20 value for their time.

Coding

The interviews were audio-recorded and transcribed verbatim. Each interview was independently coded by two investigators and the coding was subsequently discussed with other investigators. The first nine interviews were reviewed to form a coding frame to guide the analysis of the remaining 11 interviews.

RESULTS

Table 1 presents the demographic characteristics of the 20 participants. Ten of them delivered in public hospitals. All ten were reminded to return for post-partum diabetes screening, of whom eight subsequently went for their post-partum diabetes screening. The remaining ten mothers delivered in private hospitals, three of whom were reminded and returned for screening.

TABLE 1 | Demographic characteristics of study participants ($n = 20$).

Characteristics	*N* (%)
Age (years)	
26–30	3 (15%)
31–35	15 (80%)
36–40	2 (10%)
Ethnicity: (Percentage of ethnic group in study and national population)	
Chinese	13 (65%/76%)
Malay	5 (25%/15%)
Indian	1 (5%/7.5%)
Other	1 (5%/1.5%)
Primiparous	9 (45%)
Diagnosis of GDM in previous pregnancies	4 (20%)
Family/friends with GDM	11 (55%)
Family/friends with DM	11 (55%)
Highest educational level	
Secondary (O, N levels)	4 (20%)
ITE	4 (20%)
Polytechnic	3 (15%)
University	9 (45%)
Housing type	
1 to 3-room HDB flat	2 (10%)
4-room or bigger HDB flat	18 (90%)
Post-partum diabetes screening	
Attended	11
Defaulted	9
Site of antenatal/post-partum care	
Public healthcare institution	10
Private healthcare institution	10

GDM, Gestational Diabetes Mellitus; DM, Diabetes Mellitus; ITE, Institute of Technical Education; HDB, Housing Development Board.

The facilitators and barriers were organized according to the domains of the SEM (**Figure 2**). Verbatim quotes from the participants were selected to illustrate the themes.

Individual-Level

Facilitators at the Individual-Level

Self-perceived risk of developing T2DM

Mothers who were aware of their increased risk of developing T2DM were more likely to return for screening. They attained this knowledge from various sources of information, such as online readings, doctor recommendations, and family members who had T2DM.

> *"But she [mother's obstetrician] did mention that I may have a risk, since I had GDM when I was pregnant … because of my size, um that's quite unlikely for a pregnant lady to have GDM. So usually, it's uh, people who have bigger sizes. So, … I may have (been) a pre-diabetic."* P1, Chinese, attended screening at private hospital.

> *"Because my age is 34 […] I know my parents, genetics… That's why I am worried, that's why I want to go. Genetically maybe it will continue… Later pregnancy… it [GDM] will come."* P3, Indian, attended screening at a public hospital.

Understanding the need for post-partum diabetes screening

Some mothers undertook post-partum diabetes screening because they understood the rationale for the test. They were aware that the diagnosis of diabetes would impact their lifestyle habits and place them at higher risk of complications in subsequent pregnancies. These mothers recognized the need for behavior change after the affirmative results from the screening tests.

> *"No, I just have to find out, because if I had known earlier, then I would just have to take note, ok, what I can do from there onwards. If not, I'll never know and then I'll splurge on all the stuff that I have been wanting to eat."* P1, Chinese, attended screening at private hospital.

Barriers at the Individual Level

Fear about the diagnosis and consequences of T2DM

Some mothers did not go for screening as they were reluctant to find out if they had diabetes for fear that the diagnosis might disadvantage them. For instance, one mother expressed concern that this diagnosis would affect her and her child's insurance premiums.

> *"this sickness will follow you throughout your life … people will always ask, like even the doctor or like the insurer, they ask you this kind of question, do you ever have like diabetes or anything"* P12, Chinese, defaulted her screening at a private hospital.

Preference for personal attention and care to child

Some mothers preferred personal attention to their infant and other older children, and felt uneasy for an alternative caregiver to look after them.

> *"Yeah but it does pose a challenge, you know, right after that one month, where we are still … very new with the baby. You need a lot of attention and we are not sure what to do when you are away from the baby, whether another person will be able to manage. So yeah there's this concern. Maybe this is the challenge for other women."* P16, Chinese, attended screening at a public hospital.

Competing priorities

Women prioritized the comfort and needs of their children over their personal health.

> *"because of the fasting, they will make my appointment, the first thing in the morning… around 8 plus. And she (child) usually isn't up by then. Yeah, so it will be disruptive to her sleep, if I have to stay there for 2 h. The journey back and forth will be a bit tough."* P20, Chinese, attended screening at a private hospital.

> *"got appointment [referring to OGTT at hospital], and then got um therapy at school [older son's speech therapy]"* P7, Malay, defaulted screening at a private hospital.

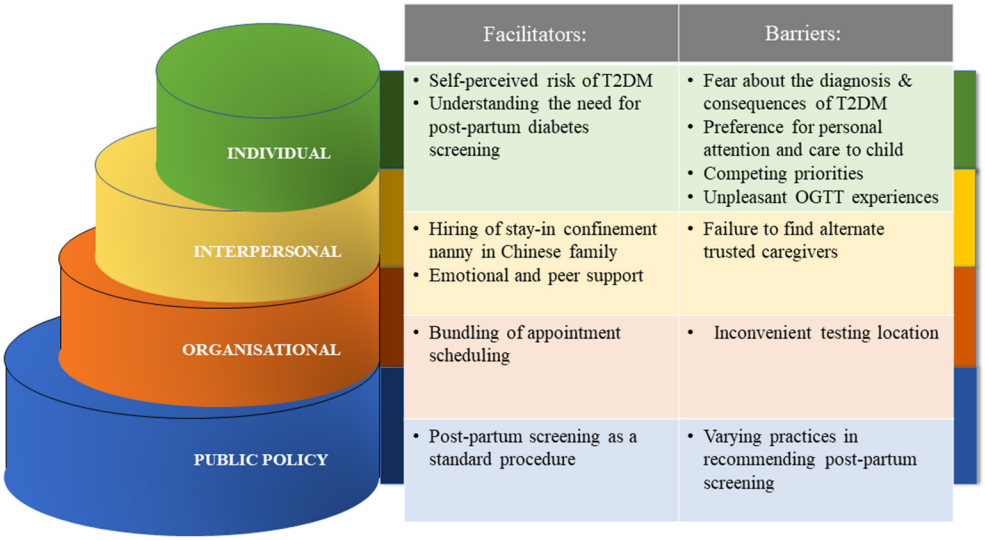

FIGURE 2 | Facilitators and barriers to post-partum diabetes screening based on the Socio-Ecological Model.

Unpleasant OGTT experience

Many of the mothers were averse to the 75 g 2-point OGTT test, which they experienced during their pregnancies. This sentiment was shared widely both by those who had the post-partum screening and those who defaulted. The deterrents included the long duration of the test, the unpalatable taste of the glucose syrup, its perceived inaccuracy and the repeated venipunctures required.

> "*It's a bit uh… long. And the water [glucose syrup] is very sweet. It's like not, not very fair, because we drink the water, it's so sweet and they don't let us drink water or walk around. It's unfair. Because we don't do that in our daily life. We will move around and we drink water. So … I think the test might not be so accurate on that part.*" P4, Chinese, defaulted screening at private hospital.

> *"I will be able to but … I don't feel like* going […] *Uhhh! The syrup is so disgusting, it's like ummm (makes a grimace), and after drinking, you feel like giddiness, you cannot stand, and walk around. You have to, like, sit down there and rest."* P12, Chinese, defaulted screening at private hospital.

> *"Wa! It's like F& N orange [soft drink brand in Singapore], but very, very, very, very, very sweet one! Sweet until you… [mimes gagging] vomit!"* P8, Chinese, had screening at a private hospital.

Interpersonal-Level

Facilitators at the Interpersonal-Level

Hiring of stay-in confinement nanny in Chinese family

The hiring of stay-in confinement nanny is more common amongst the Chinese women during the immediate 1 month after their delivery. One mother was able to attend the screening after leaving her child with her stay-in confinement nanny.

> *"my confinement lady took care of [baby] so I'm able to come out and do the test and go for my gynae review"* P1, Chinese, attended screening at a private hospital.

Emotional and peer support

A number of mothers favored a support network that encouraged them to return for post-partum screening. They described the emotional support from spouses, friends, online support groups comprising mothers with similar experiences of GDM, and healthcare professionals. Such support strengthened their decision to undertake the screening test.

> *"my husband usually helps me…I plan to have the right time when my husband can actually take leave. When the kids are on holidays, or they are not schooling… that will be the best time for extra help. My husband (is) at home, cos he can take care, looks after the 2 small ones."* P9, Malay, attended screening at public hospital.

> *"Absolutely, they will encourage me! Go and check, every time go and check the sugar levels. … the parents and husband, they are very encouraging."* P3, Indian, attended screening at a public hospital.

> *"So, going through those conversations [in online 'mummy chat groups'] helped a lot.* P1, Chinese, attended screening at private hospital.

Barriers at the Interpersonal-Level

Failure to find alternate trusted caregivers

Not every mother had ready access to alternative caregivers. They preferred immediate family member such as their spouse, parents or in-laws to look after the child in their absence. This was a common reason for mothers to default their post-partum screening test. One mother recounted that her husband was the

sole breadwinner and was not available to take over caregiving for their child.

> *"because my husband working night shift then he [didn't] sleep…"* P7, Malay, defaulted screening at a public hospital.

Organizational-Level

Facilitators at the Organizational-Level

Bundling of scheduled appointments

A number of mothers preferred bundling their screening test appointments with other post-partum investigations, such as Pap smears, for convenience.

> *"I also thought it was good, at the three-month mark, to see my gynae, for other reasons, for him to just check. I think he wanted to do a Pap smear. So, uh, just doing it all together made it convenient."* P20, Chinese, attended screening at private hospital.

> *"The main thing [that caused the mother to default post-partum screening in her previous pregnancy] is the busy schedule. [For her latest pregnancy] because I have the Pap smear there too…same day … so that's why I think, just one day off."* P4, Chinese, defaulted screening at private hospital.

Barriers at the Organizational-Level

Inconvenient testing locations

A few mothers expressed reluctance to return to their antenatal care providers for screening due to the long distance from their residences to their obstetricians' clinics. A few also preferred their screening to be at primary care clinics (polyclinics), as compared to hospitals, due to their perceived shorter wait times.

> *"I don't really have all the time to go all the way to KK [tertiary public healthcare institution]* P10, other ethnic group, defaulted screening at public hospital.

> *"…instead of going to KK [tertiary public healthcare institution], maybe polyclinics can do it also? … cos they [tertiary public healthcare institution] deal with a lot of people, the waiting time is quite long"* P13, Malay, attended screening at public hospital.

Public Policy-Level

Facilitators at the Public Policy-Level

Post-partum screening as a standard procedure

Mothers' perception of obligatory screening for T2DM was key to their uptake of the test.

> *"I thought it's like mandatory?"* P16, Chinese, attended screening at a public hospital.

> *"No, it's like a routine, so just took it."* P1, Chinese, attended screening at a private hospital.

Barriers at the Public Policy-Level

Varying practices in recommending post-partum screening

Some mothers reported a lack of advice and recommendations for T2DM screening from their antenatal care providers despite their diagnosis of GDM during their pregnancies. In particular, one mother recounted that she had to request for screening personally, as it was not offered as part of her pregnancy care "package".

> *"…nobody asked me for a check, so I didn't bother to follow-up."* P6, Chinese, defaulted screening at private hospital.

> *"But the gynae said don't need…then no need […]! I just trust him."* P12, Chinese, defaulted screening at private hospital.

The test of choice for post-partum screening also varied amongst providers, with some offering random blood glucose tests or in-office finger-prick tests instead of an OGTT. Few also revealed that their diagnoses of GDM were dismissed or downplayed when additional random blood glucose tests during pregnancy were normal.

> *"So maybe it was because of the impromptu blood test that was done without fasting so at like random timing and the value is very good […]. So I think he was not that worried about my GD [referring to GDM]. Maybe it's just borderline case."* P14, Chinese, defaulted screening at private hospital.

DISCUSSION

This study elucidated facilitators and barriers for post-partum diabetes screening among mothers with GDM across multiple domains. While the results largely echo those identified by systematic reviews, new themes have been identified at the interpersonal and public policy levels which are distinctive to Asian mothers in Singapore.

At the individual level, mothers who had greater knowledge about the risks of GDM and T2DM were more likely to take up the screening. Therefore, healthcare professionals should educate mothers about GDM, T2DM, and the importance of post-partum diabetes screening actively, even during antenatal visits (21). A systematic review revealed the short-term relationship between mother and their antenatal care provider ended soon after their delivery (13). Hence health messages were not reinforced to the mothers in the post-partum period by any healthcare professionals. The gap in care can be addressed with proper handover of care to primary care physicians to continue their health monitoring. Mothers who were reassured that GDM was only a "mild condition of pregnancy" were also not as motivated to return for screening (22). Primary care physicians have a role to play in correcting some of these misconceptions during their postnatal visits.

For mothers who are undecided on their post-partum diabetes screening, or have not been adequately counselled on their risks after delivery, a Patient Decision Aid (PDA) can encourage shared-decision making between them and their physician (23). A local pilot study at a public hospital found that mothers perceived that they had received adequate "material," "emotional," and "comparison" support. However, they claimed inadequacy of "informational" support despite the abundance of informational pamphlets and brochures which were available to them (24). The investigators are developing a PDA targeting

women with GDM on postnatal diabetes screening which may potentially overcome this lack of "informational support." PDA provides a convenient platform to trigger discussion on postnatal diabetes screening if it is readily accessible to the at-risk women at any clinical practice. Aside from presenting balanced perspectives of the screening test, including its benefits and inconvenience, the PDA will also offer tips to address common barriers such as availability of caregivers. Such PDA can be implemented in public and private healthcare practices to reach out to more women with GDM. It will be assessed for its effectiveness to increase uptake of the screening in the next phase of this project.

The use of alternative screening tests which may be more convenient or pleasant than the OGTT should be explored. The latest National Institute of Care and Excellence guidelines from the UK for post-partum diabetes screening suggest the use of a fasting plasma glucose test at 6 to 13 weeks after delivery. If a fasting glucose test has not been performed by 13 weeks, offer a fasting plasma glucose test, or an HbA1c test if a fasting plasma glucose test is not possible, after 13 weeks (25). Women will not be required to consume the glucose drink, which most Asian women in this study found distasteful and unpleasant. However, other studies reported the HbA1c to have a low sensitivity of only 14.3% in diagnosing T2DM in the post-partum population when compared to the OGTT (26). Hence the validity of diabetes screening tests other than the OGTT for the diagnosis of T2DM in mothers with GDM remains unclear.

At the interpersonal level, most women in our study reported that their child was cared for by their family members (mother, mother-in-law or spouse) while they undertook the post-partum diabetes screening. Asian women appeared to prefer personal attention and care of their child; otherwise they will entrust their child to close family members during their absence. The stay-in confinement nanny is a convenient and immediate caregiver to assist the mother. Almost one third (31%) of women of Chinese ethnic group hired such confinement assistants in a local study by Fok et al. which is less common in other ethnic groups such as the Malay (13.5%) and Indian (9.4%). (27) The confinement period usually lasts between 30 and 45 days. The women's mothers and mother-in-laws are the other major groups of care providers during the confinement period, ranging from 59.4% in Chinese to 71.5% in Malay and 83.3% in Indians. They are also trusted caregivers to take care of the child, if the screening test can be scheduled at 6-week post-partum, which is at the end of confinement period (27).

In addition, most women did not wish to bring their child to the clinic. Fok et al. also reported that Chinese mothers (83.7%) were least likely to bring their child outside the home compared to Indians (79.9%) and Malays (66.1%) (27). If possible, mothers can consider seeking help in looking after their child from their parents, in-laws, spouses, siblings, or even trusted neighbors while they attend their postnatal physician visits (28). Public and social policies such as paternity leave for fathers (29) or encouraging young families to stay near to their parents through housing incentives (30) may also help to address this barrier.

In addition, healthcare institutions can consider offering on-site childcare services or provide play areas for older children, as suggested by many mothers. This proposal aligns with the recommendations suggested by Dennison et al. in their systematic review (14), and will apply not just for postpartum visits but will facilitate mothers seeking medical attention.

At the organizational level, the bundling of the post-partum diabetes screening with other post-partum review can optimize the time and utility of each visit. Mothers should be made aware of such options early during their antenatal visits via clear, uniform instructions by both their obstetricians and primary care physicians. As these test can be planned weeks in advance, the option of scheduling a mother's post-partum diabetes screening with other appointments at suitable locations should be offered routinely by the institution (14).

Clinical practice guidelines are available to recommend the routine screening for T2DM in mothers with GDM (31). However, the variable adherence by healthcare providers to such guidelines, especially with a local two-tiered healthcare system, poses challenges to their implementation. Differences were noted from the recommendations by public and private healthcare providers, which could be due to lack of effective policies to ensure consistent adherence to the guidelines.

The inconsistent handover from obstetricians to other healthcare providers after delivery further compounds the problem. Local mothers can now access their National Electronic Health Records (NEHR) remotely using computers or smart mobile phones. However, while it is implemented across all public healthcare institutions, adoption by private healthcare providers is low. Only 27% of local private healthcare institutions have access to NEHR and a mere 3% of them contribute data (32). Therefore, details about a mother's glycemic control during and after pregnancy may not be readily available should she attend private primary care clinics or obstetricians. While we await a unified nationwide electronic health record, healthcare policy-makers may leverage on existing platforms to automate reminder delivery to mothers for post-partum diabetes screening when a diagnosis of GDM is recorded in their electronic health records. Multiple modalities of info-communication technology are currently available for mothers to fix their OGTT appointments, from phone-calls to mobile applications with various healthcare providers.

Lastly, we must also encourage mothers to take charge of their own health. This can be achieved through interventions to increase their health literacy and specific preventive measures against T2DM. Healthcare professionals and policy-makers can assist to elevate their self-efficacy and risk awareness via official portals of health education and organizing such programs at the healthcare facilities.

STRENGTH AND LIMITATIONS

A key strength of this study is the novel use of the SEM to stratify the facilitators and barriers towards post-partum diabetes screening among mothers with GDM. The model facilitates the formulation of action points targeting personal, interpersonal, organizational, and public policy factors.

The results from this study reflect the perspectives of local Asian mothers who were recruited from primary care. Nevertheless, we have used the findings from this study to construct a questionnaire for a cross-sectional survey to quantify the magnitude of the individual facilitators and barriers identified. The triangulation of the results from both the qualitative study and survey will allow us to develop and prioritize multi-pronged interventions to enhance the enablers and mitigate the barriers within each SEM domain.

The qualitative research method used in this study restricts the generalizability of the findings to the general female population in Singapore. Purposive sampling was deployed to recruit women of different ethnic groups but eventually proportionately more Malay women were interviewed compared to Chinese and Indians. The recruitment was dependent on the provision of written consent.

Another potential limitation is the recruitment of the women from a single public primary care clinic. However, these women have access to both public and private primary healthcare services, so the site of recruitment is unlikely to affect their demographic profiles significantly. More tertiary educated women were interviewed, which could reflect their higher confidence and language proficiency to interact with the interviewer in English. The subsequent questionnaire survey will allow analysis of the impact of ethnicity and educational status on postnatal diabetes screening in women with GDM, which is not appropriate in a qualitative research study.

CONCLUSION

Facilitators and barriers of post-partum diabetes screening for mothers with GDM are not only related to their personal and interpersonal factors but are also influenced by the local health system and policies. The multitude of socio-ecological factors must be acknowledged and addressed to improve the screening rates. Educating mothers on the benefits and risks of testing, assisting them in managing competing demands and policies promoting adherence to clinical practice guidelines across all healthcare providers may be packaged as a multi-dimensional intervention to improve the uptake of post-partum diabetes screening.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by SingHealth Centralised Institution Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS contributed to development of the interview guide, conducted the interviews, transcribed the interviews, coded the transcribed interviews. RM, SA, and NT contributed to development of the interview guide, conception and design of the study, and revision of the manuscript. CL, YT, YS, XH, MG, LT, SL, SK, YL, and KV were involved in designing the study, creating the interview guide, coding, and organization of the themes from the data collected and drafting of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by the Academic Medicine–Enhancing Training, Healthcare, Outcomes, & Standards (AM-ETHOS) Grant (AM-ETHOS01/FY2019/36-A36).

ACKNOWLEDGMENTS

We would like to acknowledge the contribution of the Punggol Polyclinic nurses in making this study possible and the support from the SingHealth Family Medicine Academic Clinical Program and administration staff from the Department of Research in SingHealth Polyclinics.

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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.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 27 November 2020
doi: 10.3389/fendo.2020.534873

Type 2 Diabetes Patients' Perspectives, Experiences, and Barriers Toward Diabetes-Related Self-Care: A Qualitative Study From Pakistan

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OPEN ACCESS

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

Received: *14 February 2020*
Accepted: *25 August 2020*
Published: *27 November 2020*

Citation:
Bukhsh A, Goh B-H, Zimbudzi E, Lo C, Zoungas S, Chan K-G and Khan TM (2020) Type 2 Diabetes Patients' Perspectives, Experiences, and Barriers Toward Diabetes-Related Self-Care: A Qualitative Study From Pakistan. Front. Endocrinol. 11:534873. doi: 10.3389/fendo.2020.534873

Objective: This study aimed to qualitatively explore perspectives, practices, and barriers to self-care practices (eating habits, physical activity, self-monitoring of blood glucose, and medicine intake behavior) in urban Pakistani adults with type 2 diabetes mellitus (T2DM).

Methods: Pakistani adults with T2DM were recruited from the outpatient departments of two hospitals in Lahore. Semistructured interviews were conducted and audiorecorded until thematic saturation was reached. Two researchers thematically analyzed the data independently using NVivo® software with differences resolved by a third researcher.

Results: Thirty-two Pakistani adults (aged 35–75 years, 62% female) participated in the study. Six themes were identified from qualitative analysis: role of family and friends, role of doctors and healthcare, patients' understanding about diabetes, complication of diabetes and other comorbidities, burden of self care, and life circumstances. A variable experience was observed with education and healthcare. Counseling by healthcare providers, family support, and fear of diabetes-associated complications are the key enablers that encourage study participants to adhere to diabetes-related self-care practices. Major barriers to self care are financial constraints, physical limitations, extreme weather conditions, social gatherings, loving food, forgetfulness, needle phobia, and a hectic job.

Conclusion: Respondents identified many barriers to diabetes self care, particularly related to life situations and diabetes knowledge. Family support and education by healthcare providers were key influencers to self-care practices among Pakistani people with diabetes.

Keywords: type 2 dabetes, self-care, self-monitoring blood glucose (SMBG), barriers and facilitative factors, exercice, diet

INTRODUCTION

Diabetes mellitus (DM) is one of the most challenging health care issues of the twenty first century. Type 2 diabetes (T2DM) is the most common form of diabetes and affects more than 90% of people with diabetes. In addition to genetic pre-disposition, physical inactivity,obesity, and unhealthy eating habits are significant risk factors for T2DM (1, 2). In Pakistan, the diabetes prevalence rate is currently 6.9%, but it is projected to reach 15% by 2040, giving Pakistan the fourth highest prevalence of diabetes globally (3).

Self-care practices have been positively correlated with good glycemic control and significant reductions in the progression and development of complications associated with diabetes (4, 5). Diabetes-related self-care practices include healthy eating, being physically active, self-monitoring of blood glucose, and regularly taking prescribed medications (6).

Adherence to recommended diabetes self-care activities is important in achieving the desired glycemic control and reducing diabetes-related complications (7, 8). Despite known clinical benefits associated with diabetes self-care activities, a number of studies report poor adherence to recommended diabetes-related self-care practices (9–11). Adherence to self care depends on patients' lifestyle behaviors, such as adopting healthy eating practices and physical activity (12). Inadequate disease knowledge; poor communication with healthcare providers; and psychological factors, such as depression, are frequently reported barriers to recommended self care (7). Self-care education, family support, and problem-solving skills are commonly suggested facilitators for improving diabetes self-care practices in people with diabetes (1, 13, 14).

To date, several quantitative studies have examined patient knowledge levels and self-care practices among people with diabetes in Pakistan (9, 15–18). Psychological and cultural factors are frequently reported barriers to diabetes self-care in Pakistan (15, 18). These studies reveal gaps in knowledge regarding diabetes and highlight the importance and feasibility of self-care educational interventions (9, 19). Evidence synthesized from a recent network meta-analysis shows that self-care educational interventions are effective in achieving desired clinical outcomes of people with diabetes; for example, a significant reduction in glycated hemoglobin (HbA1c) levels, systolic blood pressure, and lipid profile was observed (20).

Although there are a few published qualitative studies that address self-care experiences (21, 22) and cultural perceptions (23) of people with diabetes from rural areas of Pakistan, none has explored the perspectives and experiences of self care in adult Pakistani people with T2DM residing in urban areas of Pakistan. Second, diabetes has become a serious health challenge for low- and middle-income countries, such as Pakistan, where self-care aspects of diabetes are not properly discussed with patients (21). Exploring T2DM patients' perspective in depth and identifying facilitators and barriers to diabetes self care will not only yield new knowledge regarding self care among this population, but will also help to prioritize treatment targets and design strategies, such as tailored self-care educational interventions, specific to the culture and needs of Pakistani people with diabetes. The objective of this qualitative study is to provide insights into the experiences, behaviors, and barriers to self-care practice among urban Pakistani adults with T2DM.

METHODOLOGY

Study Design and Setting

This study utilizes qualitative research methods to comprehensively explore patients' perceptions and behaviors toward disease-management practices. In-depth interviews were conducted, using a flexible, semistructured guide with an open-ended questioning approach (24), among people suffering from T2DM at Akhuwat Diabetes Clinic Lahore and Awan Medical Complex Lahore, Pakistan (2016–2017).

Ethical Approval

This study was approved by the Monash University Human Research Ethics Committee (MUHREC, Approval Number 7767) and the data collection centers in Pakistan. Informed written consent was obtained from all study participants after providing them with a verbal and written explanation about the purpose and required procedures of the study. Participation in the study was voluntary, and participants were told that they could withdraw from the study at any time. Only verbal consent could be obtained from illiterate participants. Confidentiality was maintained by using study codes. Data access was restricted to study researchers only. The ethics procedures of the study comply with the Declaration of Helsinki.

Study Sample and Data Collection

Patients with T2DM were recruited using convenience sampling. Inclusion criteria were (1) Pakistani national of age more than 30 years, suffering from T2DM for more than 1 year (to allow patients with T2DM to familiarize with facilitators and barriers toward their diabetes self care) and (2) willingness to be interviewed in Urdu language (audiorecorded) within the hospital premises. Patients who were diagnosed with other diabetes types, pregnancy, and cognitive impairments such as dementia were excluded from the study. In order to identify patients who met the inclusion criteria, the first author screened the patients at both diabetes centers by reviewing their medical record files and after consulting physicians who were attending these patients. Patients meeting the study's inclusion criteria were physically approached by the first author while they were waiting for their appointments with the physician at the diabetes care centers. Sixty-four patients met the inclusion criteria. After explaining the purpose and process of the study to the eligible patients, consent was obtained for an audiorecorded interview at the clinic. Thirty-seven eligible patients (response rate of 57.8%) agreed to participate.

Interviews were conducted until thematic saturation was reached (25). The interviews were conducted by a single interviewer (a researcher who was not involved in the provision of healthcare to the participants in the past) to minimize interindividual variability.

Contents of the Interview

A semistructured interview guide (attached in the **Appendix**) was developed after a literature review (1, 4, 7, 8, 26–31) and discussion with academic and clinical diabetes experts to ensure that key areas of diabetes self care were covered in a culturally acceptable manner. Key domains of self care on which data were collected included knowledge and practices toward diabetes medicine, self-monitoring of blood glucose, healthy eating, physical activity, and continuity of care. It was then piloted (sample size $n = 2$) to ensure that the content of the interview guide sufficiently covered all domains of diabetes self care. Pre-test interviews were not included in the final analysis. Widely framed and open-ended questions gave ample opportunities to the study participants to share their personal experiences and factors that facilitate and impede their practices toward diabetes self care. Participants were also encouraged to shape their own narratives and share anything further relevant to the topic. In addition, during the interview, relevant keynotes were also taken so as to document key observations and issues.

Analysis

All interviews were audiotaped in the Urdu language before being translated and transcribed verbatim to English language by the first author (AB). The transcribed interviews were reviewed by a second researcher (TMK) to ensure transcriptions were accurate, complete, and unbiased (32–34).

After familiarizing themselves with the data, two researchers (AB, EZ) independently coded the data by using NVivo® software (version 11 plus). A generic thematic analysis approach (35) was used to categorize the codes through several iterations. Themes were identified from the coded data. Discrepancies in coding between the two investigators were resolved through consensus with a third author as required (CL). Emergent themes were then discussed among all the authors for consistency and to minimize the bias.

RESULTS

Thirty-two patients with T2DM participated in the study, of which 21 (65.5%) were female. The age of participants ranged from 35 to 75 years, and all spoke Urdu as their first language. Ten respondents reported being employed, and most of the female respondents were housewives. **Table 1** lists the demographic details of the study participants (demographic details of individual participants are provided in the **Appendix**).

Six themes were identified after an in-depth analysis of the participants' interviews. The list of themes and subthemes are presented in **Figure 1**.

THEME 1: ROLE OF FAMILY AND FRIENDS

Medicine Administration

Getting support from family members is one of the important determinants of compliance with medication-taking behavior. Family support in the form of reminders to take medications and help in medicine identification and administration are important facilitators to diabetes self care. Some participants shared that they can identify their medicines only by color or shape, whereas their family members (e.g., spouse and children) helped in identifying and administering their medicines.

> *"My son has the responsibility to give me medicines. I can't recognize and remember my medicines, as every time doctors change my medicines. My son buys medicines for me and has the responsibility to administer me." (P12; Male)*

Another male participant (P4) further added

> *"I started with Glucophage (Metformin), and now on insulin. I can identify my medicine from its color, but mostly my wife and my child administer me medicine. My children help me in identifying my medicine."*

Self-Monitoring of Blood Glucose

Participants repeatedly discussed how family members support and motivate them to practice regular blood glucose testing. Family support in the form of glucometer handling is a key enabler reported by most of the respondents for self-monitoring of blood glucose (SMBG). One participant stated

> *"I check [blood glucose levels] at home twice a week, I have glucometer at home, I cannot operate it, but my daughter-in-law does it for me." (P1; Female)*

Respondents' children were frequently mentioned family supports in diabetes self care. Many participants stated that their children helped them in performing blood glucose checks.

> *"I have glucometer at home, but I cannot operate it, my children often do it for me." (P15; Male)*

TABLE 1 | Demographic characteristics of the participants ($N = 32$).

Characteristic	Mean (*SD*) or percentage (*n*)
Age (years)	54.81 ± 9.59
Gender	
Male	34.5% (11)
Female	65.5% (21)
Working status	
Housewives/stay at home	53.1% (17)
Business	6.2% (2)
Doing job	31.2% (10)
Retired	9.5% (3)
Education (years)	
No formal education	34.4% (11)
Primary level	21.9% (7)
Secondary level	21.9% (7)
High secondary level	9.3% (3)
University level	12.5% (4)
Duration of diabetes (years)	9.7 ± 7.58

SD, Standard deviation.

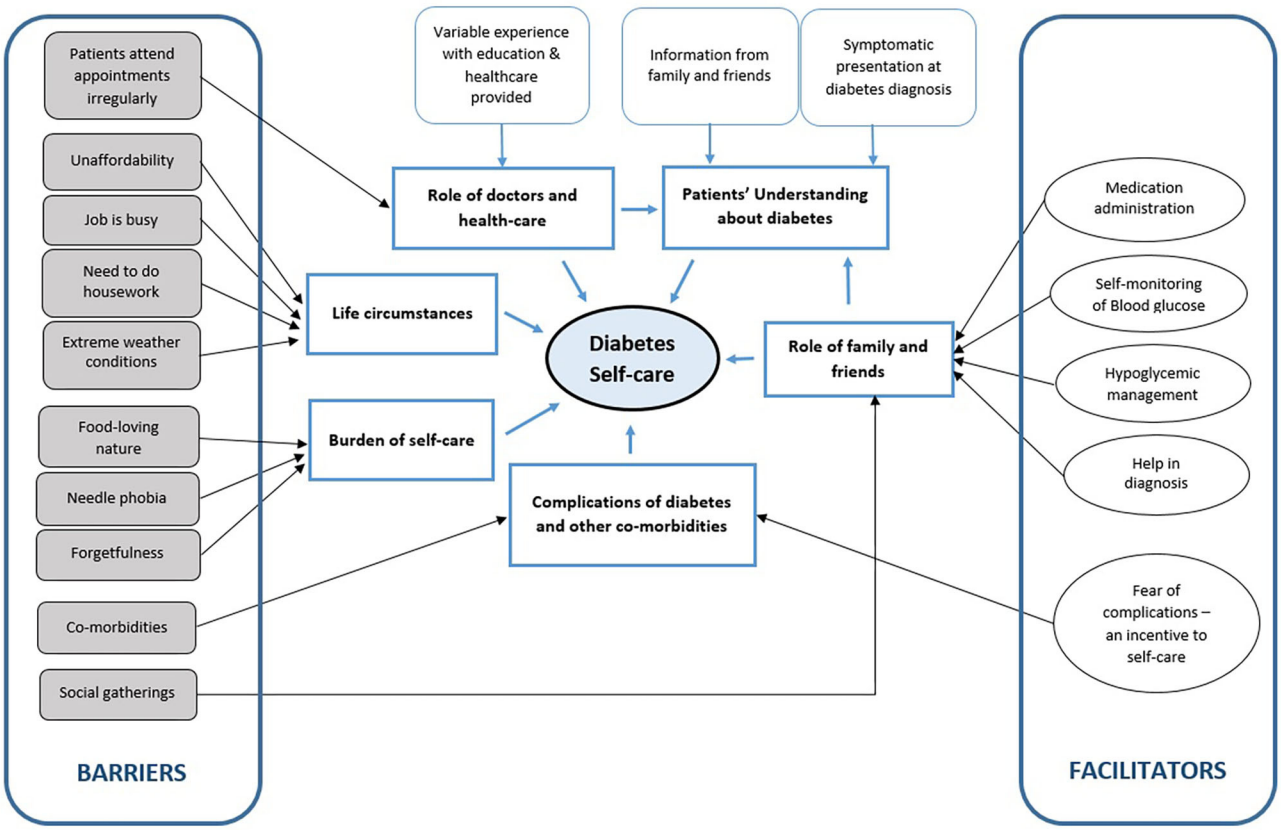

FIGURE 1 | Thematic presentation of factors influencing self care in diabetes.

Another male participant (P4) further added this:

> *"I don't feel any problem as my wife can use a glucometer, she is educated and can operate it."*

Hypoglycemia Management

Some participants mentioned family members as a source of information for their hypoglycemia:

> *"When you have so many diabetic patients in your family, you will become a doctor because of their disease experience. No one told me about hypoglycemia, I learned from my family members about the symptoms of hypoglycemia and keep a sugar candy or sugar sachet with me always." (P18; Female)*

Very few participants discussed the assistance provided by family members during their hypoglycemic episodes.

> *"Once I felt such condition [hypoglycemia], when I was sleeping, felt like shaky, tired and weak, I called my daughter-in-law, she brought for me lemonade with plenty of sugar in it. My son got frightened of my condition, but after some time I became normal, before they took me to hospital." (P1; Female)*

Help in Diagnosis

Information and support from the family is an important source, not only for diabetes self care but in diagnosing interviewees' diabetes as well. A few participants reported that they came to know about their diabetes symptoms because of their family members and friends who were already suffering from diabetes.

> *"Many of my family members and relatives are suffering from diabetes and that's why I knew about the symptoms of diabetes." (P3; Female)*

Another female participant (P9) described the importance of counseling from her family member:

> *"One of my family members who also had diabetes counseled me that I should take proper diet, follow doctor advice and regularly take my medicine, only then my diabetes will remain under control."*

Another female participant (P32) discussed how her neighbor counseled her to get checked for blood glucose levels.

> *"Thirteen years before I suffered from weakness and body pains, upon discussion with my neighbor, who was already suffering from*

diabetes, advised me to get checked from a physician for diabetes. Upon blood sugar check-up form a private hospital at Lahore, it was revealed that my random blood sugar was 320 mg/dL."

Social Gathering

Diet management is one of the most problematic self-care behaviors as described by the majority of participants. Among the several challenges for adopting a healthy lifestyle, the most commonly mentioned was difficulty in maintaining a healthy diet. Participants specifically mentioned that it was difficult to follow diabetes-related dietary recommendations when food was presented in wedding ceremonies and social get-togethers.

"On marriage ceremonies and on other social gatherings it is difficult for me to manage my diet, due to plenty of sugar-rich food served there." (P15; Male)

Some participants highlighted the unavailability of diabetes-specific food in social gatherings, especially marriage ceremonies.

"In marriage ceremonies, no food is available for diabetes patients, so I tend to eat whatever served." (P22; Female)

Problems with adhering to their medicine intake in social gatherings were also reported by the study participants.

"At maximum, I skip one dose, only when I am out of my house to attend some family get-together, but I take the rest of the medicines properly on my return to home. It's very rare that I forget my dose." (P13; Female)

A male respondent (P26) further added in to this:

"*Whenever I go out to attend family parties, I forget to take my medicine."*

THEME 2: ROLE OF DOCTORS AND HEALTHCARE

Variable Experience With Education and Healthcare Provided

Education from physicians is one of the most important determinants for change in self-care practices. Counseling and education from physicians not only improved the knowledge of the study participants, it was a source of encouragement for them as well. Many participants acknowledged and clearly valued their physician's counseling regarding medication adherence and adopting a healthy diet plan.

The majority of the study participants mentioned that they were strictly adhering to their prescribed antidiabetic medications' schedule as compared to other self-care practices.

"*I take my medicines regularly because my doctor advised that whether I take meals or not, I must take my medicines regularly." (P2; Female)*

A female participant (P24) mentioned

"*Doctor wrote for me clearly and in bold on medicine pack and blisters, and my children can read that easily."*

Participants indicated that their healthcare providers were a major source of encouragement for medication adherence.

"Initially, I use to take my antidiabetic medicines irregularly because whenever I got my blood sugar levels tested, it used to be normal (140-150), so I did not pay heed toward my regular medicine intake. But my doctor advised me to take it regularly otherwise my disease will worsen. Now I take my medicine regularly." (P3; Female)

The majority of patients reported being properly counseled by their physicians to do regular exercise and about its importance in their diabetes self care.

"Doctor guided me to do daily 30 minutes' walk early morning. It's the only exercise I have to do, and I do it regularly." (P30; Male)

Another male participant (P15) further added

"I do 45 minutes' walk daily. My doctor advised me, and I am aware of its importance as well."

Participants were aware of the need for dietary modification for their diabetes self care. Most of them commonly described being counseled either verbally or in writing by their healthcare providers about dietary modification during their visits for medical checkups.

"Doctor gave me a diet plan, which is hanging on our kitchen wall, I follow it mostly. I avoid sugar, sweets, soft drinks and meat." (P10; Female)

Another female participant (P13) mentioned

"My doctor gave me a diet plan and I follow it with true spirit. I know about my dietary precautions and I have been counseled by my doctor properly. I avoid sugar, rice, carbonated sugar drinks and beef, but take mutton sometimes."

Participants elaborated that they had received information on "what to eat and how to eat," and they had been advised "to eat more green leafy vegetables and locally available fruits." Interviewees stressed the fact that they should follow what is being advised to them for leading a healthy life and appreciated that a change in dietary behavior is good for their health.

"Doctor advised me to avoid rice, seafood, potatoes. Eat less but more frequently." (P22; Female)

Participants were aware and educated about the importance of a portion diet and ideal food choices for diabetes. A female participant (P21) shared her views:

"I am aware of my diet planning, as the doctor guided me well about it. I know the kind of food which is beneficial and harmful to me."

Some participants mentioned that they gained knowledge about hypoglycemia, associated symptoms, and its management from their physicians:

"Doctor told me that if I feel restless and sweating, I should take something sweet and always keep a sugar candy with me." (P16; Female, P14; Female; P30; Male)

Another male participant (P20) added

"My doctor counseled me about the possibility of being hypoglycemic, as I was prescribed with two types of capsules and insulin for my diabetes."

Those who received education about hypoglycemia were aware of its emergency management at home:

"Now I am aware that I will eat something sweet whenever my blood sugar levels are low." (P29; Female)

Very few participants were aware of keeping sugar with them for emergency management of hypoglycemia:

"Quite often I experience fatigue, hunger, palpitation. I know such condition is because of low blood sugar levels and I eat dates or anything sweet available at home." (P32; Female)

At the same time, a different experience with healthcare providers was shared by some of the participants. According to these interviewees, the self-care aspect of diabetes management and the significance of routine checkups were not discussed with them by their physicians during their consultations.

"Doctors did not advise me to get my eyes and kidneys checked regularly." (P3; Female)

Another female participant (P5) added

"I did not go for regular checkup of my kidney and eyes, as my doctor did not advise me for these check-ups."

One female participant (P31) mentioned

"I get my eyes and kidneys checked myself, but doctors never asked me to do so. Doctors use to ask me about my previous medicine intake behavior but never asked me about my dietary habits."

A few participants expressed their feelings that they were not treated well by their physicians.

"Doctors never guide me about my medicines, if I ask them, they simply reply, ask dispensers for this." (P2; Female)

A female participant (P24) shared her experience:

"Doctors don't give me sufficient time, just write a prescription for me…"

Another female participant (P25) shared her expectations toward her physician:

"I want my doctor to listen to my medical concerns in detail and counsel me properly."

A small number of interviewees also reported that their physicians never asked them about their routine diet and medicine intake behaviors. They insisted on getting more information from their physicians about diet planning and lifestyle modifications.

"Doctor never asked me about my diabetes medicines intake and dietary precautions." (P26; Male)

Participants showed their interest in receiving detailed information from their physicians about their lifestyle modifications:

"Doctor never asked me about my diet and medicine routine. I want my doctor to guide me about my diet plan." (P22; Female)

Another male participant (P30) further added this:

"Doctors never asked me about my diet and medicine intake. Doctors write in English language which I cannot understand, so I request him to write it for me in Urdu language." (P30; Male)

One male participant (P20) shared his experience of not receiving written diabetes educational material from the healthcare facility:

"I did not receive any written material from clinics regarding diabetes." P20

Despite the serious nature of hypoglycemia, most of the participants indicated that they did not receive education about hypoglycemia and its management from their physicians.

"My doctor never told me about the symptoms and management of hypoglycemia." (P5; Female)

Some participants mentioned that, although they were not properly educated about hypoglycemia and its management, they knew to eat something sweet in case of hypoglycemia:

"I was not told about this (hypoglycemia). But whenever I feel that I am having a low blood sugar level, I take sugar at my own." (P1; Female)

Another male participant (P12) further added

"I don't know the symptoms of a low blood sugar levels and did not experience it (hypoglycemia) yet. But I know I will eat sugar candy."

Patients Attend Appointments Irregularly

Most of the study participants shared that they were more likely to consult their physicians when they experienced ill symptoms or in case of disease severity.

"I visit my doctor only in case I feel I am having low blood [blood pressure], but most of the time blood [blood pressure] is normal but my sugar level is high." (P8; Female)

Another female participant (P29) shared her experience:

"I consult doctor irregularly, only when I am facing some medical problem."

Some patients shared that they visited their physician only in case of medical emergency:

"Without any medical issue, I never visit my doctor. Today I am visiting my doctor after about 6 months. As I believe if I am taking my medicines regularly and without any emergency condition, there is no need to visit my doctor." (P19; Female)

One female participant (P28) reported

"I visit my doctor only in case of a medical emergency and when my sugar levels are not being controlled." P28

A considerable number of study participants mentioned that they visit healthcare facilities only to get their medicines refilled free of cost rather than for a routine medical checkup.

"I visit a hospital after one month, just to take my medicines for diabetes and return home, no one (from hospital) inquires me about my disease and how I am taking my medicines and diet." (P2; Female)

The same thoughts were shared by other participants:

"I visit my doctor to refill my prescription." (P9; Female)
"I visit my doctor every month because on the visit I get free (medicine) insulin." (P15; Male, P22; Female)

A female participant (P1) shared her experience:

"I visit my doctor after every 15 to 30 days, as I have to get insulin free of cost from the diabetic clinic after consultation. Only once I got checked for my kidney and eyes."

Only a few of the study participants mentioned that they visited their physicians for routine checkups.

"I visit my doctor after every three months for a routine checkup or in case I have some problems. The doctor advised me to get my eyes checked after every 3 months because my vision is being adversely affected by my diabetes." (P11; Male)

One female participant (P24) mentioned that her physician educated her about the importance of regular medical checkups:

"I visit the doctor after every month, irrespective of having any medical issue. Doctors advised me to get myself checked regularly for follow-up purposes."

Blood glucose testing was also a reported reason for a healthcare facility visit by a few study participants.

"After every week, as I have to get my blood sugar levels checked. I visit my doctor for my lab reports review too." P7

THEME 3: PATIENTS' UNDERSTANDING ABOUT DIABETES

Information From Family and Friends

When the participants were asked how they were diagnosed with diabetes, many of them mentioned their family members and friends as primary sources of information for their diabetes.

"*People shared with me that excessive urination was due to the weakness of bladder, some said I should drink plenty of water, and some advised to take soft-drinks, but no one told me about diabetes." (P1; Female)*

Some participants perceived diabetes as a curable disease.

"My husband told me that I will be cured of diabetes, and I was not upset, as I did not know about it, and was expecting that it will be cured." (P13; Female)

A similar experience was shared by another male participant (P6).

"I realized that things will be normal, and nothing is going to happen to me. I was expecting that my diabetes will cure after taking medicine for a couple of months. But now after one year, I have realized that I have to take medication and diet control for rest of my life."

A few myths were shared by the study participants regarding the cause of their diabetes.

"I thought I became diabetic patient due to herbal medicines, which I was taking for treatment of my kidney stones treatment." (P23; Female)

According to a female participant (P5), glucose infusions were the cause of her diabetes.

"Due to excessive administration of glucose infusions, when I got gallbladder surgery around 10 years back, was the reason for my diabetes."

On the other hand, a female (P9) participant thought that depression was the cause of her diabetes

"I became diabetic patient due to depression of my friends' death, the initial symptoms I got were excessive urination."

Symptomatic Presentation at Diabetes Diagnosis

The majority of participants described experiencing a variety of ill symptoms, such as frequent urination, fatigue, and body pains, especially in their lower limbs (which they did not attribute

to diabetes), which drove them to visit a doctor. For instance, according to male participant P11,

> *"Due to pain in my legs and frequent urination, I consulted the doctor and was diagnosed with diabetes."*

Some patients went for other disease checkups and were diagnosed with diabetes:

> *"Due to vertigo and fatigue I visited my family physician along with my husband, I was diagnosed with diabetes, at that time I did not even know what diabetes is?" (P13; Female)*

Another female participant (P17) shared her experience of diabetes diagnosis:

> *"I was admitted into a hospital due to dengue fever, and was diagnosed with diabetes, at that time my blood sugar was 300 [mg/dL]."*

Delayed wound healing also led to a diabetes diagnosis in a few participants:

> *"I had a wound on my leg which was not healing despite taking antibiotics. Upon complete lab testing, I was diagnosed with diabetes, which was the reason, why my wound was not healing." (P21; Female)*

THEME 4: COMPLICATIONS OF DIABETES AND OTHER COMORBIDITIES

Fear of Complications—An Incentive to Self Care

Illness perception is a key factor that seems to influence participants' decisions to adhere to their recommended medications and SMBG levels. Irrespective of diet and lifestyle adherence, most of the study participants mentioned that they were strictly adhering to their prescribed antidiabetic medication schedule, which they attributed to fear of ill symptoms and complications associated with poor diabetes control. The appearance of body pains, fatigue, and troublesome frequent urination were the most frequently mentioned fears by the respondents.

> *"If I discontinue my medicine my blood sugar level will increase and I will suffer from body pains again, that is why I never think of discontinuing my therapy." (P16; Female)*

Fear of acquiring diabetes-related complications is the most notable patient concern if they do not adhere to their recommended medicines.
According to a female participant (P17),

> *"I know my diabetes get worse if I did not take care of it."*

A female participant (P2) further added to this:

> *"As I take my medicines regularly, I can walk and perform my daily life activities, otherwise, it becomes difficult for me to walk even."*

Staying healthy and keeping blood sugar levels within normal limits are key enablers to perform blood sugar testing as reported by many respondents.

> *"I check my blood glucose levels every 2 to 3 days, especially when I am not feeling well." (P4; Male)*

Comorbidities

Comorbidities can limit one's ability to self care. Some participants have a plethora of comorbidities, ranging from joint problems to body pain and fatigue, which restricts them from pursuing regular physical activity. Body pains, especially in the legs and feet, are the most commonly reported barrier to maintaining daily exercise. Some remarks by patients that brought forth this point are

> "*I have been doing a walk regularly. But for the last 6 months, I am not doing a regular walk, because of pain in my legs." (P11; Male)*

Another female participant (P18) further added to this:

> *"For a long time, I am not doing exercise because of the pain in my legs and feet. I got weak now and cannot exercise due to muscles pain."*

Many of the study participants mentioned that they tried to do exercise at the same intensity and duration as their healthcare providers advised them, but fatigue, body pains, and injuries to the knee and hip bone hamper their ability to sustain a regular exercise.

> "*My doctor advised me to do walk, but I can't walk or do any sort of exercise because of my hip bone problem." (P21; Female)*

Some of the participants reported that they were no longer able to do exercise because of their comorbid condition, such as heart problems.

> *"Before having a heart attack I used to do exercise. Now after having a heart attack I cannot do exercise. I feel like my muscles become weak and get exhausted with a light walk." (P4; Male)*

THEME 5: BURDEN OF SELF-CARE

Loving Food

Cravings for particular types of foods, such as desserts, make it difficult for several respondents to avoid sugar and other foods that are restricted in diabetes. One female participant (P1) shared her experience:

> *"I don't strictly avoid sugary food, sometimes I do eat those. I love to eat sweets. One month back someone gifted a pack of sweets to us, my family members kept it inside the refrigerator, so that I should not be aware of it, but once I looked at it, I ate it in the absence of my family and nothing happened to me." (ha-ha.. patient laughs aloud)*

Participants voiced frustration with sacrificing their food liberty. In regard to dietary issues as barriers to their diabetes self care, one participant stated

"*I feel it very difficult to sacrifice my food liberty. I am a food lover and it is hard for me to live a tasteless life, so quite often I enjoy the food of my choice." (P20; Male)*

A female participant (P32) shared her experience:

"Sometimes I do take sweets, for example, I am fond of a traditional sweet 'Halwa,' and I eat it despite knowing the fact that it is full of sugar."

Needle Phobia

Fear of pain associated with fingertip pricking is a reported barrier for frequent SMBG by a few participants. One participant stated

"Doctors advised me to check (blood glucose levels) daily, but I am afraid of needle prick." (P24; Female)

Another male (P30) mentioned a fear of the needle linked with his insulin injections:

"Because of my extensive insulin therapy, I am afraid of needle now,"

Forgetfulness

A few respondents claimed to be negligent in taking their medicine and refilling prescriptions.

"I forget to take medicines sometimes and don't take when medicine stock is finished at home." (P14; Female)

A male participant (P15) further added

"I take my medicines regularly, but sometimes I forget to take, as I feel I am losing memory due to diabetes. I do take insulin with me when I travel outstation and keep it in the refrigerator but still, sometimes I tend to forget."

THEME 6: LIFE CIRCUMSTANCES

Unaffordability

Affordability of healthy food is a commonly mentioned barrier to adopting a recommended diet plan.

"There is no question about the diet plan and food restrictions for a person who can hardly afford two times meal for her, I can hardly manage to buy 250 ml of milk and four slices of bread a day, which I utilize for my whole day and sometimes my neighbors give me bread for my lunch." (P31; Female)

A female participant (P9) further added

"I can't follow the diet plan because the food mentioned in it is difficult to understand and afford. Only rich people can afford such menu and time schedule, like two servants are required to serve it and make you stick with that diet plan. I follow some parts of the diet plan, which I can understand and afford."

A lot of the interviewees admitted that, despite receiving a diet plan, they ate whatever was cooked at their home:

"My doctor gave me a diet plan. I can understand it but cannot follow it due to unaffordability issues, so eat the food which is cooked at home." (P16; Female)

The cost associated with blood glucose monitoring is also reported as one of the reasons why participants did not practice blood glucose testing regularly.

"*I don't have a blood sugar checking facility in my village … above all it is expensive too, and hard for me to afford." (P18; Female)*

Even so, the cost associated with insulin is also reported as a reason for medicine non-adherence:

"*Insulin is very effective, during my job I was provided with free insulin, but as of now I am retired from my job, it's expensive and difficult for me to afford. But the person who discovered insulin God bless him, as he saved millions of lives like mine." (P15; Male)*

A female participant (P18) further added

"I don't have a blood sugar checking facility at my village and its available far away from my home and above all it is expensive and difficult to afford."

Job Is Busy

Hectic work schedules and other job-related responsibilities and obligations are reasons why some of the participants could not adhere to their recommended healthy eating habits. According to one respondent,

"I know to eat less and more frequently, but due to the nature of my job, I cannot adopt it." (P26; Male)

In regard to the medicine intake schedule, one male participant (P12) mentioned

"I do take medicines regularly but due to business when I have to go out of the city, I don't take medicine stock with me for days"

Participants indicated that it was difficult to incorporate recommended physical activities into their daily life due to the hectic nature of their job:

"I do not do regular exercise due to my overburdened job nature." (P26; Male)

Some participants further added to this, citing fatigue due to the tiring nature of their job, which impeded their exercise routine:

"I have no spare time from my work to do exercise, after the job I am so tired to even think of exercise" (P8; Male)

Need to Do Housework

Several participants expressed that they are not required to do regular exercise as they think that their routine life activities are a fair substitute for their exercise. One response pointing this aspect is

"I perform my household work which I consider enough replacement for my exercise." (P21; Female)

Another female participant (P9) further added to this:

"My working at my home and kitchen is my exercise, as I am the only working lady at my home."

Extreme Weather Conditions

Some respondents mentioned that the harsh weather conditions during winter and summer impede their engagement in regular physical activity.

"*I regularly go for a morning walk for about 25 to 30 minutes, except when I had severe body pains and during unfavorable weather conditions, like rain, hot and cold weather. Nearly one month during winter I do not go for a walk due to foggy weather." (P32; Female)*

A similar experience was shared by male respondent (P20):

"*I walk for around one hour daily. But for the last few weeks due to extreme weather conditions [hot weather], I am avoiding my routine walk."*

DISCUSSION

This study explores the perceptions, experiences, enablers, and barriers to diabetes self care by patients with T2DM living in urban areas of Pakistan. Diabetes self care requires adopting a healthy lifestyle in addition to adhering to prescribed medicine and regular blood glucose testing. Overall, participants exhibited a poor knowledge about diabetes, complications associated with diabetes, and the importance of healthy diet and regular exercise.

Counseling by healthcare providers and family support assists the participants for better disease management. Those who are unsuccessful in adopting self care identified several barriers, especially adhering to a healthy diet plan and physical activity. Previously published studies focus on views and self-care experiences of people with diabetes living in rural areas of Pakistan (21, 22).

Support from family members promotes self-care practices among study participants in a variety of ways, including medicine identification, medication administration, blood glucose testing, and managing hypoglycemia. Several participants remarked that they had difficulty in medicine identification and glucometer handling for their blood glucose testing although assistance and encouragement provided by their family members facilitated them in medication adherence. The importance of family support as an enabler to improve medication adherence and blood glucose testing in people with diabetes living in rural areas is reported in both low- and middle-income (4, 36) and high-income countries (1, 8).

Participation in social gatherings, such as wedding ceremonies, is a frequently shared barrier to self care by the participants, because the food served at such occasions is highly unsuitable for people with diabetes. Our results are consistent with those of Tewahido and Berhane (37) and Lekoubou et al. (38), which indicate food related to sociocultural norms poses a significant barrier to effective diabetes management. Healthy eating practices can be improved in people with diabetes by considering the cultural aspects of food and individuals' taste preferences (39).

Living as a joint family is a part of Pakistani culture, and the eating behaviors of family members can influence the eating habits of diabetes patients in the family (40). Cultural norms coupled with affordability issues are posing a lot of difficulties for Pakistani people with diabetes in adopting healthy eating practices (21) as is evident from the fact that most of the study participants mentioned that they had to eat whatever was cooked at home. Our results are also consistent with those of Ansari et al. (21), who find a lack of social and family support in dietary adherence of middle-aged diabetic patients residing in rural areas of Pakistan.

Variable experience with healthcare providers and disease education is shared by the participants. Most of the participants describe education by healthcare providers as one of the major facilitators to their diabetes self care. Interviewees expressed that their physicians were not only a source of information for their medicines, blood glucose level monitoring, diet planning, and hypoglycemia management, their encouragement also supported the participants in improving medication compliance, physical activity, and healthy eating habits. These findings are consistent with many published studies in which the knowledge and reassurance provided by healthcare providers assists participants in behavior modifications and managing their diabetes in a better way (8, 41).

At the same time, a different experience was shared by other interviewees. Concerning the patient–doctor relationship, some participants shared the fact that they were not educated about various aspects of self care. A similar experience of dissatisfaction with physicians' attitudes has been reported by Ansari et al. (21), in which the self-care component of disease management was not discussed with Pakistani people with diabetes dwelling in rural areas.

Hypoglycemia is an acute medical complication and requires immediate identification and management to minimize vital organ damage. Although the incidence rate of hypoglycemic episodes is very low in T2DM patients in the first few years of their diagnosis, it can increase up to 25% with disease progression and the patient's shift to insulin (42). While attaining the target of glycemic control in people with diabetes, prevention of hypoglycemia remains one of the main hurdles (43). In our study, only a few participants shared that they were instructed by their physicians about hypoglycemia and its management at

home. Whereas the majority were unaware of the symptoms of hypoglycemia and its management and urged their physicians to guide them about hypoglycemia and its emergency management at home. Educating people with diabetes about symptoms of hypoglycemia, associated risk factors, and preventive strategies will result in achieving desired health-related outcomes (44).

Delayed and irregular access to healthcare services leads to poor disease management and increased morbidity (45, 46). In our study, an irregular pattern of healthcare access was reported by the participants; patients visit healthcare facilities only when they are experiencing ill symptoms, in case of a medical emergency, to refill their prescription for free medicine, and for free blood sugar testing. Unaffordability, low education levels, and poor counseling by healthcare professionals about the importance of regular medical visits are the main barriers to regular healthcare facility visits.

Surprisingly, the majority of interviewees stated that their diabetes diagnosis was unexpected: They were suffering from diabetes symptoms, but they did not know that these symptoms were due to diabetes. Family and friends were the source of information for diabetes and its associated symptoms, which mentally prepared the participants for healthcare facility visits and arriving at their diabetes diagnosis.

After being diagnosed with diabetes, many of the participants in our study believed that diabetes was a curable disease. A realm of myths about the cause of diabetes was cited by study participants. Some attributed cause of their diabetes to herbal medicine use, depression, and as a consequence of medication side effects.

Self-perception about their health is a strong facilitator that emerged from this study. In the case of chronic diseases, illness perceptions can shape a positive framework that promotes self-care (47). Fear of complications due to poorly controlled diabetes motivates study participants to adhere to their therapeutic regimens. Broadbent et al. (48) also report similar findings, in which adherence to medication, physical activity, and diet is significantly influenced by patients' diabetes perceptions.

Several barriers to self-care practices emerge from this study. These barriers include financial constraints, the hectic nature of their job, physical limitations, needle phobia, a food-loving nature, and extreme weather conditions. Unintentional non-adherence to medicine due to financial constraints and being over-occupied with a job among Pakistani people suffering from chronic diseases are also reported in another recently published study (30). Injection site pain, unaffordability, and being fed up with routine medicine intake significantly reduces medication compliance and frequency of blood glucose testing.

Cravings for specific foods coupled with unaffordability are among serious challenges that make dietary adjustments difficult for people with diabetes. High costs associated with healthy food choices make it difficult to adopt recommended dietary practices for patients with chronic diseases with a low socioeconomic status (27, 29).

Physical activity in people with diabetes is an important aspect of effective glycemic control and controlling the progression of the disease. Adopting healthy lifestyle modifications, especially physical activity, are frequently reported barriers in many studies (49, 50). Similar to the finding of Lawton et al. (28), in our study, the hectic nature of the job, suffering from comorbid conditions, and extreme weather conditions are commonly reported barriers to physical activity. Several myths are also observed, such as respondents (especially housewives) thinking that their household work was a fair replacement for their exercise.

Our study findings have some practical implications for the healthcare system of Pakistan. First, the inadequate knowledge about a healthy diet and the importance of exercise necessitates healthcare providers to educate their patients about these important aspects of diabetes self care by dedicated face-to-face educational sessions supplemented with informational leaflets and other relevant materials. Second, self-care education must also include information about the causes, complications, and prognosis of diabetes and should be tailored to the cultural perspective and individual patient needs.

Limitations

Although our study presents new insights into the practices and experiences of T2DM patients in urban areas of Pakistan, there are a few limitations. First, being a qualitative study, one of the limitations is its possible selection bias. Second, there is gender asymmetry in our study participants. Third, self-care practices have not been explored with respect to socioeconomic status and educational background of the study participants. We planned to recruit an equal number of male and female T2DM patients, but due to a higher proportion of female patients at the data-collection sites, more females volunteered for the study. However, it is important to bear in mind the qualitative design of the study, in which the objective of the study is in-depth exploration of problem rather than generalizability.

Conclusion

Overall, study participants demonstrated poor knowledge about diet planning, the importance of regular exercise, blood sugar testing, and hypoglycemia management. The interviewees also demonstrated the need for counseling by their healthcare providers for diabetes-related self-care practices. Barriers to self care received more prominence in comparison to the facilitating factors. Thus, catering to the informational needs of people with diabetes by an individualized and culturally sensitive self-care educational program should be considered an ideal approach to achieve the desired therapeutic outcomes. Patient education and motivation for appropriate diabetes self care are of paramount importance to improve patients' disease knowledge and self-care practices. The findings of this study will help in designing culturally appropriate and patient-tailored self-care educational interventions for people with diabetes in Pakistan.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study will be made available by the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Monash University Human Research Ethics Committee (MUHREC; Approval Number 7767) and the data collection centers in Pakistan. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB and TK: study concept and design. AB: data collection. AB, TK, and EZ: analysis or interpretation of data. AB, TK, and EZ: thematic analysis. AB, TK, B-HG, CL, K-GC, and SZ: administrative and technical or material support. TK, B-HG, SZ, K-GC, and CL: study supervision. AB: drafting of manuscript. TK, B-HG, SZ, K-GC, and CL: critical revision of the manuscript for important intellectual content.

ACKNOWLEDGMENTS

The authors of the study acknowledge the Pakistani people with diabetes who participated in this study and Monash University Malaysia for providing a Ph.D. merit scholarship to the first author of this study. K-GC thanks the University of Malaya Research Grant (FRGS Grant No. FP022-2018A).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2020.534873/full#supplementary-material

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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.

frontiers in Endocrinology

SYSTEMATIC REVIEW
published: 30 March 2021
doi: 10.3389/fendo.2021.617902

Sex Disparities in Cardiovascular Risk Factor Assessment and Screening for Diabetes-Related Complications in Individuals With Diabetes: A Systematic Review

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OPEN ACCESS

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

Received: 15 October 2020
Accepted: 11 February 2021
Published: 30 March 2021

Citation:
de Jong M, Peters SAE, de Ritter R, van der Kallen CJH, Sep SJS, Woodward M, Stehouwer CDA, Bots ML and Vos RC (2021) Sex Disparities in Cardiovascular Risk Factor Assessment and Screening for Diabetes-Related Complications in Individuals With Diabetes: A Systematic Review. Front. Endocrinol. 12:617902. doi: 10.3389/fendo.2021.617902

Background: Insight in sex disparities in the detection of cardiovascular risk factors and diabetes-related complications may improve diabetes care. The aim of this systematic review is to study whether sex disparities exist in the assessment of cardiovascular risk factors and screening for diabetes-related complications.

Methods: PubMed was systematically searched up to April 2020, followed by manual reference screening and citations checks (snowballing) using Google Scholar. Observational studies were included if they reported on the assessment of cardiovascular risk factors (HbA1c, lipids, blood pressure, smoking status, or BMI) and/or screening for nephropathy, retinopathy, or performance of feet examinations, in men and women with diabetes separately. Studies adjusting their analyses for at least age, or when age was considered as a covariable but left out from the final analyses for various reasons (i.e. backward selection), were included for qualitative analyses. No meta-analyses were planned because substantial heterogeneity between studies was expected. A modified Newcastle-Ottawa Quality Assessment Scale for cohort studies was used to assess risk of bias.

Results: Overall, 81 studies were included. The majority of the included studies were from Europe or North America (84%).The number of individuals per study ranged from 200 to 3,135,019 and data were extracted from various data sources in a variety of settings. Screening rates varied considerably across studies. For example, screening rates for retinopathy ranged from 13% to 90%, with half the studies reporting screening rates less

than 50%. Mixed findings were found regarding the presence, magnitude, and direction of sex disparities with regard to the assessment of cardiovascular risk factors and screening for diabetes-related complications, with some evidence suggesting that women, compared with men, may be more likely to receive retinopathy screening and less likely to receive foot exams.

Conclusion: Overall, no consistent pattern favoring men or women was found with regard to the assessment of cardiovascular risk factors and screening for diabetes-related complications, and screening rates can be improved for both sexes.

Keywords: diabetes, sex disparities, risk factors, diabetes-related complications, healthcare provision, screening, systematic review

INTRODUCTION

In 2019, an estimated 463 million adults aged between 20 and 79 years had diabetes, affecting 9.0% of women and 9.6% of men globally. Cardiovascular diseases (CVD) are one of the most common complications of diabetes, with individuals with diabetes being two to three times more likely to develop CVD compared to those without diabetes (1). Other common diabetes-related complications include diabetic nephropathy, retinopathy, neuropathy, certain cancers, physical and cognitive impairment, depression and several types of infectious diseases (1, 2).

Although incidence rates of major CVD have been reported to be higher in men than women with and without diabetes (3, 4), there is a growing body of evidence showing that the relative risk of major cardiovascular complications conferred by diabetes is larger in women than men (2–8). Several large studies have shown that the relative risk of ischemic heart disease conferred by diabetes can be up to 50% higher in women than men (3, 5, 8). A sex differential in the consequence of diabetes has also been reported for stroke, where the relative risk of stroke was 27% higher among women than men (6). Less is known about sex differences in the effects of diabetes on microvascular complications. A meta-analysis has demonstrated that diabetes confers a 19% higher relative risk of vascular dementia in women than men (9). Sex differences have also been shown for end-stage renal disease, but not for chronic kidney disease (10).

Underlying mechanisms that explain the higher excess risk of (vascular) complications, conferred by diabetes, in women remain uncertain but may include sex disparities in the uptake and provision of healthcare (2). Currently, many guidelines on diabetes management exist. These evidence-based guidelines provide similar recommendations for both sexes on the assessment of risk factors and screening for diabetes-related complications. Therefore, throughout this systematic review, the term "disparity" will be explicitly used to refer to differences in risk factor assessment and screening for cardiovascular risk factors between men and women.

More insight in sex disparities concerning the uptake and provision of diabetes management may eventually result in more personalized diabetes care, thereby helping to further diminish the burden in both sexes. We conducted a systematic review to study whether sex disparities exist in the assessment of cardiovascular risk factors and screening for diabetes-related complications among people with diabetes.

METHODS

The protocol of this study was registered at the international prospective register of systematic reviews (PROSPERO) registry (registration number: CRD42018104414). We performed this review according to the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (11).

Search Strategy and Study Selection

Observational studies (including before-after studies) on the assessment of cardiovascular risk factors (HbA1c, lipids, blood pressure, BMI, and smoking status), and screening for complications (retinopathy, nephropathy, and foot ulcerations/deformities/sensory decline), in men and women with diabetes, were identified through systematically searching PubMed (1/1/2009 up to April 2020) (**Supplemental Table I**). After having identified a set of eligible studies using our search strategy, we performed manual reference and citation screening (snowballing) using Google Scholar. This method has previously been described as a good alternative to database searches once a number of eligible studies have been identified (12). Studies were included if data on the assessment of cardiovascular risk factors or screening for diabetes-related complications were provided separately for men and women. Studies presenting insufficient information about the effect size or direction of sex disparities were excluded (i.e. studies only presenting p-values). Only full-text articles written in English or Dutch were considered eligible for inclusion. Studies also including individuals without diabetes were eligible if results for individuals with diabetes were presented separately. Studies on gestational diabetes were excluded, as well as studies on which data on risk factor assessment were only adjusted for, rather than analyzed by, sex. Furthermore, studies primarily focusing on children or adolescents were excluded.

Outcomes

The outcomes of interest were; assessment of HbA1c, lipids, blood pressure, smoking status, and BMI, screening for

nephropathy, retinopathy, and performance of foot examinations, or any combination, all reported as binary variables (yes vs. no). For all outcomes of interest, we used "assessment of cardiovascular risk factors" and "screening for complications" as defined by the original article. When studies showed multiple outcome definitions, we chose the one closest to (inter)national guidelines.

Data Collection and Management

Data extraction was performed by one author (MJ) and checked by a second author (RV). Any discrepancies between the authors during data collection were discussed with a third author (SP). The extracted data comprised: authors' names and year of publication, country, study period, number of participants (% women), age, reported outcomes (including measures of association with corresponding confidence intervals (CIs)), and data source (**Supplemental Table II**).

Quality Assessment

The methodological quality of the included studies was assessed by one author (MJ) and checked by a second author (RV), using a modified Newcastle-Ottawa Quality Assessment Scale for cohort studies (13). The modified scale includes six items under three categories: selection, comparability and outcome. Any discrepancies were discussed with a third author (SP).

Data Synthesis and Analyses

It was decided beforehand not to perform any meta-analyses due to the expected heterogeneity between the included studies. Qualitative analyses were restricted to studies adjusting their analyses for age or when age was considered as an important covariable but left out from the final analyses for various reasons (i.e. backward selection). Studies only presenting crude numbers and percentages or unadjusted results are presented in **Supplemental Table III**. Where reports with overlapping study populations were found and similar outcomes of interest were studied, the study presenting data from the most recent study period or the study with most participants was included. Similarly, where studies were repeated over time, only studies with the most recent data or largest number of study participants were included. For example, the UK National Diabetes Audit is repeated every year and only data from the most recent report relevant for the outcomes of interest were extracted. Characteristics of the studies excluded from qualitative analyses are shown in **Supplemental Table IV**.

The results are presented as odds ratios (ORs) or risk ratios (RRs) with 95% CIs, with men as the reference category, unless otherwise specified. When studies only reported stratified results, e.g. by age group, ORs/RRs and the 95% CIs in each stratum were summarized using a fixed effect model. For studies that stratified the results by year, with potential overlap of included participants between strata, results from the most recent year were extracted. If studies presented multiple models, only the most extensive adjusted models were extracted. Forest plots without pooled effects were used to visualize the adjusted estimates and corresponding CIs across studies included for qualitative analysis.

RESULTS

Overall, 81 studies were included for qualitative analyses (14–92) (**Figure 1**). Characteristics of the included studies are presented in **Supplemental Table II**. The majority of studies were from Europe or Northern America (37% and 47% respectively), eight from Asia, two from Oceania, one from Africa, and one from South America. Of the 81 studies, 55 (68%) reported data on individuals with diabetes (without specifying the subtype), and 24 (30%) on individuals with type 2 diabetes. In addition, two

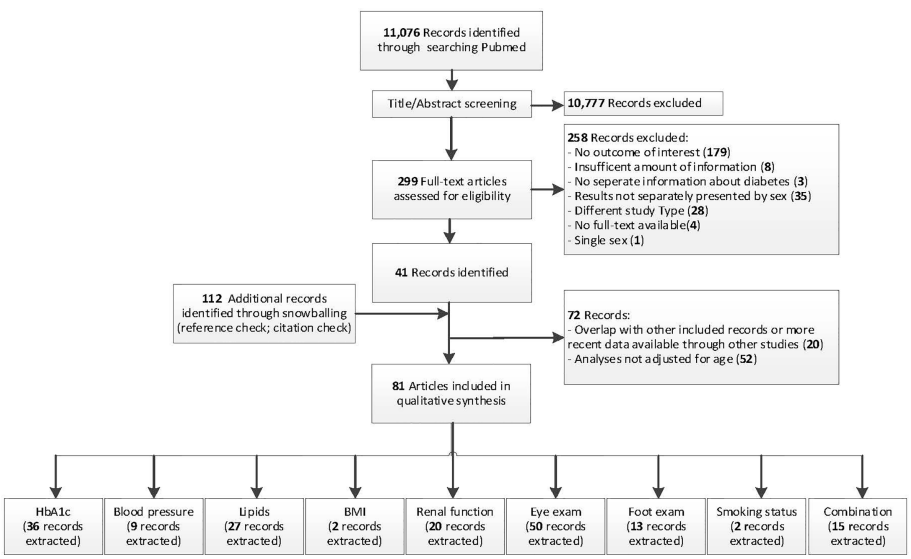

FIGURE 1 | Flowchart of study selection. PubMed search was used to obtain a suitable start set for snowballing.

reports from the UK National Diabetes Audit reported data on individuals stratified by diabetes subtype. Given that no other reports presented data on individuals with type 1 diabetes, only data from individuals with type 2 diabetes were extracted from the two reports. The number of included individuals per study ranged from 200 to 3,135,019. Data were extracted from various data sources (i.e. (population-based) surveys, medical records and administrative claims data) in a variety of settings, including primary care, outpatient clinics, and hospital settings.

Risk of Bias

The risk of bias was moderate with 78% of studies showing either fair or good study quality with clearly reported information about study design, in- and exclusion criteria, data collection, and assessment of the outcome. Although most studies included a representative sample, there was considerable heterogeneity between studies with regard to the study populations making it more challenging to score this aspect **(Supplemental Table IV).**

Assessment of HbA1c

In total, 36 studies, including 6.6 million individuals, were included with median assessment rates of 74% in women and 73% in men. Most studies showed no statistically significant sex disparities in the assessment of HbA1c (70%), while 19% showed that women were more often receiving assessment of HbA1c than men, and 11% showed that men were more often receiving assessment of HbA1c than women **(Figure 2).**

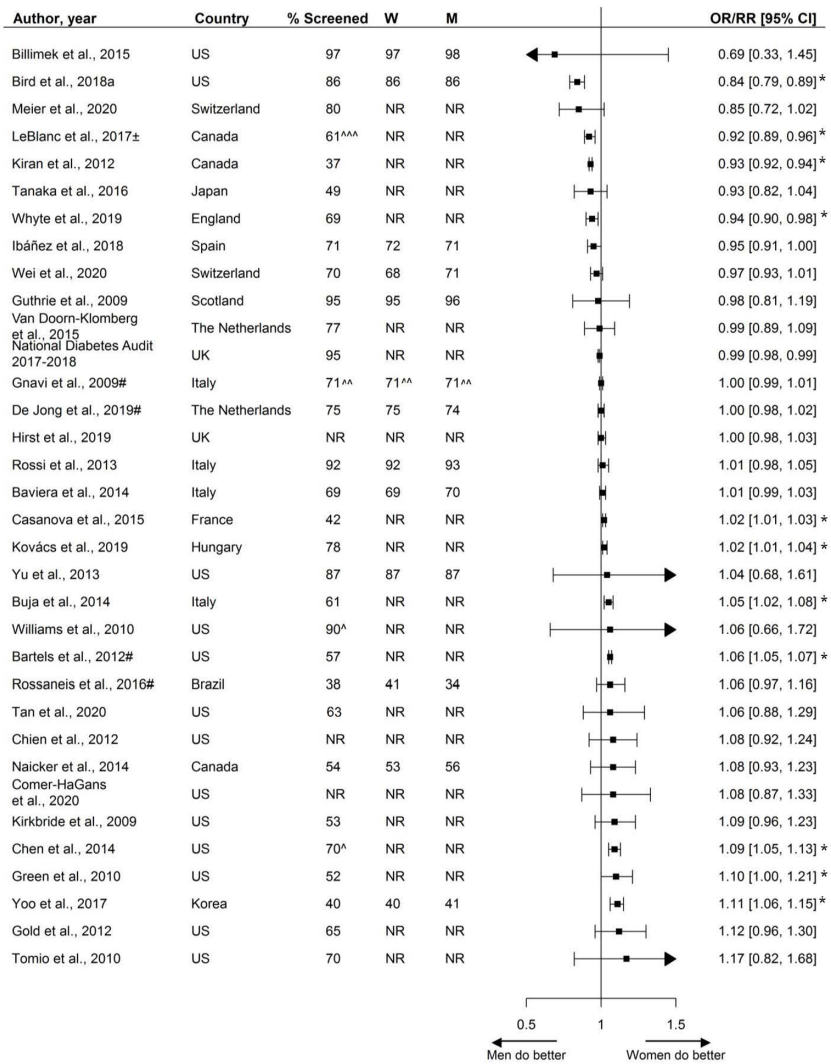

FIGURE 2 | Assessment of HbA1c, expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). Two studies are not presented in this figure because of their measure of association: Swietek et al. (33): Average Marginal Effect, (SE; p-value): –0.00031 (–0.0044; >0.05), Du et al. (92): Prevalence difference (95% CI): 3.5 (–1.0;8.0). W = % of screened women; M = % of screened men; US, United States; UK, United Kingdom; ± = 99% CI; # = Relative risk; ^ Weighted %; ^^ = Kaplan-Meyer estimates; ^^^ = Estimated %; * = statistically significant. Men = reference.

Assessment of Blood Pressure

The assessment of blood pressure, by sex, was reported by nine studies including 3.7 million individuals. Median assessment rate across studies was 79% (range 48% - 98%). Sex-specific percentages of blood pressure assessment were reported by three studies, ranging from 78% to 94% in women and 77% to 96% in men. Five studies showed no statistically significant disparities in the assessment of blood pressure, while three studies showed that women were more likely to receive blood pressure screening and one study reported men being more likely to receive blood pressure screening (**Figure 3**).

Assessment of Lipids

The assessment of lipids, by sex, was reported by 27 studies, including 5.4 million individuals. These studies reported on various lipid measurements, including the assessment of LDL, HDL, lipid profile, (total) cholesterol, HDL/TC-ratio, and triglycerides. Among the fifteen studies reporting the assessment of either lipids or (total) cholesterol, assessment rates ranged from 40% to 96%, with a median of 73%.

Over half the studies (8/15) reported no statistically significant or only small sex disparities, while four studies reported that, compared with men, women were less likely to receive screening, and three studies showed that women were more likely to receive screening.

Twelve studies, including data from 829,819 individuals, reported sex-specific assessment of LDL. Five studies reported that women were less likely to receive screening, four studies reported that women were more likely to receive screening than men, and the remaining three studies showed no sex disparities.

Two studies investigated sex disparities in the assessment of HDL measurements, with one reporting that women were more likely to receive screening.

One study reported on the assessment of triglycerides, showing that women were less likely to receive screening than their male counterparts (**Figure 4).**

Assessment of BMI

Two studies reported sex-specific BMI assessment; one study found that women were less likely to receive screening and the other found no sex differences (**Figure 5**).

Nephropathy Screening

Twenty studies, including 3.9 million individuals, examined sex disparities in nephropathy screening. These studies reported on various measures to assess renal function, including estimated glomerular filtration rate (eGFR), microalbuminuria, urine albumin, albumin/creatinine ration, and serum creatinine. Two-thirds of studies reported screening rates less than 70%. Overall, there was no consistent pattern in nephropathy screening favoring either women or men (**Figure 6**).

Retinopathy Screening

Fifty studies, including 3.4 million individuals, reported on retinopathy screening. Screening rates ranged from 13% to 90% across studies, with nearly half the studies reporting screening rates equal to or less than 50%. Five studies reported that women were less likely to receive retinopathy screening than men and 22 studies showed that women were more likely to receive screening (**Figure 7**).

Foot Exams

Thirteen studies, including over 3.9 million individuals, reported on the sex-specific performance of foot exams. Screening rates varied from 13% to 99% across studies, with a median screening rate of 58%. Six reported that women were less likely to receive foot exams, and one study reported women being more likely to receive foot exams. The other studies reported no sex differences (**Figure 8**).

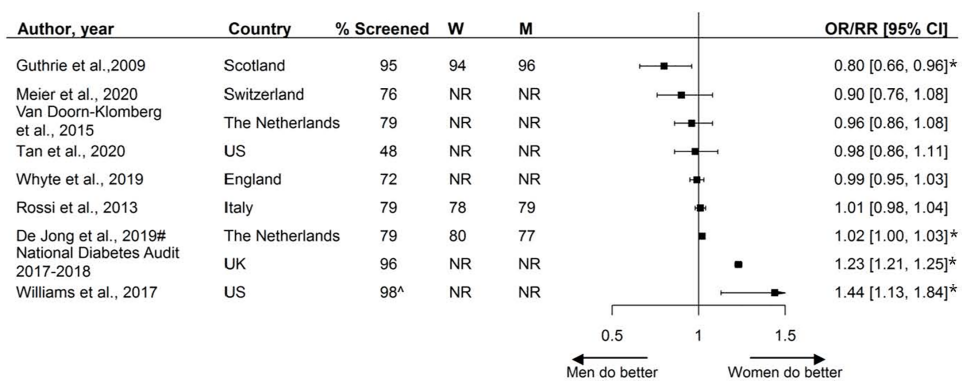

FIGURE 3 | Assessment of blood pressure, expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). W = % of screened women; M = % of screened men; US, United States; UK, United Kingdom; # = Relative risk; ^ Assumed to be weighted %; * = statistically significant. Men = reference.

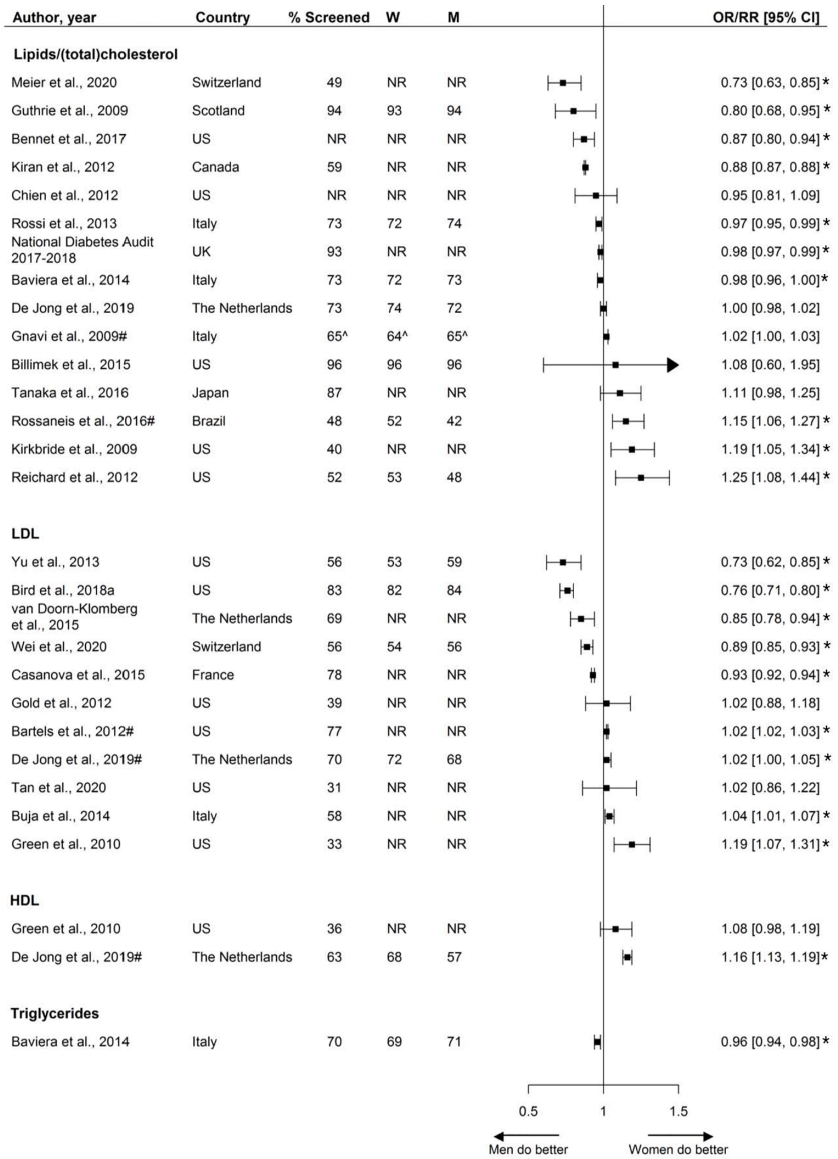

FIGURE 4 | Assessment of lipids, expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). One study is not presented in this figure because of the measure of association: Swietek et al. (33): Average Marginal Effect (LDL), (SE; p-value): 0.0045 (–0.0042; >0.05). W = % of screened women; M = % of screened men; US, United States; UK, United Kingdom; # = Relative risk; ^ = Kaplan-Meyer estimates; * = statistically significant. Men = reference.

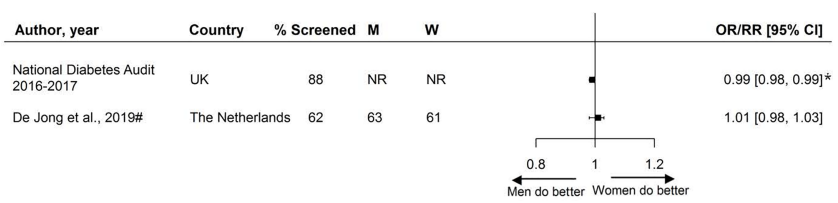

FIGURE 5 | Assessment of BMI, expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). W = % of screened women; M = % of screened men; UK, United Kingdom; # = Relative risk. Men = reference. * = statistically significant.

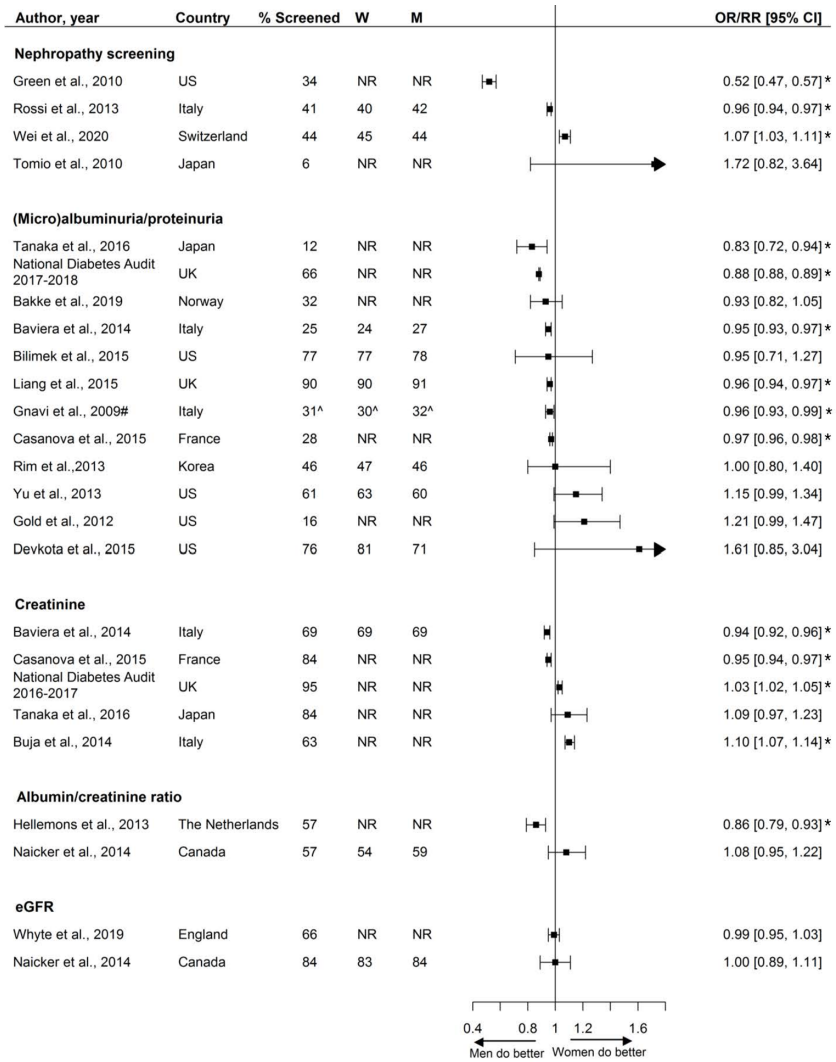

FIGURE 6 | Nephropathy screening, expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). One study is not presented in this figure because of the measure of association: Swietek et al. (33): Average Marginal Effect, (SE; p-value): –0.0073 (–0.0042; <0.05 (women less likely to receive screening). W = % of screened women; M = % of screened men; US, United States; UK, United Kingdom; # = Relative risk; ^ = Kaplan-Meyer estimate. Men = reference. * = statistically significant.

Assessment of Smoking Status

Two studies reported on the assessment of smoking status. Both studies found high screening rates (95%), and women were more likely to be screened for smoking status than men (**Figure 9**).

Combination

Fifteen studies reported on the assessment of a combination of risk factors and screening activities. The presence and direction of sex disparities varied across studies, with a third of the included studies reporting that, compared with men, women were less likely to receive a combination of care, one-third of studies found no sex disparities, and one-third found that women were more likely to receive a combination of care than men (**Figure 10**).

DISCUSSION

This systematic review including 81 studies showed that the presence, magnitude, and direction of sex disparities in the assessment of cardiovascular risk factors and screening of diabetes-related complications varied considerably across studies, with some evidence suggesting that women, compared with men, may be more likely to receive retinopathy screening and less likely to receive foot exams. In addition, only two studies reported on the assessment of smoking status; both showing that women were more likely to be screened. Overall, screening rates can be improved for both sexes.

To our knowledge, this is the first systematic review studying sex disparities in the assessment and screening of cardiovascular

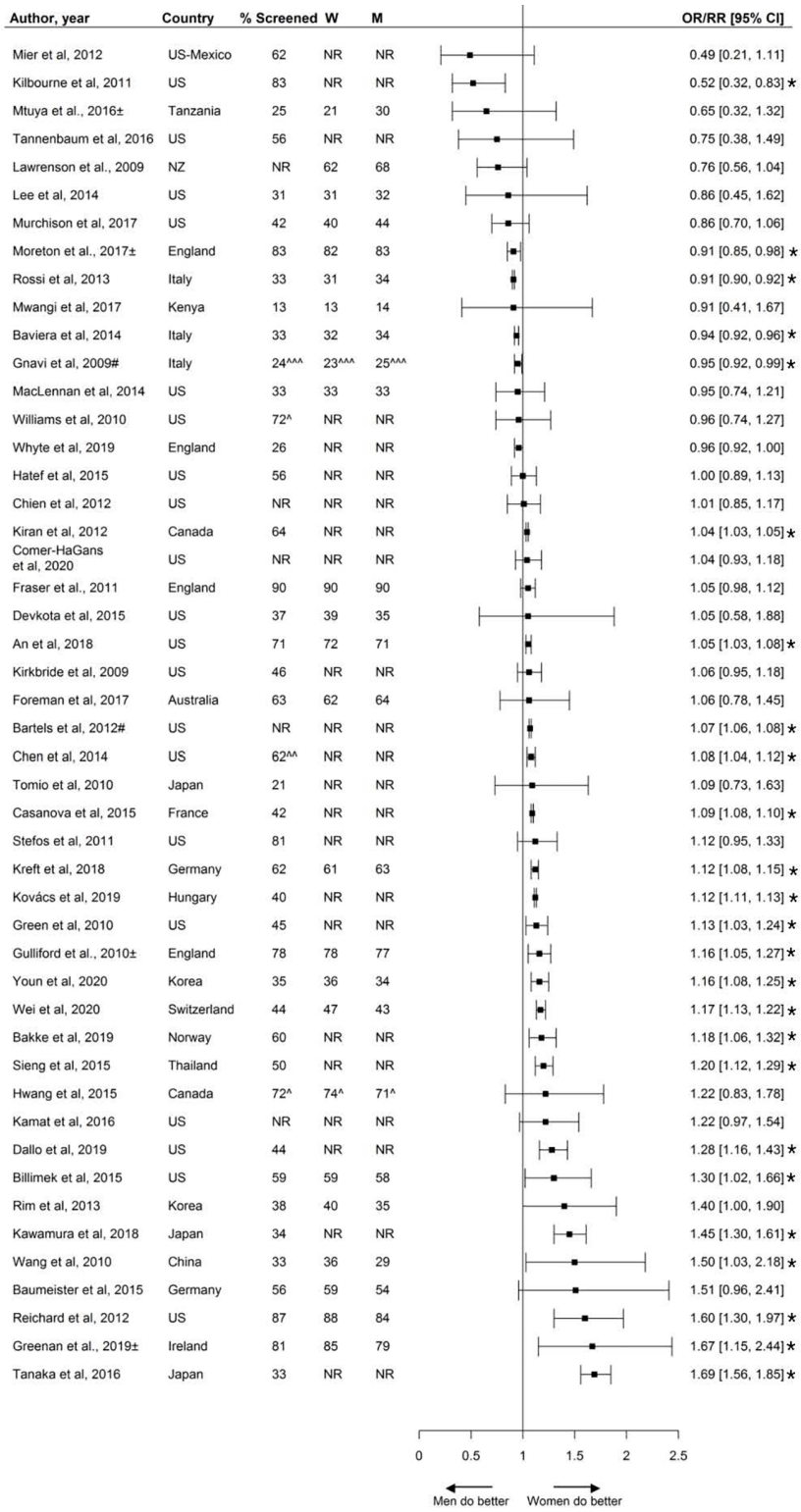

FIGURE 7 | Retinopathy screening, expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). Two studies are not presented in this figure because of their measure of association: Swietek et al. (33): Average Marginal Effect, (SE; p-value): 0.017 (–0.0043; <0.01 (women more likely to receive screening), Du et al. (92): Prevalence difference (95% CI): 12.6 (4.1;21.2). W = % of screened women; M = % of screened men; US, United States; UK, United Kingdom; # = Relative risk; ^ = 662 weighted %; ^^ = assumed to be weighted %; ^^^ = Kaplan-Meyer estimate; ± = Studies assessing screening adherence after screening invitation. Men = reference. * = statistically significant.

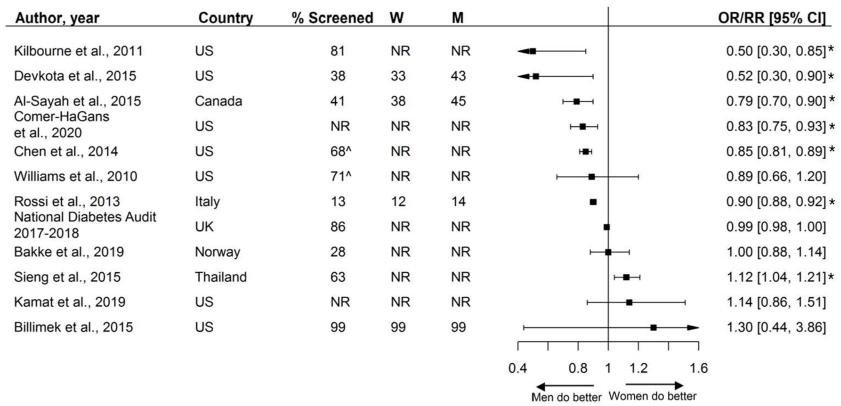

FIGURE 8 | Foot exams, expressed as adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI). One study is not presented in this figure because of the measure of association: Du et al., (92): Prevalence difference (95% CI 4.2 (–6.4; 14.9).W = % of screened women; M = % of screened men; US, United States; UK, United Kingdom; ^ = assumed to be weighted %. % Chen et al. extracted from the last available year. Men = reference. * = statistically significant.

risk factors and diabetes-related complications among individuals with diabetes. A recent meta-analysis, including 22 studies with 4,754,782 individuals from the general population in primary care setting, showed that assessment rates of CVD risk scores and risk factors were similar between the sexes (93). In contrast to our study, the authors did find evidence of women being less likely to be assessed for smoking (93). Nevertheless, the results were comparable to our study in that no consistent pattern in risk factor assessment and complication screening favoring either men or women was found and screening rates could be improved for both sexes.

Assessment of cardiovascular risk factors and screening for diabetes-related complications is critical in guiding treatment decisions. The present study demonstrates that there is no consistent pattern in screening activities favoring men or women, suggesting that disparities in risk factor assessment and screening activities do not account for the higher relative risk of CVD conferred by diabetes previously found in women compared with men (2–8). However, other factors related to the uptake and provision of healthcare, such as treatment and adherence, may still be involved in explaining these sex differences. Although assessment of cardiovascular risk factors is one of the first steps in guiding treatment decisions, it may not necessarily be followed by equal treatment. For example, a recently published meta-analyses, including data from 2.2 million individuals in primary care, showed that women at high risk or with established CVD were less likely to be prescribed aspirin, statins, and angiotensin-converting enzyme (ACE) inhibitors, and more likely to be prescribed diuretics, than men (94). Other studies have suggested that women are less adherent to statins than men (95–97). Differences in biology may also impact women's excess risk of CVD and it has previously been hypothesized that women experience a relatively greater increase of cardiovascular risk factor levels in the transition from normal glycaemia to diabetes (98). Differences in body anthromorphy and fat storage may be of particular interest in explaining the women's excess risk of CVD, as fat distribution differs by sex. Sex differences in fat distribution may impact the duration of the transition from normoglycemia to overt diabetes and consequently impact the increase of other related cardiovascular risk factor levels (2).

Strengths and Limitations

The main strength of this systematic review is the inclusion large number of studies providing sex-specific data. The majority of studies included more than 1000 individuals, of which 41 (51%) studies included over 10.000 individuals. This study also has several limitations. First, there was substantial heterogeneity between studies regarding patient population, outcome definitions, and data source and no meta-analyses were performed. Second, there was a lack of studies that specifically evaluated risk factor assessment in individuals diagnosed with type

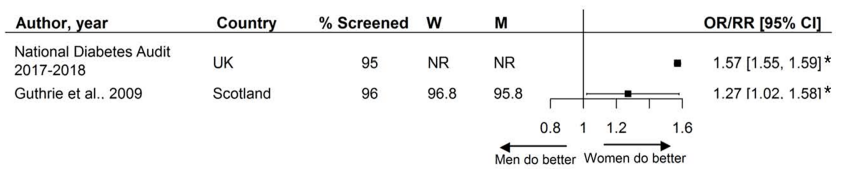

FIGURE 9 | Assessment of smoking status, expressed as adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI). W = % of screened women; M = % of screened men; Men = reference. * = statistically significant.

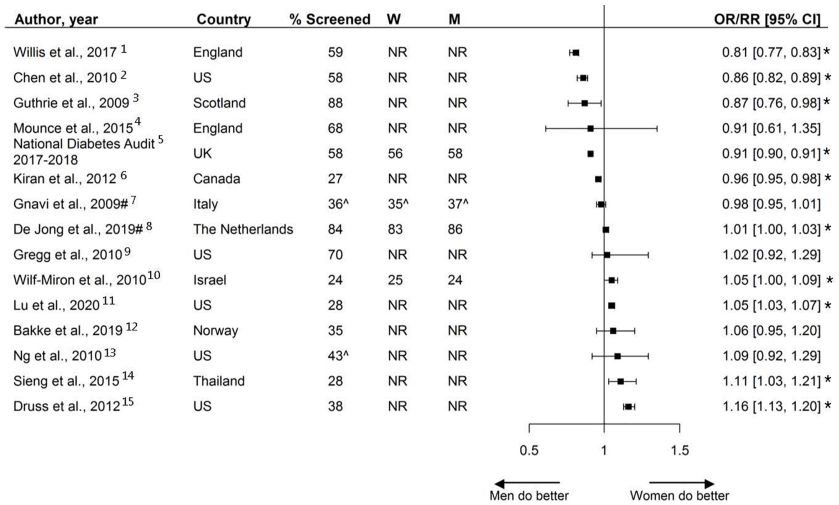

FIGURE 10 | Combination of risk factor assessment and screening, expressed as adjusted odds ratios (OR) or risk ratios (RR) with corresponding 95% confidence intervals (CI). # = risk ratio; ^ = Kaplan-Meyer estimates; * = statistically significant. W = % of screened women; M = % of screened men; Men = reference. 1 = All measurements received within 12 months: blood pressure, HbA1c, cholesterol, urine albumin: creatinine ratio/protein:creatinine or proteinuria, eGFR or serum creatinine, foot and eye exams, BMI, smoking status, within 15 months (6 for HbA1c). 2 = Receiving at least 2 HbA1c measurements and 1 LDL measurement received within 12 months. 3 = All measurements received within 12 months: HbA1c, blood pressure, cholesterol, smoking status. 4 = At least one of the following measurements received within 12 months: HbA1c, proteinuria, foot exam. 5 = All measurements received within 15 months: HbA1c, blood pressure, cholesterol, serum creatinine, urine albumin, foot exam, BMI, smoking status. 6 = All measurements received within 24 months: eye exam, four HbA1c tests, and two cholesterol tests. 7 = Assessment of HbA1c and at least two measurements from among eye exams, total cholesterol, and microalbuminuria. 8 = Receiving one or more measurements within 12 months: HbA1c, blood pressure, total cholesterol, LDL, HDL, or BMI. 9 = All measurements received within 36 months: HbA1c, lipid profile, urine albumin, eye exam, and foot exam. 10 = All measurements received within 12 months: HbA1c, LDL, microalbuminuria, eye and foot exams, blood pressure and BMI. 11 = All measurements received within 12 months: HbA1c, LDL, eye exam, and medical attention for nephropathy (including screening and treatment). 12 = Receiving at least two out of three measurements: albuminuria and monofilament (foot exam) within 12 months, eye exam within 30 months. 13 = Receiving all measurements within 12 months: HbA1c, eye and foot exams. 14 = Receiving all measurements within 12 months: HbA1c, LDL, eye and foot exams. 15 = Receiving at least 2 measurements: HbA1c during 708 the measurement year, eye exam, LDL, and medical attention for nephropathy (screening test during the past year or evidence of nephropathy).

1 diabetes. Of the studies that included individuals with diabetes without specifying the subtype, we assume that majority of the included study participants were diagnosed with type 2 diabetes. The results of this systematic review are therefore mainly applicable to those with type 2 diabetes. An appropriate method to study sex disparities separately for type 1 and type 2 diabetes would be an individual participants data (IPD) analysis, and future research should attempt to obtain individual-level patient data. Third, the majority of studies were from Europe and Northern America, thereby limiting the generalizability to other parts of the world. Fourth, screening rates varied widely between studies and across the outcomes of interest and can be improved for both sexes, nonetheless strategies on how to improve these rates are not discussed in this review. Further research is needed to explore the reasons for the suboptimal screening rates found in both sexes within the context of local and national healthcare settings.

CONCLUSION

Mixed findings were found regarding the presence, magnitude, and direction of sex disparities with regard to the assessment of cardiovascular risk factors and screening for diabetes-related complications. Overall, no consistent pattern favoring men or women was found and screening rates can be improved for both sexes.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

RV, SP, MB, and MJ conceived the research. MJ and RV conducted the analyses and drafted the manuscript. All authors contributed critical intellectual content and made important revisions to the manuscript. RV is the guarantor of this work. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Netherlands Organization forHealth Research and Development (ZonMw), Gender andHealth Programme (Project no 849200001).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.617902/full#supplementary-material

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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.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 14 April 2021
doi: 10.3389/fendo.2021.603277

Preterm Birth and Birth Weight and the Risk of Type 1 Diabetes in Chinese Children

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OPEN ACCESS

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

Received: *06 September 2020*
Accepted: *12 March 2021*
Published: *14 April 2021*

Citation:
Huang K, Si S, Chen R, Wang C, Chen S, Liang Y, Yao H, Zheng R, Liu F, Cao B, Su Z, Mireguli M, Luo F, Li P, Du H, Zhu M, Yang Y, Cui L, Yu Y and Fu J (2021) Preterm Birth and Birth Weight and the Risk of Type 1 Diabetes in Chinese Children. Front. Endocrinol. 12:603277. doi: 10.3389/fendo.2021.603277

Aims: Findings from previous studies about the association of preterm birth as well as birth weight with the risk of T1DM were still inconsistent. We aimed to further clarify these associations based on Chinese children and explore the role of gender therein.

Methods: A nationwide multicenter and population-based large cross-sectional study was conducted in China from 2017 to 2019. Children aged between 3 and 18 years old with complete information were included in this analysis. Multiple Poisson regression models were used for evaluating the associations of birth weight as well as preterm birth with T1DM in children.

Results: Out of 181,786 children, 82 childhood T1DM cases were identified from questionnaire survey. Children with preterm birth (<37 weeks) had higher risk of type 1 diabetes (OR: 3.17, 95%CI: 1.76-5.71). Children born with high birth weight (≥4,000g) had no statistically significant risk of T1DM (OR:1.71, 95%CI: 0.90-3.22). However, children's gender might modify the effect of high birth weight on T1DM (girls: OR: 3.15, 95%CI: 1.33-7.47; boys: OR: 0.99, 95%CI: 0.38-2.55, *p* for interaction=0.065). In

addition, children with low birth weight were not associated with T1DM (OR: 0.70, 95%CI: 0.24-2.08). The findings from matched data had the similar trend.

Conclusions: In China mainland, preterm birth increased the risk of childhood T1DM, but high birth weight only affected girls. Therefore, early prevention of T1DM may start with prenatal care to avoid adverse birth outcomes and more attention should be paid to children with preterm birth and girls with high birth weight after birth.

Keywords: China, preterm birth, birth weight, type 1 diabetes, gender difference

HIGHLIGHTS

What is already known about this subject?

- Some previous studies, including meta-analyses, have indicated that preterm birth and high birth weight had higher risk for childhood type 1 diabetes, but inconsistent results are still emerging.

What is the key question?

- Whether the associations between preterm birth and birth weight and type 1 diabetes based on Chinese children are different for other countries and whether the gender plays a role therein?

What are the new findings?

- Preterm birth was associated with higher risk of childhood T1DM in China.
- High birth weight was only associated with higher risk for T1DM in girls, which had not been reported before.

How might this impact on clinical practice in the foreseeable future?

- Prevention of T1DM may start with prenatal care to avoid adverse birth outcomes.
- More attention should be paid to children with preterm birth and girls with high birth weight after birth to improve the adverse effects.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an immune-mediated disease characterized by destruction of pancreatic β-cells, resulting in absolute insulin deficiency (1). The incidence of T1DM is increasing globally with an average annual increase of 3–4% (2). Although, China is at low incidence of T1DM, the incidence among children under 15 years old increased from 0.51 per 100,000 in 1985-1994 to 1.93 per 100,000 in 2010-2013 (3). Human leucocyte antigen (HLA) genotypes is thought to be the major genetic contribution to T1DM but genetic factors fail to completely account for its rapid increase and regional differences under similar genetic background (4–6). In the last 2 decades, there is an increasing clinical interest in birth history. Perinatal factors, including preterm birth and birth weight, have been thought to play an important role in T1DM (2, 7). The estimated rate of preterm birth (gestational age < 37 weeks), low birth weight (<2,500g) and high birth weight (≥4,000g) in China were approximately 6.9%, 4.0% and 7.6%, respectively (8–10). Although previous meta-analyses have shown that preterm birth as well as high birth weight was associated with increased risk of T1DM and low birth weight was not associated with significantly decreased risk of T1DM, several limitations existed as highlighted by authors. For example, lack of consistent adjustment for appropriate confounding factors and most studies were conducted in Europe, America and Australia, which might limit the findings to be extrapolated to population in other countries (11–13). Moreover, inconsistent results are still emerging recently. The latest findings from Swedish cohort of over 4 million people published in 2020 reported that preterm birth (22-36 weeks) was associated with approximately 1.2-fold risk of T1DM among people younger than 18 years (14). While another cross-sectional study in the Middle East indicated that preterm birth was not associated with T1DM during childhood (15). In addition, to our knowledge, a paucity of evidence exists on the association of adverse birth outcomes and childhood T1DM in China and few studies have focused on gender difference. To narrow these gaps, we conducted a population-based cross-sectional study with large sample size in China to determine whether birth weight and preterm birth were significantly associated with T1DM and whether the association could be modified by gender.

METHODS

Study Design and Population

This study was a nationwide large population-based cross-sectional study, conducted at kindergarten, primary, secondary and high schools in 13 medical centers of China (Beijing, Chongqing, Fujian, Guangdong, Guangxi, Henan, Hubei, Jiangxi, Jilin, Shanghai, Tianjin, Xinjiang and Zhejiang) from 2017 to 2019, but Jiangxi was not included in this analysis due to missing the information of T1DM. Schools were selected using stratified cluster random sampling. The study protocol was approved by the ethics board of Zhejiang University. All participants' informed consents were acquired from children

or their parents. 231,937 children aged between 3 and 18 years old were included, and children with serious disease, logic errors in the questionnaire, type 2 diabetes or missing information of key variables were excluded. Finally, 181,786 children were included in this final analysis (**Figure 1**).

Exposure Variables

Birth weight (g), whether preterm birth or not (according to the definition of <37 gestational weeks, which is the internationally accepted definition of preterm, ICD10 P07.3) were self-reported by parents and children who were born prematurely were further asked about their delivery gestational age. According to the World Health Organization (16), we categorized birth weight into 3 groups: low birth weight (<2,500g), normal birth weight (2,500-3,999g) and high birth weight (≥ 4,000g). Preterm birth was further divided into gestational age of 32th to 37th week and before gestational age of 32th week.

Outcome Measurement

Childhood T1DM cases were identified by questionnaire surveys with the question: "Has your child been diagnosed with type 1 diabetes? ① Yes ② No." The questionnaire was completed by their guardians. In addition, to minimize errors, we again asked those who answered yes to confirm the diagnosis of type 1 diabetes.

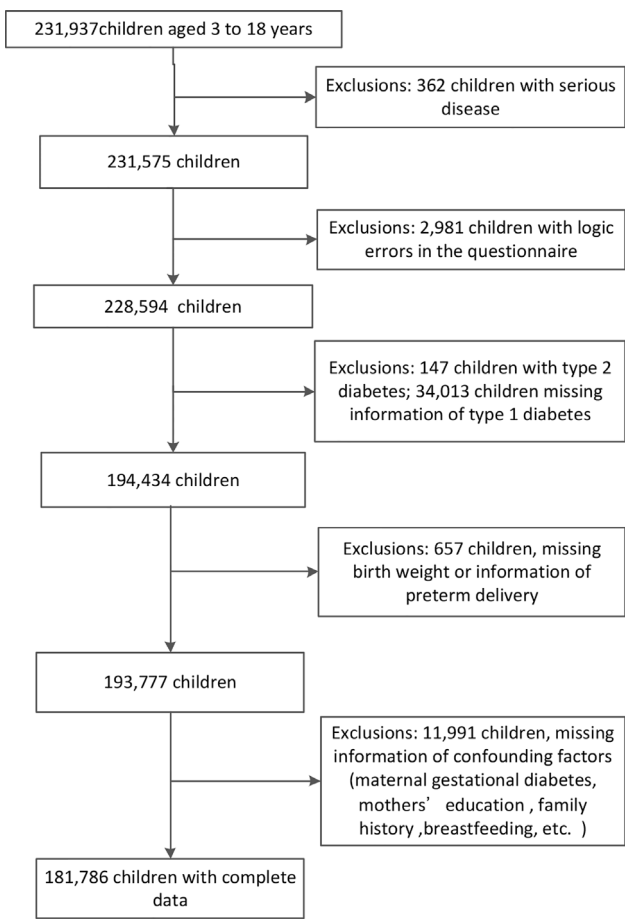

FIGURE 1 | The flowchart of study subjects.

Other Variables Definition

The height was measured to the nearest 0.1 cm, whereas weight was measured with a precision of 0.1 kg. The children were weighted without shoes and wearing light clothing. Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared. We categorized children's BMI into four status according to the BMI Z-score (underweight:< -2, normal: -2 to 1, overweight: 1 to 2, and obesity: >2), as defined by WHO 2007 standards and classifications (17). Other variables (demographic characteristics, family history of diabetes, intrauterine exposure and breast feeding) were all acquired from questionnaires. Maternal age at delivery was calculated as maternal age subtracts children's age at the time of the survey. According the common definition of advanced maternal age (18), we classified into two categories (<35 years old and ≥35 years old).

Statistical Analysis

We used mean and standard deviations (Mean ± SD) to describe continuous variables, and frequency and percentage (n, %) were reported for categorical variables. Student's t test and Chi square test were used for continuous variables and categorical variables, respectively, to compare the characteristic difference between groups. Associations of preterm birth as well as birth weight with T1DM were analyzed by multiple Poisson regression, respectively. To explore independent effects, we adjusted potential confounders, including maternal age at delivery, maternal education, annual family income, diabetes of mother, father and siblings, maternal gestational diabetes, children's characteristics including age, gender and breast feeding. To control the effect of gestational age when analyzed the effects of birth weight on T1DM, whether preterm birth or not was further adjusted. The crossover analysis was conducted to further elucidate the role of preterm birth and birth weight in increasing the risk of T1DM in children. In addition, we also explored the interaction between birth outcomes and gender on childhood T1DM. Interaction analyses with multiplicative interaction terms were conducted. The $P<0.05$ was considered as statistically significant and all statistical analyses were performed using R software (version 3.6.0).

Sensitivity Analyses

In sensitivity analyses, we repeated the analyses but used the matched data. We identified children with T1DM (n=82) as cases and randomly selected children without T1DM (n=328) as controls on a 1:4 ratio through Propensity Score Matching based on maternal age, maternal education, annual family income, diabetes of mother, father and siblings, maternal GDM, children's characteristics including age, gender and breast feeding. And conditional logistic regression was used to test the association between preterm birth as well as birth weight and T1DM.

RESULTS

A total of 181,786 children aged between 3 and 18 years old were included in the analysis (**Figure 1**), among which 82 children were T1DM cases and the prevalence was 45.1 per 100,000. In boys, the prevalence of low birth weight, high birth weight and preterm birth was 3.0%, 11.5% and 5.8%, respectively. In girls, the prevalence of low birth weight, high birth weight and preterm birth was 3.6%, 7.6% and 5.1%, respectively. The comparisons of general characteristics between children with and without T1DM were depicted in **Table 1**. Children with T1DM had a higher proportion of family history (including diabetes of mother, father and siblings), higher proportion of maternal GDM and poor maternal education in comparison with normal children. However, the similar distributions were showed about children's gender, breastfeeding and obesity, maternal age at delivery and diabetes of grandparents in two groups. All variables were balanced between two groups after Propensity Score Matching (**Supplementary Table 1**).

Association of Preterm Birth and Birth Weight With T1DM

As showed in **Table 2**, preterm birth was significantly associated with an increased risk of T1DM after adjusting for or matching potential confounding factors (whole sample size: OR: 3.17, 95%CI: 1.76-5.71; matched sample size: OR: 2.31, 95%CI: 1.14-4.68) and the dose effect emerged when preterm birth was further divided into gestational age of 32th to 37th week (whole sample size: OR: 2.32, 95%CI: 1.14-4.71; matched sample size: OR: 1.68, 95%CI: 0.74-3.81) and before gestational age of 32th (whole sample size: OR: 9.14, 95% CI: 3.63-23.05; matched sample size: OR: 7.01, 95%CI: 1.68-29.78), taking term birth (≥ 37 weeks) as reference. As for birth weight, we initially did not find statistically significant association between children born at neither low birth weight (<2,500g) nor high birth weight (≥4,000g) with childhood T1DM (OR: 0.70, 95% CI: 0.24-2.08; OR: 1.71, 95% CI: 0.90-3.22, respectively). However, high birth weight tended to increase the risk of T1DM in children and then we found that it had significantly higher risk of T1DM (OR: 2.25, 95% CI: 1.03-4.91) when using matched sample size.

To further elucidate the independent effect of preterm birth, birth weight on the risk of T1DM in children, we took children with normal birth weight and term birth as reference and found that children with preterm birth but normal birth weight had higher risk of childhood T1DM (OR: 3.61, 95%CI: 1.50-8.67) than children with high birth weight but term birth (OR: 2.24, 95%CI: 1.02-4.89), using the matched sample size. Similar trends were shown when we used original data (**Table 3**).

Gender-Specific Analyses

Considering the possible modification by gender, we conducted analyses stratified by gender. It turned out that findings were different between girls and boys. As shown in **Table 4**, compared to girls born with normal birth weight, girls born with high birth weight had higher risk of T1DM (OR: 3.15, 95%CI: 1.33-7.47), but high birth weight was not associated with T1DM in boys (OR: 0.99, 95%CI: 0.38-2.55). And P for interaction was close to statistically significant (*P* for interaction = 0.065 and 0.069 for adjusted model and matched data, respectively.). However, there was no interaction between gender and preterm birth (*P* for

TABLE 1 | Comparison of characteristics between children with and without T1DM.

Variables	T1DM*		*P*	Variables	T1DM		*P*
	No (N=181704)	Yes (N=82)			No (N=181704)	Yes (N=82)	
	n (%)				n (%)		
Maternal age at delivery, years			0.297	Breast feeding duration			0.472
≥35	13370 (7.4)	9 (11.0)		No	37309 (20.5)	21 (25.6)	
Maternal Education			**<0.001**	<6 months	21137 (11.6)	12 (14.6)	
primary school	12993 (7.2)	15 (18.3)		6 to 10 months	60313 (33.2)	23 (28.0)	
junior high school	49299 (27.1)	18 (22.0)		>10 months	62945 (34.6)	26 (31.7)	
senior high school	44927 (24.7)	24 (29.3)		Children's BMI status			0.839
junior college and above	74485 (41.0)	25 (30.5)		underweight	4931 (2.7)	1 (1.2)	
Annual family income, ¥			0.086	normal	131343 (72.3)	60 (73.2)	
<100,000	86550 (47.6)	49 (59.8)		overweight	29903 (16.5)	13 (15.9)	
100,000~199,999	54390 (29.9)	18 (22.0)		obesity	15527 (8.5)	8 (9.8)	
≥200,000	40764 (22.4)	15 (18.3)		Birthweight			0.213
Diabetes of mother			**0.003**	<2,500g	5997 (3.3)	4 (4.9)	
Yes	1349 (0.7)	4 (4.9)		2,500~3,999g	158110 (87.0)	66 (80.5)	
Diabetes of father			**0.031**	≥4,000g	17597 (9.7)	12 (14.6)	
Yes	3870 (2.1)	5 (6.1)		Preterm birth			**<0.001**
Diabetes of grandparents			0.470	Yes	9993 (5.5)	14 (17.1)	
Yes	41550 (22.9)	22 (26.8)		Gestational age			**<0.001**
Diabetes of siblings			**0.020**	≥37 weeks	171711 (94.5)	68 (82.9)	
Yes	471 (0.3)	2 (2.4)		32~37 weeks	8896 (4.9)	9 (11.0)	
Maternal GDM†			**0.024**	<32 weeks	1097 (0.6)	5 (6.1)	
Yes	7788 (4.3)	8 (9.8)			mean ± SD		
Gender			0.810	Children's age, years	9.57 ± 3.81	11.79 ± 4.05	**<0.001**
girls	85500 (47.1)	37 (45.1)					

**T1DM, Type 1 diabetes; †GDM, gestational diabetes.*
Bold values means statistically significant.

TABLE 2 | Associations of preterm birth and birth weight with Type 1 diabetes in Chinese children.

Variables	whole sample size				1:4 Matched sample size*			
	n	Type 1 diabetes			n	Type 1 diabetes		
		n (%)	OR (95%CI)	*P*		n (%)	OR (95%CI)	*P*
Preterm birth†								
No	171779	68(0.04)	ref.	–	369	68(18.43)	ref.	–
Yes	10007	14(0.14)	**3.17 (1.76-5.71)**	**<0.001**	41	14(34.15)	**2.31 (1.14-4.68)**	**0.021**
Gestational age†								
≥37 weeks	171779	68(0.04)	ref.	–	369	68(18.43)	ref.	–
32~36 weeks	8905	9(0.10)	**2.32 (1.14-4.71)**	**0.020**	33	9(27.27)	1.68 (0.74-3.81)	0.211
<32 weeks	1102	5(0.45)	**9.14 (3.63-23.05)**	**<0.001**	8	5(62.50)	**7.01 (1.68-29.78)**	**0.008**
Birth weight‡								
<2,500g	6001	4(0.07)	0.70 (0.24-2.08)	0.520	351	66(18.80)	0.38 (0.10-1.46)	0.157
2,500~3,999g	158176	66(0.04)	ref.	–	20	4(20.00)	ref.	–
≥4,000g	17609	12(0.07)	1.71 (0.90-3.22)	0.099	39	12(30.77)	**2.25 (1.03-4.91)**	**0.043**

**Cases were selected according to questionnaire, controls were matched by Propensity Score Matching and the matching variables included maternal age at delivery, maternal education, annual family income, diabetes of mother, father and siblings, maternal gestational diabetes, children's characteristics including age, gender and breast feeding; Each variable had one model. †Adjustment for variables the same as matching variables above, when using original data; ‡Further adjustment for preterm birth or not when using both original and matched data. Bold values means statistically significant.*

TABLE 3 | The association of birth weight and preterm birth on Type 1 diabetes in Chinese children.

Preterm birth	Birth weight	whole sample size				1:4 Matched sample size*			
		n	Type 1 diabetes			n	Type 1 diabetes		
			n (%)	OR (95%CI)†	*P*		n (%)	OR (95%CI)‡	*P*
No	2,500~4,000g	151362	56(0.04)	ref.	-	328	56(17.07)	ref.	-
No	<2,500g	2808	0(0.00)	-	-	27	0(0.00)	-	-
No	≥4,000g	17609	12(0.07)	1.68 (0.89-3.16)	0.110	14	12(30.77)	**2.24 (1.02-4.89)**	**0.043**
Yes	2,500~4,000g	6814	10(0.15)	**3.43 (1.72-6.81)**	**<0.001**	23	10(43.48)	**3.61 (1.50-8.67)**	**0.004**
Yes	<2,500g	3193	4(0.13)	**3.24 (1.16-9.03)**	**0.025**	18	4(22.22)	1.45 (0.46-4.41)	0.530

**Cases were selected according to questionnaire, controls were matched by Propensity Score Matching and the matching variables included maternal age at delivery, maternal education, annual family income, diabetes of mother, father and siblings, maternal gestational diabetes, children's characteristics including age, gender and breast feeding; Each variable had one model. †Adjustment for variables the same as matching variables above. ‡Adjustment for nothing.*
Bold values means statistically significant.

interaction = 0.906 and 0.865 for adjusted model and matched data, respectively. Data was not shown).

DISCUSSION

In present national study, both preterm birth and high birth weight were associated with increased risk of T1DM and the effect of preterm birth was stronger than that of high birth weight. However, children's gender modified the effect of high birth weight on T1DM, with high birth weight only increasing the risk of T1DM in girls.

The adverse effect of preterm birth on T1DM demonstrated in the current study was in line with the findings from previous meta-analysis with 18 studies and 22,073 cases published in 2014 (13) After 2014, three cohort studies in Sweden (14, 19, 20), one cohort study in England (21) and one cohort study in Taiwan (22) also came to similar conclusions. However, one cross-sectional study in Israel indicated that neither early preterm birth (<34 weeks) nor late preterm birth (34-36 weeks) was associated with T1DM during childhood (15). The different results from Israel may be due to different study designs and absence of adjusting for some important confounders, such as family history of diabetes. There are several alternative mechanisms supported the association of preterm birth and T1DM. Firstly, the adverse effects of preterm birth may be related to the accelerator hypothesis (23), which may be plausibly explained by the mechanism that rapid growth increases the demand of insulin secreting and causes β-cell stress and insulin resistance (24, 25). Secondly, permanent changes in insulin sensitivity emerges during the early third trimester (26) and preterm birth may alter development of β-cell mass (27, 28). Thirdly, intrauterine growth restriction is regard as one of mechanisms (29). In addition, preterm birth may also be linked to infection-driven inflammation and gut dysbiosis, which play an important role in the pathophysiology of T1DM (30–32).

When further subdivided gestational age, we found that both children born before 32 and born between 32 and 36 gestational weeks were associated with increased T1DM, furthermore, the dose-response effect was observed. However, results from other studies were different. A population-based register study from Swedish with 14,949 cases found that compared to full-term infants, birth between 32 and 36 gestational weeks had a higher

TABLE 4 | The association between birth weight and Type 1 diabetes stratified by gender in Chinese children.

	n	Type 1 diabetes			n	Type 1 diabetes			*P* for interaction**
		n (%)	OR (95%CI)†	*P*		n (%)	OR (95%CI)‡	*P*	
		boys				girls			
Birth weight									
Original data									0.065
2,500-3999g	82236	39 (0.05)	ref.	–	75940	27 (0.04)	**ref.**	–	
<2,500g	2918	1 (0.03)	0.28 (0.04-2.22)	0.230	3083	3 (0.10)	1.40 (0.36-5.45)	0.630	
≥4,000g	11095	5 (0.05)	0.99 (0.38-2.55)	0.976	6514	7 (0.11)	**3.15 (1.33-7.47)**	**0.009**	
1:4 Matched data*									0.069
2,500-3,999g	186	39 (20.97)	ref.	–	165	27 (16.36)	**ref.**		
<2,500g	9	1 (11.11)	–	–	11	3 (27.27)	0.99 (0.15-6.62)	0.994	
≥4,000g	23	5 (21.74)	1.23 (0.40-3.80)	0.723	16	7 (43.75)	**8.24 (1.63-41.74)**	**0.011**	

**Cases were selected according to questionnaire, controls were matched by Propensity Score Matching and the matching variables included maternal age at delivery, maternal education, annual family income, diabetes of mother, father and siblings, maternal gestational diabetes, children's characteristics including age, gender and breast feeding. †Adjustment for variables the same as matching variables above and preterm birth or not; ‡Adjustment for preterm birth or not. **P value of the interaction between birth weight and gender.*
Bold values means statistically significant.

risk (OR: 1.24, 95%CI: 1.14-1.35), while birth before 32 weeks of gestation had a lower risk of childhood-onset T1DM (OR: 0.54, 95%CI: 0.38-0.76) (20). Another national cohort study with 4,193,069 singletons born in Sweden reported increased risk of T1DM among children born at late preterm (34 to 36 gestational weeks) and early term (37 to 38 gestational weeks), while decreased risk among extremely preterm children (22 to 28 gestational weeks) (14). A register-based case-cohort study in Finland reported 21% and 17% increased risk among those born at 33 to 36 gestational weeks and 37 to 38 gestational weeks, respectively but failed to demonstrate decreased risk among birth before 33 gestational weeks (33). We speculate that the difference above might be caused by different divisions of gestational age, different reference levels, study designs and countries.

We found that high birth weight was associated with increased risk of T1DM but low birth weight had no statistically significant effect on T1DM, using the matched sample. It was consistent with one meta-analysis published in 2010 (12). However, inconsistent with our findings, Khashan et al. found no association between high birth weight and T1DM (OR: 1.01, 95%CI: 0.96-1.05) in 2015 (19) and Raphael found a significantly decreased risk of T1DM in children with low birth weight (OR: 0.82, 95%CI: 0.67-0.99) in 2018 (21), which might be explained by different reference levels. The reference levels of birth weight in Khashan's study (3,000 - 3,999g) and Raphael's study (3,000- 3,499g) were relatively higher than that in our study (2,500 - 3,999g). Overall, the mechanism behind birth weight and T1DM remains unclear. Kuchlbauer et al. found that there was no sign of excessive weight gain before T1DM among children born at high birth weight (34). Therefore, the effect of high birth weight on T1DM may not be explained by the accelerator hypothesis. Moreover, birth weight might be unlikely to have a direct association with T1DM, and may be a marker of intrauterine exposure, such as maternal nutrition and disease (35). For example, Larsson et al. have demonstrated that general population with high-risk HLA genotypes of T1DM had higher birth weight, but it was due to infections during pregnancy (36). To speculate, the effect of birth weight on T1DM is less direct than that of preterm birth and thus the effect of preterm birth is more obvious and stable.

To our knowledge, only one prior cohort study has reported there was no potential sex-specific difference between preterm birth and T1DM, which was consistent with present study (14). However, we also observed that high birth weight was significantly associated with an increased risk of T1DM among girls while not among boys, which has not been previously reported. The incidence of high birth weight in boys was higher than that in girls but the incidence of T1DM was opposite in China (3). Therefore, we hypothesized that high birth weight had a greater effect on the increased risk of T1DM in girls than in boys. This finding indicated that more attention should be paid to girls with high birth weight after birth for timely detection and treatment of type 1diabetes. Of course, the number of cases in our study was small, which led to poor power (whole sample size: 0.36; matched sample size: 0.68), and thus well-powered studies are warranted to confirm the finding. Whatever, our result may suggest that differences in gender composition may be responsible for inconsistent findings in previous studies and we also provide some information for future research to promote target prevention.

Strengths and Limitations

There were several strengths in our study. Firstly, to our knowledge, this was the largest study to show the association between birth outcomes and childhood T1DM in China Mainland. Secondly, we considered a wide range of confounders, including demographic characteristics, family history of diabetes, intrauterine exposure and feeding patterns. Thirdly, we also explored the gender differences, which had been less taken into account in previous studies. However, some limitations also should not be ignored. Firstly, although present study was based on large sample size but the number of cases was still relatively small. The power of high birth weight was only 0.36, which might prevent us from finding that the effect of high birth weight was statistically significant. After using propensity score matching, the power increased to 0.68. However, due to the limited number of cases, we were still unable to further divide the gestational weeks into more subgroups. Secondly, in this study, we only investigated the

gestational age of children with preterm birth, so it was not possible to assess whether all children had intrauterine growth restriction. However, we adjusted whether preterm birth when exploring the role of birth weight to avoid the effect of preterm birth on birth weight to some extent. Thirdly, cases in this study were from self-report, which might lead to recall bias. But generally, those without disease are not likely to be filled in as sick, so the prevalence rate is likely to be underestimated, and the impact of exposure on the outcome may be underestimated. However, recall bias may also be overestimated, because parents of children with diabetes may be more likely to associate possible factors and remember exposure factors. Finally, we still could not exclude potential confounders such as pregnancy history, pre-pregnancy obesity and pregnancy complications due to the limitations of the investigation and the cross-sectional study failed to consider the effects of recent life styles, which might be influenced by interventions after diagnosis. But previous studies with the adjustment only led to a little alteration, which would have probably made no difference.

In conclusion, children with preterm birth had independently higher risk of childhood T1DM, and girls with high birth weight were more susceptible to have T1DM. Therefore, early prevention should start with prenatal care to avoid adverse birth outcomes and more attention should be paid to children with preterm birth and girls with high birth weight after birth for timely detection and treatment of type 1diabetes.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study protocol was approved by the Institutional Review Board of The Children's Hospital of Zhejiang University School of Medicine (Approval Number 2016-JRB-018). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JF is the chief of the study and is responsible for the study concept and design, funding acquisition and critical revision of the manuscript. KH and SS contributed to analysis and interpreting of the data and writing of the draft. RC, CW, SC, YL, HY, RZ, FL, BC, ZS, MM, FHL, PL, HD, MZ, YY, and LC contributed to study design, investigation and data curation. YXY contributed to the study concept and design, analysis and interpreting of the data and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by Chinese National Natural Science Foundation (81973055), the national key research and development program of China (2016YFC1305301) and the Fundamental Research Funds for the Central Universities. The funder/sponsor did not participate in the work.

ACKNOWLEDGMENTS

We cordially thanked for all medical centers, all participants and the family members.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.603277/full#supplementary-material

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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.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 10 June 2021
doi: 10.3389/fendo.2021.613389

Sodium-Glucose Cotransporter-2 Inhibitors Ameliorate Liver Enzyme Abnormalities in Korean Patients With Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease

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

Received: *02 October 2020*
Accepted: *24 May 2021*
Published: *10 June 2021*

Citation:
Euh W, Lim S and Kim J-W (2021) Sodium-Glucose Cotransporter-2 Inhibitors Ameliorate Liver Enzyme Abnormalities in Korean Patients With Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease. Front. Endocrinol. 12:613389. doi: 10.3389/fendo.2021.613389

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are reported to reduce body fat in patients with type 2 diabetes mellitus (T2DM), and SGLT2i-induced weight reduction may help improve comorbid nonalcoholic fatty liver disease (NAFLD). This study aimed to investigate the potential benefit of SGLT2is over other oral antidiabetic drugs (OADs) in patients with T2DM-associated NAFLD. We enrolled real-world Korean patients with T2DM-associated NAFLD in whom initial metformin therapy had been modified by stepwise addition of OAD(s) due to insufficient glucose control. Propensity score (PS) matching was used for the comparison of changes in clinical and biochemical parameters to balance potential covariates. Among the 765 enrolled patients, 663 patients received additional OADs other than SGLT2i and 102 patients received SGLT2i therapy. PS matching selected 150 and 100 patients from the control and the SGLT2i group, respectively. The SGLT2i group lost more weight than the control group at 6 months (mean –1.3 kg *vs.* 0.0 kg; $P < 0.001$). Alanine aminotransferase (ALT) levels also decreased more in the SGLT2i group at 3 (–11 U/L *vs.* –1 U/L), 6 (–12 U/L *vs.* –1 U/L), and 12 months (–14 U/L *vs.* –2 U/L) (all $P < 0.05$). Addition of SGLT2is was an independent predictor of ALT improvement in a multivariate logistic regression model (odds ratio 1.91; $P = 0.016$). Compared with other OADs, addition of SGLT2is was more effective in weight reduction and ALT improvement in patients with T2DM and comorbid NAFLD.

Keywords: type 2 diabetes mellitus, sodium-glucose cotransporter 2 (SGLT2) inhibitor, alanine aminotransferase, body weight, propensity score (PS) matching (PSM)

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common comorbidity of type 2 diabetes mellitus (T2DM) and one half to two thirds of T2DM patients have NAFLD (1). Close association between T2DM and NAFLD is related to the fact that metabolic syndrome is a common risk factor for both conditions, frequently associated with adiposity and insulin resistance (2, 3).

The shared disease pathogenesis between T2DM and NAFLD raised the possibility of the potential role of antidiabetic drugs in NAFLD management. There have been several studies which investigated the effects of oral antidiabetic drugs (OADs) such as metformin (4), thiazolidinediones (5, 6) and dipeptidyl peptidase 4 inhibitors (DPP4is) (7) on NAFLD. Although some studies reported histologic improvements in NAFLD, the clinical benefit of OADs lack sufficient evidence for them to be routinely recommended in NAFLD treatment (8, 9).

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) decrease blood sugar levels by increasing urinary glucose excretion. Interestingly, SGLT2is are shown to decrease total body and visceral fat masses in patients with T2DM (10–12). Since weight reduction is the main strategy for decreasing hepatic steatosis, it may be postulated that SGLT2is have potential for the management of T2DM-associated NAFLD. In a recent phase 4 study (n = 84), empagliflozin 25 mg/day for 24 weeks reduced liver fat content by 22% as measured by magnetic resonance imaging (MRI) in European patients with T2DM (13). Notably, the addition of 10 mg empagliflozin daily led to a significant reduction in the MRI proton density fat fraction (MRI-PDFF), a useful quantitative indicator of the liver fat content, from 16.2% to 11.3% at 20 weeks in Indian patients with T2DM (n = 50) (14). After treatment for 24 weeks with 2.5 mg luseogliflozin, another SGLT2i, the MRI-PDFF was reduced significantly from 21.5 ± 7.2% to 15.7 ± 6.8% in Japanese patients with T2DM (n = 40) (15). In another European study (n = 32), treatment with dapagliflozin 10 mg/day for 8 weeks significantly decreased liver MRI-PDFF by 13% in patients with T2DM (16). These findings suggest that SGLT2is may have additional benefit of improving steatosis in T2DM-associated NAFLD.

Since alanine aminotransferase (ALT) is commonly used to measure liver injury, ALT has been used as an endpoint marker in many NAFLD and nonalcoholic steatohepatitis (NASH) studies. Several observational studies and recent small, controlled trials also reported that SGLT2i therapy improved ALT levels in T2DM-associated NAFLD (17–19). A recent meta-analysis reported that SGLT2is could reduce the level of ALT, an easily accessible serum marker of hepatic steatosis, although heterogeneity of the studies included in this analysis was substantial (I^2 = 73%) (20). Thus, the effect of SGLT2i on liver enzyme levels is yet to be confirmed in larger studies.

In this study, we aimed to investigate the benefit of SGLT2is over other OADs, especially effect on serum transaminase levels, in a real-world practice of T2DM-associated NAFLD. For this purpose, we assessed changes in serum transaminase levels as an endpoint in a propensity score (PS) matched cohort of T2DM patients with comorbid NAFLD.

METHODS

Study Design

This single-center retrospective cohort study recruited consecutive patients with T2DM and NAFLD who visited Seoul National University Bundang Hospital (SNUBH), a tertiary medical center in South Korea, between September 2014 and September 2018. An electronic cohort was established retrospectively by using the electronic medical record system of SNUBH (21). The eligibility criteria were as follows: patient age >18 years, presence of fatty liver by ultrasound, and at least 3 months of metformin-alone therapy for T2DM followed by stepwise addition of OADs and maintenance for at least 3 months. The exclusion criteria were as follows: treatment with a glucagon like peptide-1 receptor agonist (GLP-1 RA) or insulin within 6 months from the initial metformin therapy, chronic liver diseases other than NAFLD (e.g., viral hepatitis, autoimmune liver disease and drug-induced liver injury), significant alcohol consumption (daily intake >30 g for men and >20 g for women), or malignancies.

The enrolled patients were classified into either SGLT2i or control groups according to the modification of metformin therapy. The SGLT2i group added one of the available SGLT2is (dapagliflozin, empagliflozin, or ipragliflozin) to metformin. The control group added OAD(s) other than SGLT2is, i.e., DPP4is, sulfonylureas, or thiazolidinedione, to metformin. The choice of additional OADs was at the discretion of the attending physicians. All patients in this study were advised to maintain a healthy lifestyle by being more active in daily life and to avoid consuming a high fat, high carbohydrate diet. Diagnosis of fatty liver was made when ultrasonographic findings showed increased hepatic echogenicity compared with the right renal cortex (22). Hepatic steatosis manifests as increased echogenicity and beam attenuation in the ultrasonographic examination (22). This results in liver parenchyma appearing relatively hyperechoic compared with the renal cortex (normally liver and renal cortex are of a similar echogenicity) (23). Fatty liver also shows hyperechogenicity relative to the spleen (23).

PS matching was used to balance potential covariates between the two groups by matching the following baseline variables as covariates: age, body mass index (BMI), hypertension, dyslipidemia, and circulating glycated hemoglobin (HbA1c) and ALT levels. The PS was calculated from a logistic model, and k-nearest-neighbor matching without replacement and caliper of 0.01 was performed using the "psmatch2" tool of STATA software (version 14, STATA Corporation, College Station, TX, USA).

This study was performed in accordance with the *Ethical Principles for Medical Research Involving Human Subjects* outlined in the Declaration of Helsinki in 1975 (revised in 2013; https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). The institutional review board of SNUBH reviewed the study protocols and case report form and approved this study (IRB No: B-1810/497-007). Informed consent was waived because of the retrospective nature of the study and anonymous nature of the clinical data according to the by Guideline for Good Clinical Practice of International Council for Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use (E6R2).

Assessment of Anthropometric Parameters

Clinical parameters, including blood pressure, body weight, and BMI, were measured using standard methods. The BMI was calculated by dividing the subject's weight (kg) by height squared (m^2). Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured with subjects in a seated position using an electronic blood pressure meter (UA-1020 device; A&D Co., Tokyo, Japan). Blood pressure was measured twice 5 min apart and the mean value was used in the analysis.

Measurement of Biochemical Factors

Blood sampling was carried out after a 10-h overnight fast. The samples were centrifuged immediately at 3,000 rpm for 10 min at 4°C. HbA1c level was measured using a Bio-Rad Variant II Turbo HPLC analyzer (Bio-Rad, Hercules, CA, USA) in SNUBH, the National Glycohemoglobin Standardization Program level II certified laboratory. Fasting plasma glucose (FPG) levels were analyzed using the hexokinase method. Triglyceride (TG) levels were measured by the glycerol-3-phosphate oxidase peroxide method, and high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol were measured by homogeneous enzymatic assays. ALT and aspartate aminotransferase (AST) levels were measured using the NADH-UV method. Hepatic steatosis index (HSI) was calculated: HSI = 8 × ALT/AST ratio + BMI (+2, if diabetes mellitus; +2, if female) (24). Serum creatinine (Cr) was measured by Jaffe's kinetic method using a Hitachi 747 chemistry analyzer (Hitachi, Tokyo, Japan). The Chronic Kidney Disease Epidemiology Collaboration (EPI) equations were employed to derive the estimated glomerular filtration rate (eGFR).

Efficacy Assessment

The primary endpoint was a change in the ALT concentration from baseline. Secondary outcomes included changes in FPG and HbA1c levels, changes in AST, and changes in lipid profiles. Renal function was also assessed. The relationship between changes in ALT levels and pre-specified parameters such as age, sex, and BMI was also investigated.

Statistical Analysis

Clinical and biochemical parameters were compared using Student's *t* tests for continuous variables and chi-square tests for categorical variables. The Mann–Whitney nonparametric *U* test and χ^2 test were used for the assessment of continuous and categorical variables, respectively. Subgroup analysis was performed to identify subsets of patients who would be more likely to benefit from therapy with SGLT2is. The "ipdover" tool of STATA was used to generate data for forest plots outside the context of meta-analysis, without pooling or heterogeneity testing. Ipdover creates forest plots of subgroup analyses within one trial dataset. A p value < 0.05 was considered to be significant.

RESULTS

Baseline Characteristics Before and After PS Matching

The selection process of the study population is shown in **Figure 1**. A total of 1,736 records of patients with T2DM were retrieved from the databank, who had received initial metformin-based therapy for at least 3 months and subsequent additional OAD(s) for ≥3 months. After excluding 971 patients due to use of insulin or GLP-1 RA (n = 397), missing laboratory data (n = 87), a lack of liver ultrasound data (n = 416), and other liver diseases such as viral hepatitis, autoimmune liver diseases and drug-induced liver injury (n = 71), 765 patients with T2DM and NAFLD were finally enrolled.

The baseline characteristics of the study population are presented in **Table 1**. Before PS matching, the SGLT2i group (n = 102) was significantly younger and had higher body weight and BMI compared with the non-SGLT2i control group (n = 663). The HSI was significantly higher in the SGLT2i group (24). The prevalence of hypertension, triglyceride levels, HbA1c and ALT levels were also significantly different between the two groups. The PS matching procedure selected 95 patients from the SGLT2i group and 188 from the control group. After PS matching, the two groups were balanced for all parameters, including HSI.

Among other OADs, DPP4is were the most common agent used (n = 160), followed by sulfonylureas (n = 23) and thiazolidinedione (n = 5). Among the SGLT2is, dapagliflozin was most frequently used (n = 58), followed by empagliflozin (n = 34) and ipragliflozin (n = 3).

Changes in Body Weight, FPG, HbA1c, Lipid Profiles, and Transaminases by SGLT2is

Table 2 shows the changes in body weight and laboratory values at 6 months after the addition of OADs to metformin. Body weight reduced more in the PS-matched SGLT2i group (mean –2.5 kg, 95% confidence interval [CI]: –0.6 to –4.5) compared with controls (mean –0.2 kg, 95% CI: 0.2 to –0.5) (P = 0.001). Changes in HbA1c and lipid levels were similar between the two groups, whereas glomerular filtration rate increased significantly in the PS-matched SGLT2i group. Changes in AST levels were similar between the two groups, whereas ALT levels decreased more in the PS-matched SGLT2i group than in controls 6 months (–13 U/L *vs.* –5 U/L; P = 0.033) and 9 months (–15 U/L *vs.* –5 U/L; P = 0.014; **Table 3**). The HSI also decreased significantly more at 6 months in the SGLT2i group (–1.1 *vs.* 0.2, P = 0.005; **Table 3**). When the comparison was limited to DPP4i *vs.* SGLT2i, ALT responses were still better in the SGLT2i group (**Supplementary Table 1**).

Predictors of ALT Improvement by SGLT2i Therapy

Next, logistic regression analysis was performed to identify predictors of ALT improvement (>15% reduction from baseline) during the OAD therapy (**Table 4**). Younger age, male sex, body

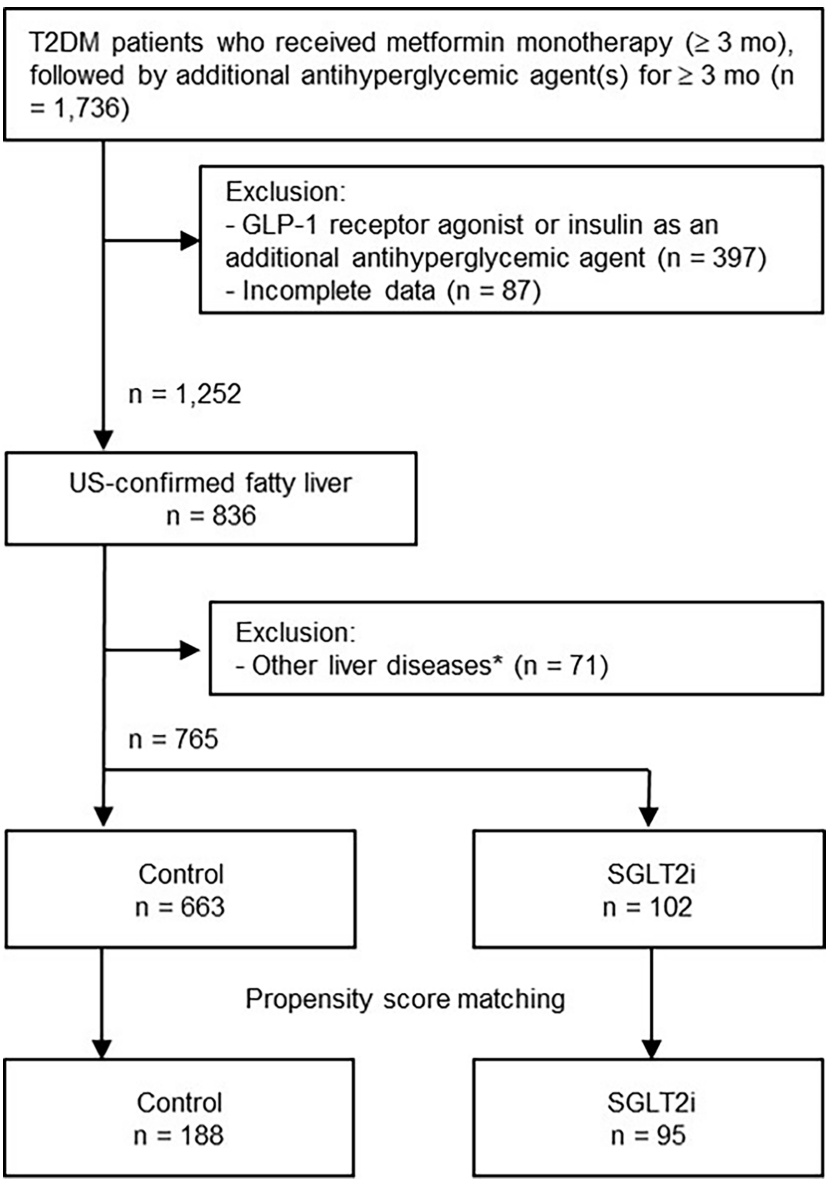

FIGURE 1 | Flowchart of the selection process. *Other liver diseases included viral hepatitis B and C, autoimmune hepatitis, drug-induced liver injury, and history of excessive alcohol intake (daily intake > 30 g for men and > 20 g for women). GLP-1, glucagon-like peptide-1; US, ultrasound; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

mass index, TG levels and addition of SGLT2is were identified as significant predictors by univariate analysis. In the multivariate analysis, addition of SGLT2is remained significant as a predictor for ALT improvement (odds ratio [OR] 1.73; 95% CI: 1.04–2.92; $P = 0.036$), along with baseline TG levels.

Finally, we performed a sensitivity analysis to gain additional insights as to how SGLT2i therapy might improve ALT levels in T2DM-associated NAFLD (**Figure 2**). The beneficial effect of SGLT2is over other OADs was evident in younger patients (<55 years), male patients, patients with baseline BMI >26 kg/m^2, and patients with less weight reduction during treatment with the study drugs.

DISCUSSION

Our study showed that addition of SGLT2is induced significantly greater ALT and HSI improvements compared with other OADs in patients with T2DM and ultrasound-confirmed NAFLD on metformin. SGLT2is have emerged as a promising candidate for treating NAFLD because of their potential favorable effect on hepatic fat content in several small studies (14, 25, 26). A retrospective study of 102 Korean patients with T2DM and NAFLD showed that dapagliflozin therapy exhibited greater improvement in liver enzyme levels than DPP4is when used with metformin (27). A few small placebo-controlled trials

TABLE 1 | Baseline characteristics of the study population.

	Original cohort			Propensity score-matched cohort		
	Control *n*=663	**SGLT2i *n*=102**	***P***	**Control *n*=188**	**SGLT2i *n*=95**	***P***
Age (years)	63 (18)	54 (17)	<0.001	58 (17)	56 (14)	0.138
Male gender	338 (52%)	63 (62%)	0.080	112 (60%)	58 (61%)	0.811
Body weight (kg)	69.0 (15.7)	76.5 (22.4)	<0.001	72.7 (16.4)	73.0 (22.2)	0.240
BMI (kg/m^2)	25.7 (3.9)	27.7 (5.3)	<0.001	26.7 (4.2)	27.5 (5.0)	0.229
Fasting glucose (mg/dL)	146 (41)	145 (38)	0.256	130 (38)	125 (35)	0.105
HbA1c (%)	7.4 (0.9)	7.3 (1.0)	0.007	7.4 (0.8)	7.3 (1.1)	0.438
Total cholesterol (mg/dL)	165 (35)	170 (34)	0.201	159 (55)	162 (49)	0.376
Triglyceride (mg/dL)	134 (83)	155 (104)	0.006	140 (76)	147 (93)	0.135
HDL-cholesterol (mg/dL)	49 (10)	50 (10)	0.482	47 (12)	49 (12)	0.220
LDL-cholesterol (mg/dL)	90 (38)	90 (34)	0.926	89 (39)	87 (35)	0.889
Serum creatinine (mg/dL)	0.8 (0.2)	0.8 (0.2)	0.395	0.8 (0.3)	0.8 (0.4)	0.394
eGFR-EPI (mL/min/1.73 m^2)	91 (21)	99 (21)	<0.001	95 (16)	99 (29)	0.075
AST (U/L)	27 (25)	29 (15)	0.501	29 (18)	29 (17)	0.908
ALT (U/L)	26 (25)	36 (31)	0.021	30 (37)	35 (31)	0.809
γGT (U/L)	56 (65)	54 (68)	0.768	37 (48)	32 (28)	0.319
Hepatic steatosis index*	36.8 (7.2)	40.1 (10.1)	< 0.001	37.9 (8.5)	39.4 (7.1)	0.409
Comorbidity						
Hypertension (%)	343 (52%)	42 (41%)	0.047	89 (47%)	41 (43%)	0.505
Dyslipidemia (%)	324 (49%)	52 (51%)	0.691	99 (53%)	48 (51%)	0.734
Statin usage (%)	458 (69%)	75 (74%)	0.363	134 (71%)	73 (77%)	0.318
Liver cirrhosis (%)	28 (4%)	1 (1%)	0.110	2 (1%)	0 (0%)	0.313

Continuous variables are expressed as the median (interquartile range) and categorical variables are expressed as the number (percentage). P values were calculated by using Mann–Whitney nonparametric U test and χ^2 test for continuous and categorical variables, respectively. BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, γ-glutamyl transferase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

**Hepatic steatosis index = 8 × ALT/AST + BMI (+2 if diabetes mellitus yes, +2 if female) (24).*

TABLE 2 | Comparison of 6-month changes in body weight, serum glucose, and lipid profiles between the propensity score-matched control and SGLT2i groups.

	Control *n*=188	**SGLT2i *n*=95**	***P***
ΔWeight (kg)	-0.2 (–0.5, 0.2)	–2.5 (–4.5, –0.6)	0.001
ΔHbA1c (%)	–0.5 (–0.6, –0.4)	–0.6 (–0.8, –0.4)	0.273
ΔFasting glucose (mg/dL)	–14 (–20, –8)	–21 (–26, –15)	0.130
ΔTriglyceride (mg/dL)	–11 (–20, -1)	–16 (–28, –4)	0.510
ΔHDL-cholesterol (mg/dL)	0 (–1, 1)	1 (0, 2)	0.267
ΔLDL-cholesterol (mg/dL)	–1 (–4, 2)	–4 (–7, 0)	0.309
ΔeGFR (mL/min/1.73 m^2)	–1.6 (–3.0, –0.3)	1.2 (–1.4, 3.9)	0.035

Δ: changes at 6 months from baseline values, expressed as the mean and (95% confidence interval). P values were calculated using Student's t-test. HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

TABLE 3 | Comparison of changes in transaminase levels and hepatic steatosis index between the propensity score-matched control and SGLT2i groups.

	Control *n*=188	**SGLT2i *n*=95**	***P***
AST changes (IU/L)			
3 months	–2 (–5, 0)	–7 (–12, –1)	0.109
6 months	–4 (–7, –1)	–7 (–13, –1)	0.363
9 months	–4 (–7, 0)	–8 (–14, –2)	0.135
ALT changes (IU/L)			
3 months	–4 (–8, 0)	–11 (–18, –4)	0.063
6 months	–5 (–9, 0)	–13 (–20, –6)	0.033
9 months	–5 (–9, 0)	–15 (–22, –7)	0.014
HSI change at 6 months	0.2 (–0.5, 1.0)	–1.1 (–2.0, 0)	0.005

Values are expressed as the mean (95% confidence interval). P values were calculated using Student's t-test. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HSI, hepatic steatosis index.

reported significant decreases in hepatic fat content and/or serum ALT levels by SGLT2i treatment in patients with T2DM and NAFLD (14, 19). However, decreases in ALT were not significantly different in other randomized trials of patients with NAFLD using metformin (26) and pioglitazone (28) as an active control. Inadequate statistical power might have been the reason for these negative results. Our present study included sufficient patient numbers to observe significant changes in ALT levels produced by SGLT2i therapy. Of note, our PS-matching analysis suggests that the use of SGLT2is might confer additional benefits for liver function compared with other OADs among patients with T2DM and NAFLD.

In this study, the HSI was improved by SGLT2i therapy. HSI was derived and validated in a large cohort of >10,000 individuals who underwent health check-ups (24). However, it has a moderate accuracy to detect fatty liver as determined by ultrasonography (24, 29). In a recent prospective cohort study from the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN), changes in the ALT levels were significantly associated with fibrosis regression in NAFLD (30).

Reductions in body fat mass and subsequent improvements in insulin resistance might account for the reduction in hepatic fat and ALT levels by SGLT2i therapy. Indeed, addition of SGLT2is significantly reduced body weight compared with other OADs (**Table 2**). Interestingly, the superiority of SGLT2is over other OADs in ALT improvement was observed in patients with less than 5% of weight reduction (**Figure 2**). This result suggests that other mechanisms, such as reduction in inflammatory markers,

TABLE 4 | Logistic regression analyses for predictors of ALT decrease greater than 15% of baseline over 9 months in the propensity score-matched cohort (*n*=283).

Baseline parameter	Univariate analyses			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	0.98	0.96–1.00	0.047	1.00	0.98-1.2	0.995
Male sex	1.63	1.00–2.64	0.049	1.48	0.88–2.49	0.140
Body mass index (kg/m^2)	1.10	1.03–1.18	0.008	1.07	0.99–1.16	0.076
Fasting glucose (mg/dL)	1.00	0.99–1.01	0.532			
HbA1c (%)	1.06	0.84–1.35	0.623			
Triglyceride (mg/dL)	1.01	1.00–1.01	0.003	1.01	1.00-1.01	0.010
LDL-cholesterol (mg/dL)	1.00	0.99–1.01	0.427			
HDL-cholesterol (mg/dL)	0.99	0.97–1.02	0.681			
SGLT2i *vs.*control	1.78	1.08–2.93	0.023	1.73	1.04–2.92	0.036

OR, odds ratio; CI, confidence interval; other abbreviations as described in ***Table 1****.*

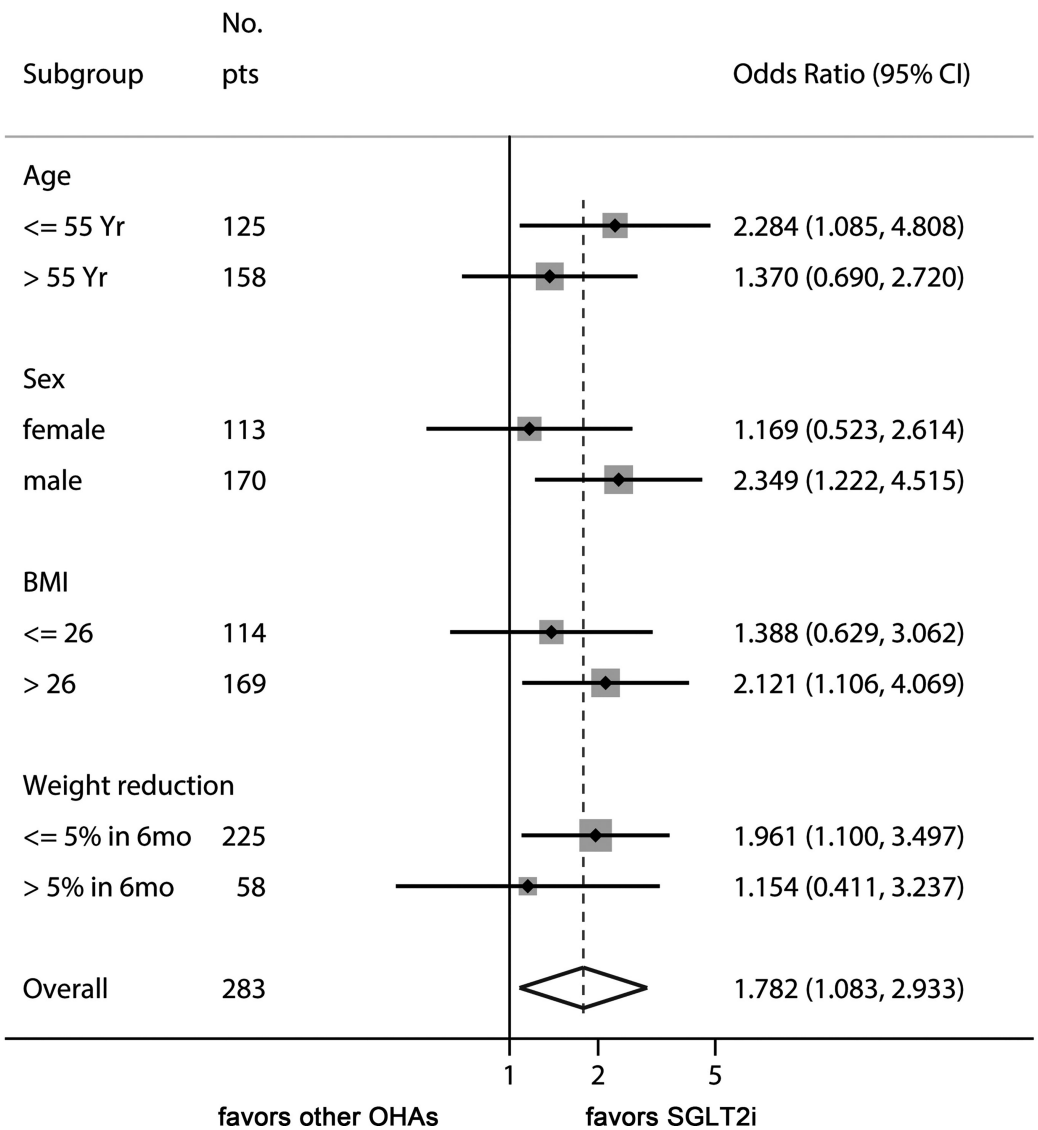

FIGURE 2 | Sensitivity analysis of odds ratio of SGLT2is for managing ALT levels. This Forest plot indicates the odds ratio of SGLT2i over control for the endpoint of ALT decrease ≥ 15% of baseline values. The benefit of SGLT2i for ALT decrease was more prominent in younger patients, male sex, high baseline BMI, and patients with less weight reduction.

decreased oxidative stress, and decreased hepatic lipogenesis might have been involved independently of weight reduction (31, 32). Further studies are needed for a mechanistic explanation for the SGLT2i-induced reduction of ALT levels. Being younger and male were also found to be better factors for responding to therapy with SGLT2is in terms of the improvements in liver function.

Small case studies have reported histological improvements in T2DM-associated NAFLD by SGLT2i therapy (33–35). Although our study did not take histological changes into account, previous studies reported associations between ALT improvement and hepatic fat content reduction, as assessed by MRI or computed tomography (14, 19, 26). Because we only assessed ALT changes up to 9 months, long-term hepatic outcomes such as prevention of hepatic fibrosis and hepatic carcinogenesis need to be determined by longer studies.

Current standards of medical care guidelines for T2DM (36, 37) and NAFLD (8) do not recommend specific classes of OADs for T2DM patients with NAFLD, except for pioglitazone in patients with biopsy-proven NASH. Collaborative studies by endocrinologists and hepatologists might help elucidate the natural history and long-term prognosis of T2DM-associated NAFLD and establish a standard-of-care guideline for optimal management. We believe that our real-world study may be of use in designing further collaborative studies on the role of SGLT2is in such patients.

In this study, we found that male sex and younger age group showed more favorable results with SGLT2is. In a recent study on patients with T2DM, empagliflozin treatment decreased liver fat content in males but not in females, although the interaction of sex and treatment was not significant (13). In a randomized, active-controlled trial on patients with T2DM and NAFLD, 5 mg dapagliflozin treatment for 24 weeks improved the controlled attenuation parameter, which was significantly correlated with younger age (18). In another study on patients with T2DM and NAFLD, younger age was associated with a greater reduction in ALT levels with dapagliflozin treatment, but it was not statistically significant (OR = 0.954, P = 0.147) (27). Thus, males and younger age people are likely to respond to the SGLT2i therapy for fatty liver. Additional targeted randomized controlled trials focusing on age and sex are required to confirm this finding.

We also found that the advantage of SGLT2i in the improvement of ALT levels was more prominent in patients with baseline BMI > 26 kg/m^2 and with less weight reduction during follow-up. To our knowledge, the effect of SGLT2i therapy on liver enzyme activities relative to BMI has not been reported in previous studies. This finding warrants mechanistic explanation through further studies and may provide some clue to the mechanism of action of SGLT2i on fatty liver. Since the effect on glucose control was similar between SGLT2i and other OADs (**Table 2**), SGLT2is may improve adipose tissue-induced hepatic inflammation (38) and oxidative stress (39) before weight reduction is achieved. Of note, the effect of non-pharmacologic intervention of body weight reduction might have overshadowed the weight-reducing effect of SGLT2i therapy.

Many studies have discovered a close association between NAFLD and impaired glucose regulation, resulting in the development of T2DM (40). Recent studies provide much evidence for an association between NAFLD and atherosclerosis and cardiovascular diseases (CVD) (41). Of note, the new descriptor 'metabolic dysfunction-associated fatty liver disease' (MAFLD) is proposed to replace the term NAFLD, because it more closely implicates obesity and metabolic dysregulation, leading to better identification of individuals with metabolic liver disease (42). MAFLD is not only associated with liver-related complications, but also with adverse cardiometabolic outcomes. Moreover, since many international guidelines recommend using SGLT2is for patients with established atherosclerotic CVD (ASCVD) or chronic kidney disease (CKD) or at high such risk (43, 44), it would be more prudent to conduct randomized controlled trials on people with good glycemic control and no ASCVD or CKD, in order to confirm the magnitude of the beneficial effect of SGLT2is and its mechanism of action.

Our study had several limitations. First, ALT was used as a surrogate marker for NAFLD activity in this study. It has been reported that ALT is a suboptimal marker for diagnosis of NASH with the area under the receiver operating characteristics for ALT level of 0.61–0.62 for NASH (45, 46). However, since ALT response may reflect histologic improvement in NASH (47), transaminase response is suggested as a better endpoint in early phase development trials (48). Apparently, the effect of SGLT2is on NAFLD needs to be further validated by long-term studies with histologic confirmation. Second, since our study was retrospective and observational, our results were prone to selection bias. We have matched most relevant variables by PS to minimize unbalancing, but the potential influence of unmeasured variables might still have biased the outcome. Applying PS matching is likely to achieve a better balance of covariates, but there is no consensus on the best way of capturing all relevant confounders for incorporation into the PS model. PS matching has advantages in situations with large numbers of covariates but relatively few outcome events captured in databases. By contrast, unmatched patients are excluded from analysis, thus increasing validity but at the expense of loss of information and generalizability (49). Moreover, various combinations of OADs have been used in our patients, so the potential interactions of SGLT2is and other OADs could not be fully controlled. These potential sources of bias can only be controlled by further prospective randomized trials. Third, different types of SGLT2is might have affected the outcome differently, but we did not assess the potential difference between individual SGLT2is because of limitations in statistical power given the patient numbers were not large. Fourth, as mentioned above, the hepatic histologic improvement by SGLT2i therapy needs to be assessed by long-term follow-up trials. Finally, since our data were obtained from Korean patients, further validation would be warranted in other ethnic groups.

In conclusion, this PS-matched comparative real-world study showed that the addition of SGLT2is decreased body weight and ALT levels significantly compared with other OADs in T2DM

patients with NAFLD on metformin therapy. SGLT2is might be a preferable option for these patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of Seoul National University Bundang Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

J-WK: designed the research study, analyzed the data and wrote the paper. WE: collected and analyzed the data and wrote the paper. SL: analyzed the data and wrote the paper. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by a National Research Foundation of Korea (NRF) grant to J-WK, funded by the South Korean Government (2017R1D1A1B03031483). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.613389/full#supplementary-material

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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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ORIGINAL RESEARCH
published: 19 August 2021
doi: 10.3389/fendo.2021.666194

Observations of the Effects of Maternal Fasting Plasma Glucose Changes in Early Pregnancy on Fetal Growth Profiles and Birth Outcomes

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Edited by:
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Reviewed by:
Carol Huang,
University of Calgary, Canada
Viva Ma,
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Specialty section:
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

Received: 09 February 2021
Accepted: 30 July 2021
Published: 19 August 2021

Citation:
Guo F, Liu Y, Ding Z, Zhang Y, Zhang C and Fan J (2021) Observations of the Effects of Maternal Fasting Plasma Glucose Changes in Early Pregnancy on Fetal Growth Profiles and Birth Outcomes. Front. Endocrinol. 12:666194. doi: 10.3389/fendo.2021.666194

Introduction: Although the role of maternal hyperglycemia on birth outcomes is clear, literature regarding fetal growth is scarce. We examined the possible associations between maternal fasting plasma glucose (FPG) and fetal growth.

Materials and Methods: A total of 35,981 singleton-pregnant women with FPG in the first trimester were included. Fetal growth parameters were measured during pregnancy by ultrasound at mid and late pregnancy. Information on birth characteristics was retrieved from medical records. We used multivariable linear and logistic regression to determine the associations between FPG and z-scores of fetal parameters and risks of birth outcomes and to assess effect modification by maternal characteristics.

Results: A per-unit increase in FPG levels was negatively associated with fetal parameters in mid pregnancy but positively correlated with those in late pregnancy and with birth characteristics. The effect estimates in late pregnancy were attenuated by maternal pre-pregnancy body mass index (BMI). A significant relationship between FPG and abdominal circumference (AC), an indicator of fetal adiposity, was sustained in subgroups of women with advanced age, positive family history of diabetes, and multiparity in fully adjusted models. After stratification by BMI, high FPG was associated with accelerated AC only in normal controls (0.044 SD; 95% CI: 0.010, 0.079) and overweight/obese women (0.069 SD; 95% CI: -0.002, 0.140) but not in underweight women. High FPG was an independent risk factor for large-for-gestational age in the whole group and stratified subgroups.

Conclusions: Increased FPG in early pregnancy is closely related to fetal growth. Maternal characteristics may modify the associations between FPG and fetal adiposity in late pregnancy.

Keywords: pregnancy, fetal grow, modification effects, body mass index, fasting plasma glucose

INTRODUCTION

Since the human fetus is highly dependent on glucose derived from maternal circulation, the glucose homoeostasis transferred from mother to placenta is considered to be the dominant determinant of fetal development (1). Substantial studies have shown that a higher gestational glycemia in each trimester, regardless of fasting or postprandial state, is associated with increased risks of adverse birth outcomes, even in non-diabetic pregnancy (2–5). However, the majority of neonates with abnormal fetal growth are unidentified until birth. Given the prolonged exposure to hyperglycemia from early pregnancy, the impact of metabolic variation in mothers on the fetus in uterus is poorly understood. This notion is reinforced by the view that birth weight is only the endpoint of different fetal exposures, and different fetal growth parameters and body proportions may result in the same birth size (6). Altered fetal growth is a critical predictor of neonatal morbidity and mortality and may increase the susceptibility to multiple diseases later in life (7). For instance, accelerated fetal growth predisposes individuals to obesity later in life, and fetal growth retardation is related to adult diabetes and cardiovascular diseases (8–10).

To our knowledge, only two studies have reported the impact of maternal blood glucose in early pregnancy on fetal growth trajectories. Specifically, Geurtsen et al. (11) reported that high maternal early-pregnancy random blood glucose levels contributed to decreased fetal growth in mid pregnancy and increased fetal growth from late pregnancy onward in the US. Li et al. (12) only found early-pregnancy random blood glucose increased fetal growth in late pregnancy in China. However, non-fasting glucose levels can be affected by the collection date and timing of the last meal and may not truly represent women's insulin resistance levels. At present, there are few reports about the effect of maternal fasting plasma glucose (FPG) levels in early pregnancy, which are relatively steady, on fetal intrauterine growth. In addition, the International Association of Diabetes and PregnanThe associations with LGAcy Study Groups (IADSPG) has once recommended women with FPG of ≥5.1 mmol/L as having early gestational diabetes mellitus (GDM) (13). However, little is known about fetal growth trajectories in early GDM and non-early GDM pregnancies. Meanwhile, easily obtained clinical subject characteristics such as family history of diabetes, maternal age, parity, fetal sex, and pre-pregnancy BMI, are important factors influencing intrauterine growth and birth outcomes, but few studies have investigated the potential interplay between circulating glucose and these variables (14–18).

In this study, our primary objective was to quantify the associations between maternal first-trimester FPG and the processes of fetal growth in different developmental periods. Our secondary objective was to explore potential modifiers.

MATERIALS AND METHODS

Study Participants

Retrospective medical records of pregnant women who underwent their first trimester antenatal care in the International Peace Maternity and Child Health Hospital (IPMCH) in Shanghai, China, from January 2016 to December 2018, were obtained. Women who did not take the FPG test in the first trimester (9–14 weeks), had twin or multiple pregnancies, had preexisting diabetes, became pregnant through *in vitro* fertilization treatment or the use of ovulation stimulation drugs, or had incomplete medical data were excluded from the analysis. A total of 35,981 women were included in our study after excluding the abovementioned subjects (**Figure 1**). To evaluate potential selection bias, we conducted non-response analyses to compare the characteristics between the included (N = 35,981) and excluded pregnant women without first-trimester FPG data (N = 6,960). The results showed that there was no significant difference in maternal age, pre-pregnancy BMI, or birth outcomes, except for that mothers with FPG measurements had a higher proportion of multiparity (69.22% *vs.* 61.26%, p = 0.001), a lower rate of preterm birth (5.25% *vs.* 5.86%, p = 0.039), and slightly higher gestational age (39.1 *vs.* 39 weeks, p < 0.001) (**Supplementary Table 1**). The study was approved by the ethics committee of IPMCH (GKLW 2019-58) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Data Collection

During the first antenatal visit, fasting blood samples were drawn for later measurement of glucose. Information about maternal age, education level, obstetrical history, last menstrual period (LMP), family history of diabetes, and anthropometry measurements were extracted from the medical record system. Previous study reported that advanced maternal age, defined as 35 years or greater, plays an important role in fetal growth (19). Therefore, maternal age was categorized as young (<35 years) and advanced age (≥35 years) in this study. Pre-pregnancy body mass index (BMI; kg/m^2) was calculated using nurse-measured height in early pregnancy and self-reported weight from weight prior to pregnancy. Pre-pregnancy BMI was calculated as weight divided by height squared and was further classified into three groups: underweight (<18.5 kg/m^2), normal weight (18.5–23.9 kg/m^2), and overweight/obese (≥24.0 kg/m^2). Dichotomous variables were used to indicate maternal parity (nulliparous and multiparous), fetal sex (male and female), and family history of diabetes (positive and negative). Gestational age was estimated using ultrasound screening of the crown–rump length (CRL). If the difference between LMP and CRL based on gestational age was >10 days, we chose the latter method.

Women who have not previously been diagnosed with diabetes underwent a 75-g oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. The diagnosis of GDM was made when any of the following plasma glucose values were met or exceeded: fasting, 5.1 mmol/L; 1 h, 10.0 mmol/L; 2 h, 8.5 mmol/L.

Fetal Growth and Neonatal Outcomes

In the follow-up prenatal visits, pregnant women were monitored with routine ultrasound measurements using transabdominal sonography (Philips iU22, Netherlands) to measure fetal head circumference (HC), abdominal circumference (AC), and femur length (FL) to the nearest millimeter in mid pregnancy (18–24 weeks of gestation) and

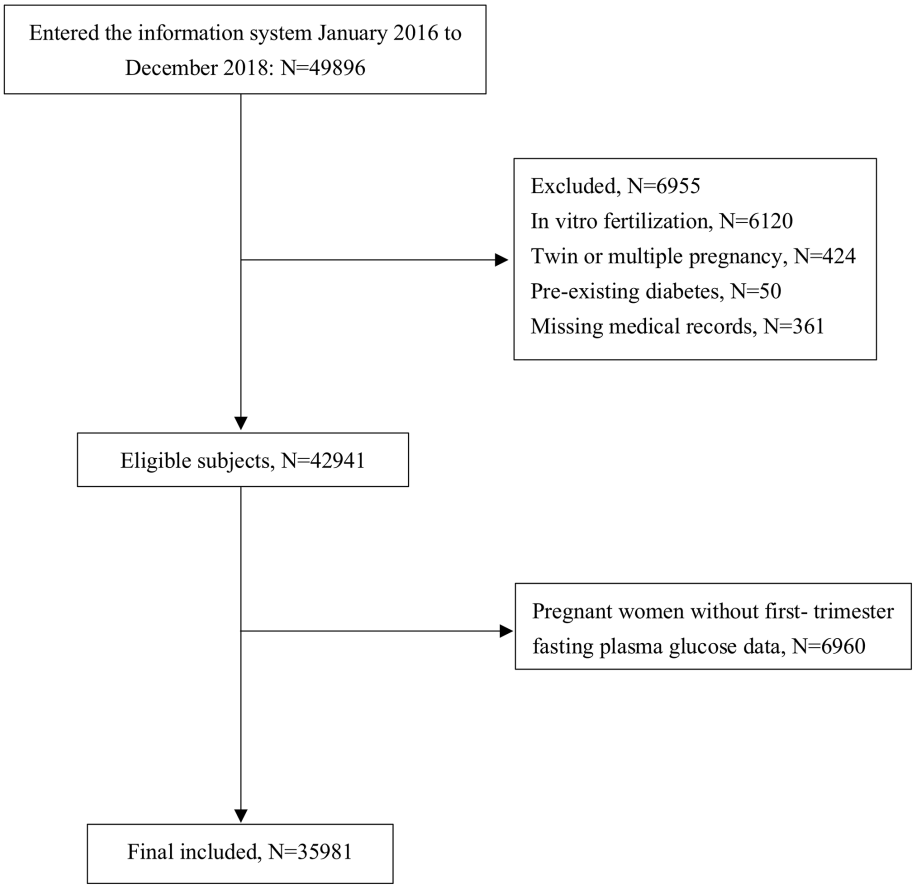

FIGURE 1 | Flowchart of the study population.

late pregnancy (28–34 weeks of gestation). All ultrasound measurements were conducted by experienced faculty.

Information on fetal sex, date of birth, birth weight (BW), and birth length (BL) was obtained from hospital medical records. Gestational age-adjusted z-scores for fetal biometry, estimated fetal weight (EFW), and newborn BL and BW were constructed according to the INTERGROWTH-21st Standard (20). The INTERGROWTH-21st Standard is a multicenter, multi-ethnic, population-based project, conducted between 2009 and 2014, in eight countries. The project strictly selected eligible pregnancies and assessed longitudinal fetal growth and newborn size to construct prescriptive intrauterine growth standards for each gestational age (21).

Preterm birth was defined as birth at <37 weeks of gestation (20). Small-for-gestational age (SGA) was defined as BW <10th percentile gestational age- and sex-specified BW, and large-for-gestational age (LGA) was defined as BW >90th percentile gestational age- and sex-specified BW based on the INTERGROWTH-21st Standard (21).

Statistical Analysis

In this analysis, we investigated the relationship between the first trimester FPG concentrations and offspring growth patterns (mid pregnancy, late pregnancy, and at birth) using unbalanced repeated measurement regression models. Since body length cannot be estimated by ultrasound, we used FL instead to assess overall length growth (22). This regression technique considers the correlation of repeated measurements within one subject into account, assesses both the time-independent and time-dependent effects of FPG in early pregnancy, and allows for incomplete data (23). We included early-pregnancy FPG in these models as an intercept and as an interaction term with gestational age to estimate fetal growth rates over time (23). The models performed with R can be written as: fit<-lmer (weight ~ FPG + time + FPG * time + $\beta0 + \beta1 + \beta j$ + (1|id), data = newdata). The term "weight," including the estimated fetal weight in the second and third trimesters and weight at birth, reflects the time-dependent outcome variable, while "time" is a continuous variable that reflects the gestational week of estimated weight in the second and third trimesters and weight at birth. "FPG" and "FPG * time" reflect the time-independent and time-dependent growth differences, respectively. "(1|id)" refers to a random intercept for subjects (repeated subject = id). "$\beta0 + \beta1 + \beta j$" is the regression coefficient for covariates 0 to j, where j is the number of covariates. A similar model was used for length

growth. Crude models were adjusted for model 1 (including maternal age, parity, education levels, family history of diabetes, and fetal sex) and model 2 (model 1 plus pre-pregnancy BMI).

Differences in fetal weight growth through pregnancy by early GDM and pre-pregnancy BMI were examined by linear mixed modeling. Analysis was repeated with the exception of women with GDM.

Furthermore, we examined the association of early FPG concentrations with fetal growth characteristics in the second and third trimesters and at birth using linear regression models. The results are expressed as β coefficients (95% CIs). Crude models were adjusted for model 1 (including maternal age, parity, education levels, family history of diabetes, and fetal sex) and model 2 (model 1 plus pre-pregnancy BMI). Subsequently, we assessed the associations with the risks of adverse birth outcomes using logistic regression models adjusted for the same covariates.

Stratified analyses by maternal characteristics and fetal sex mentioned in the covariates were conducted in each pregnancy period to examine which group was more affected by FPG. Analyses were adjusted for covariates when they were not the strata variables conducted in model 1 and model 2.

To validate the confidence of the association of higher maternal FPG with fetal growth during pregnancy, sensitivity analyses were performed in two steps. First, we repeated the analyses limited to fetuses from mothers without GDM because we were interested in non-diabetic women. The second analysis conducted excluded pregnancies with complications, such as gestational hypertension, preeclampsia, placenta previa, placental abruption, and cholestasis of pregnancy.

Normally distributed variables are presented as the means ± SD; non-normally distributed variables are presented as medians with 95% ranges. All statistical analyses were performed using R statistical software version (package rms, lme4, ggplot).

RESULTS

Population Characteristics

Descriptive characteristics of mothers and newborns are listed in **Table 1**. The mean (SD) maternal age was 30.89 (3.86) years, and the mean BMI (SD) was 21.13 (2.71) kg/m^2. Delivery took place at a median of 39.1 weeks (95% CI: 35.6, 41), and the mean (SD) birth weight was 3,327.67 (437.23) g. A total of 69.22% of women were nulliparous, and 12.95% were overweight/obese. The mean maternal FPG values was 4.49±0.36 mmol/L, with 2,015 (5.6%) women having over 5.1 mmol/L. The rates of LGA, SGA, and preterm birth were 13.13%, 3.29%, and 5.25%, respectively. When compared to women delivering average-for-gestational age (AGA) newborns, higher mean FPG concentrations in early pregnancy were observed in women delivering LGA newborns (4.55±0.38 *vs*. 4.48±0.36 mmol/L, p < 0.001), and lower mean FPG concentrations were observed in mothers who gave birth to babies with SGA (4.45±0.37 *vs*. 4.49 ± 0.36 mmol/L, p = 0.001). Women who gave birth to premature babies also had higher levels of FPG than women who gave birth to term (4.51 ± 0.39 *vs*. 4.49 ± 0.36 mmol/L, p = 0.03).

TABLE 1 | Baseline characteristics of study participants.

Characteristics	All (N = 35,981)
Maternal characteristics	
Age, mean±SD, years	30.89 ± 3.86
<35, n (%)	29,387 (81.67)
≥35, n (%)	6,594 (18.33)
BMI, mean±SD, kg/m^2	21.13 ± 2.71
<18.5, n (%)	4,694 (13.05)
18.5–23.9, n (%)	26,626 (74)
≥24, n (%)	4,661 (12.95)
Nullipara, n (%)	24,905 (69.22)
Family history of diabetes, n (%)	2,491 (6.92)
Maternal education levels, n (%)	
Primary education	6,240 (17.34)
Bachelor's	24,049 (66.84)
Master's	5,242 (14.57)
Doctoral	450 (1.25)
FPG in first trimester, mean ±SD, mmol/L	4.49 ± 0.36
FPG ≥5.1 mmol/L, n (%)	2,015 (5.6%)
Neonatal characteristics	
Fetal gender (boys, %)	18,520 (51.47)
Gestational weeks, median (95% CI)	39.1 (35.6, 41)
Birth weight, g	3,327.67 ± 437.23
Birth length, mm	49.81 ± 1.41
Pregnancy complications and outcomes, n (%)	
GDM	4,758 (13.22)
Preeclampsia	845 (2.35)
Pregnancy-induced hypertension	990 (2.75)
Intrahepatic cholestasis	238 (0.66)
Placental abruption	86 (0.24)
Placenta previa	398 (1.11)
Preterm birth	1,888 (5.25)
LGA	4,723 (13.13)
SGA	1,186 (3.29)

Values are means±SD.

First-Trimester Fasting Plasma Glucose Concentrations With Fetal Growth and Birth Outcomes

Considering the variation in maternal FPG during early pregnancy, we first modeled a curve to evaluate the potential effect of gestational week on maternal FPG values by using a Locally Weighted Scatterplot Smoothing procedure. The results showed a small fluctuation at the end of the first trimester (**Figure 2**). Repeated measurement analysis showed that first-trimester FPG levels were positively associated with the fetal growth trajectory based on fetal weight and length from visits 2 and 3 and delivery [adjusted for model 1: length: 0.046 SD (0.030–0.082), p < 0.001; weight: 0.039 SD (0.014–0.064), p = 0.002]. After additional adjustment for pre-pregnancy BMI, the significant association for fetal weight no longer reached statistical significance.

In mid pregnancy, fetuses of early GDM mothers had lighter EFW [mean difference in EFW SDS: -0.10 (-0.14, -0.07)] compared to non-early GDM mothers (reference). From this time until birth, they grew faster [difference in mean EFW at late pregnancy and weight at birth was 0.10 (0.07, 0.13) and 0.20 (0.16, 0.25), respectively] (**Figure 3A**). This pattern was maintained after excluding fetuses of mothers who were later

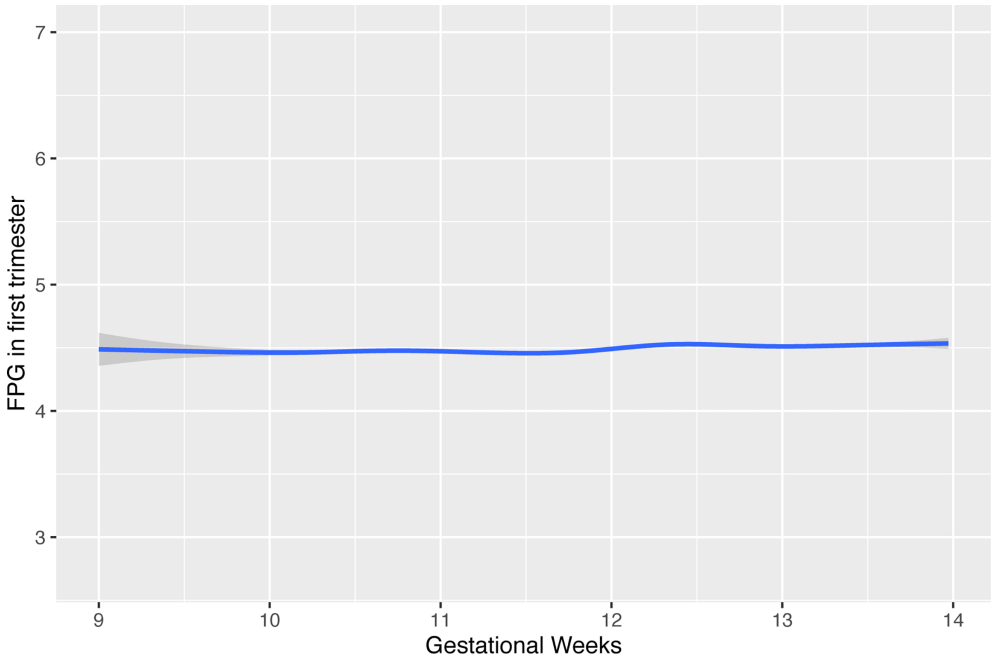

FIGURE 2 | The effect of timing in gestation for FPG values during early pregnancy. FPG, fasting plasma glucose.

diagnosed with GDM (**Figure 3B**). Compared to fetuses of normal-weight women (reference), fetuses of underweight women were smaller from mid to birth [mean difference in EFW SDS: -0.09 (-0.13, -0.05); -0.22 (-0.26, -0.18); -0.3 (-0.33, -0.27), respectively], and fetuses of overweight/obese women were heavier across pregnancy [mean difference in EFW SDS: 0.06 (0.01, 0.11); 0.24 (0.19, 0.28); 0.26 (0.23, 0.29), respectively] (**Figure 3C**). Results were similar after excluding fetuses of mothers who were later diagnosed with GDM (**Figure 3D**).

The effects of maternal first-trimester FPG on fetal growth patterns during each pregnancy period are summarized in **Table 2**. Higher FPG was associated with a pattern of reduction in z-scores for all fetal growth parameters in mid pregnancy in multivariable-adjusted model 2, except for FL. However, as in late pregnancy, higher FPG was associated with increased AC, EFW, and FL SDS in model 1, resulting in significantly increased weight and length at birth. The positive associations between FPG and AC or EFW in late pregnancy lost statistical significance after additional correction for pre-pregnancy BMI, while the association with birth weight and length remained significant in the fully adjusted model.

Higher first-trimester FPG was independently associated with an increased risk of LGA after correction for model 2 [odds ratio (OR): 1.250 (95% CI: 1.148, 1.436)]. There was a protective effect on SGA and an increased risk of preterm birth in the crude model [OR_{SGA}: 0.766 (95% CI: 0.652, 0.898) and OR_{PTB}: 1.159 (95% CI: 1.022, 1.313); respectively], but both became non-significant after adjustments for model 1 and model 2 (**Table 2**).

Response of Trimester-Specific Fetal Biometry Parameters to First-Trimester Fasting Plasma Glucose Stratified by Known Maternal Phenotypes

No interaction terms for maternal traits were found in mid pregnancy (all p-interaction >0.05; **Figure 4A** and **Supplementary Table 2**). In late pregnancy, although no evidence of an association between FPG and AC growth was present in the fully adjusted model, analyses stratified by maternal characteristics showed significantly positive estimates among mothers who were older (35 years), had a family history of diabetes, and had multiparity after controlling for BMI [0.067 SD (0, 0.134), 0.103 SD (-0.001, 0.207), and 0.054 SD (0.002, 0.105), respectively). However, the effect estimates in subjects with age younger than 35 years, without a family history of diabetes, and nulliparity were all close to zero (**Figure 4B** and **Supplementary Table 2**). Analysis stratified by BMI showed that the positive association between FPG and AC was evident in women with BMI ≥18.5 kg/m^2 (**Figure 4B** and **Supplementary Table 2**). No clearly different effects between groups stratified by age, family history, parity, and BMI were present for FL.

The estimates of FPG with birth weight and length were similar between subgroups, except for women carrying female fetuses and those with BMI ≥18.5 kg/m^2, who showed a pattern of higher estimates for the association between FPG and BL (**Figures 5A, B** and **Supplementary Table 3**). The associations with LGA were similar to the results shown for the continuous birth weight results (**Supplementary Table 3**). However, the curves for LGA showed an incremental separation of their

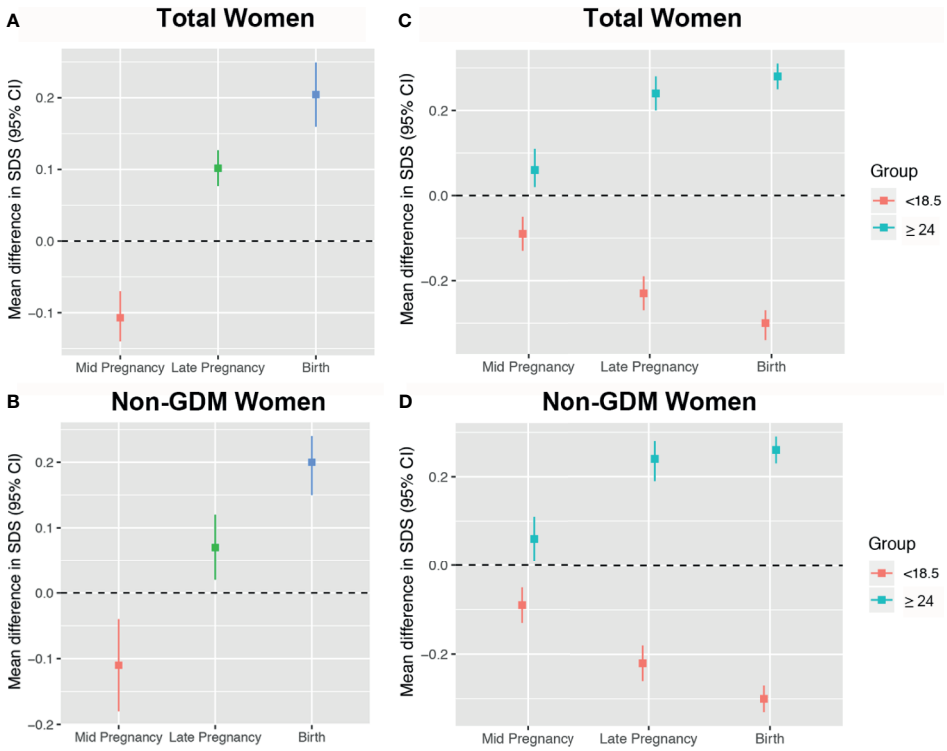

FIGURE 3 | Mean differences in estimated fetal weight (EFW) across pregnancy stratified by early gestational diabetes mellitus (GDM) and pre-pregnancy body mass index (BMI). Women with non-early GDM are the reference group in panels **(A, B)**, represented by the black zero-line. Normal weight women are the reference group in panels **(C, D)**.

TABLE 2 | Association of maternal early-pregnancy glucose concentrations with fetal growth during pregnancy and birth outcomes.

Period	Basic model beta (95% CI)	Model 1† beta (95% CI)	Model 2‡ beta (95% CI)
Mid pregnancy			
AC (N = 35,569)	-0.011 (-0.041, 0.019)	-0.03 (-0.046, 0)*	-0.051 (-0.081, -0.02)*
HC (N = 35,532)	-0.068 (-0.099, -0.037)*	-0.074 (-0.105, -0.044)*	-0.08 (-0.111, -0.049)*
EFW (N = 35,516)	-0.037 (-0.069, -0.005)*	-0.051 (-0.086, -0.016)*	-0.073 (-0.109, -0.037)*
FL (N = 35,698)	0.032 (0.004, 0.06)*	0.022 (-0.007, 0.05)	0.008 (-0.021, 0.037)
Late pregnancy			
AC (N = 35,273)	0.111 (0.08, 0.142)*	0.079 (0.047, 0.111)*	0.019 (-0.013, 0.051)
HC (N = 34,272)	0.029 (-0.009, 0.067)	0.014 (-0.024, 0.051)	-0.013 (-0.051, 0.025)
EFW (N =,34,254)	0.104 (0.073, 0.136)*	0.072 (0.04, 0.103)*	0.014 (-0.018, 0.046)
FL (N = 35,261)	0.071 (0.041, 0.101)*	0.059 (0.029, 0.09)*	0.048 (0.017, 0.078)*
Birth size			
Weight	0.2 (0.167, 0.223)*	0.162 (0.135, 0.189)*	0.083 (0.059, 0.066)*
Length	0.083 (0.062, 0.103)*	0.063 (0.042, 0.083)*	0.028 (0.007, 0.048)*
Birth outcomes	**Basic model OR (95% CI)**	**Model 1† OR (95% CI)**	**Model 2‡ OR (95% CI)**
LGA	1.658 (1.528, 1.8)*	1.546 (1.422, 1.679)*	1.25 (1.148, 1.362)*
SGA	0.766 (0.652, 0.898)*	0.82 (0.697, 0.965)	0.92 (0.781, 1.091)
Preterm birth	1.159 (1.022, 1.313)*	1.094 (0.963, 1.241)	1.061 (0.932, 1.208)

†*Adjusted for maternal age, education levels, parity, family history of diabetes, fetal gender, and gestational age of sample collection.*

‡*Adjusted for maternal age, education levels, parity, gestational age of sample collection, pre-pregnancy BMI.*

BMI, body mass index; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; LGA, large-for-gestational age; SGA, small-for-gestational age; AC, abdominal circumference; HC, head circumference; EFW, estimated fetal weight; FL, femur length; OR, odds ratio.

*$p < 0.05$.

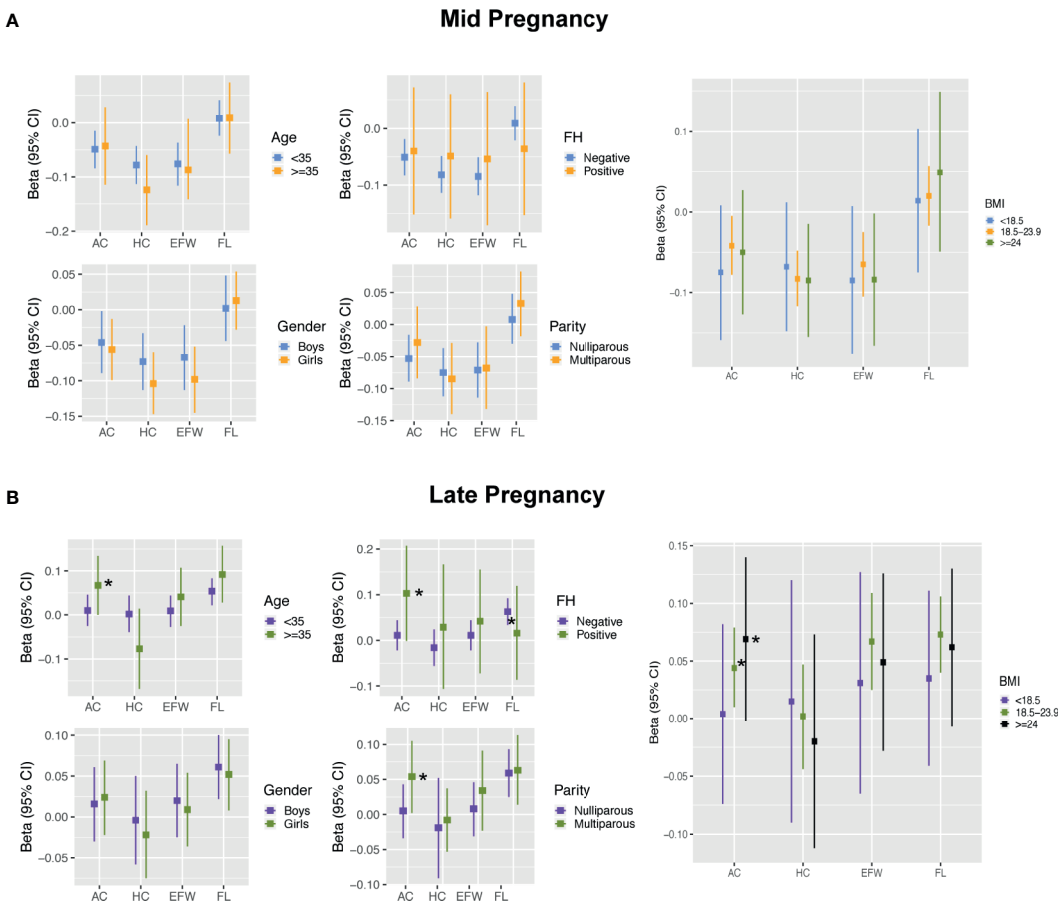

FIGURE 4 | Results for effect modification by maternal and fetal characteristics in mid pregnancy **(A)** and late pregnancy **(B)**. Covariates of adjustment in models: maternal age, parity, pre-pregnancy BMI, gestational age of sample collection, family history of diabetes, and fetal gender. AC, abdominal circumference; HC, head circumference; EFW, estimated fetal weight; FL, femur length; FH, family history of diabetes; BMI, body mass index. *Represent significant association after full adjustment in subgroups for AC.

probabilities in the three BMI subgroups with increasing FPG at the lower levels of FPG and exhibited overlap or reversal of their relative probabilities at higher levels (**Figure 5C**). Stratified analyses showed that the OR values (95% CI) of LGA for women who were underweight, normal weight, and overweight/obese were 1.802 (1.285, 2.513), 1.351 (1.219, 1.497), and 1.333 (1.129, 2.574), respectively. There were no statistical associations for SGA and PTB in any subgroup (data not shown).

Sensitivity Analysis Results

In the sensitivity analyses, the negative relationship between maternal FPG and fetal growth in mid pregnancy and the positive relationship in late pregnancy were not materially changed after excluding pregnant women with GDM. Exclusion of individuals with GDM and further exclusion of individuals with pregnancy complications did not materially change the results (data not shown).

DISCUSSION

In this study, we showed that higher early FPG levels were associated with lower fetal growth in mid pregnancy, and subsequently compensatory increased growth from late pregnancy, resulting in significantly heavier weight and elevated risk of LGA delivery. The whole associations between maternal FPG and detailed measurements of fetal growth parameters in late pregnancy except for FL were fully explained by maternal pre-pregnancy BMI. Furthermore, we showed that advanced age, multiparity, positive family history of diabetes, and higher BMI were associated with an increased AC response to maternal FPG in early pregnancy. Based on pre-pregnancy BMI stratification, FPG was associated with significantly increased risks of LGA in all the three BMI subgroups.

FPG is one of the most commonly used indicators for diabetes, as it reflects beta cell function and generally indicates the secretion of basal insulin (24). This was the first study using

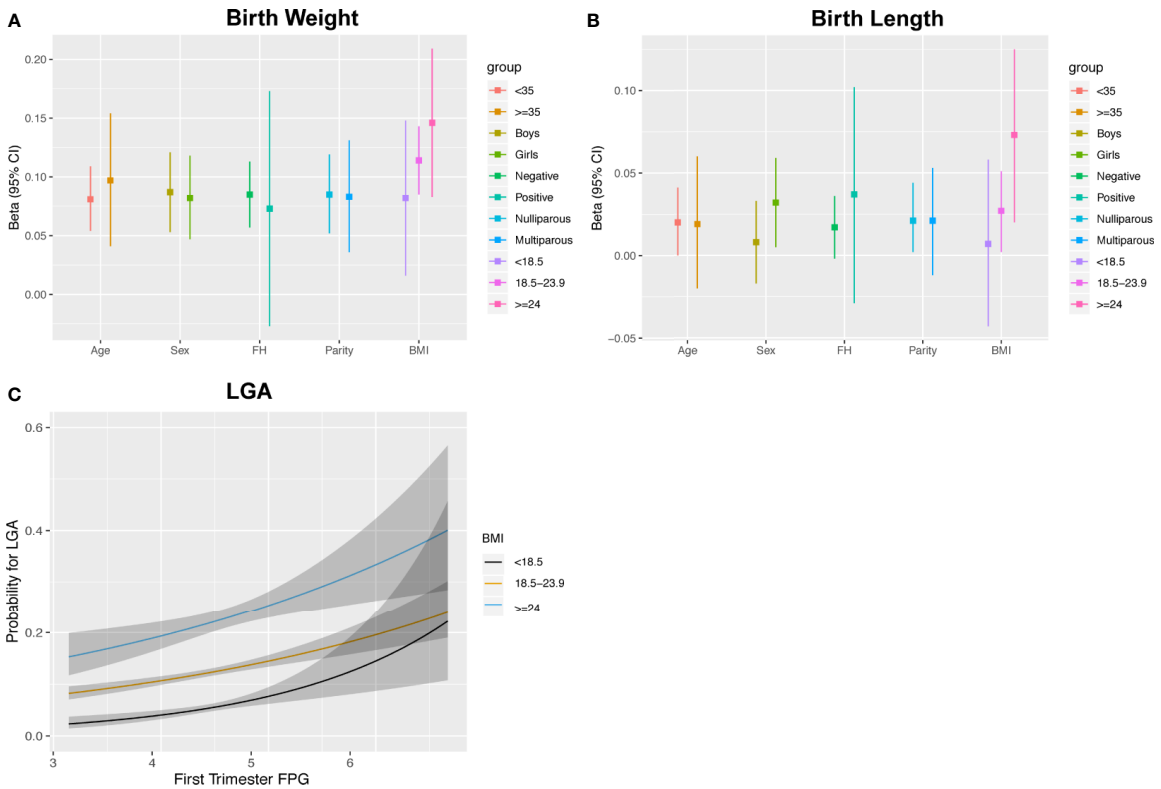

FIGURE 5 | Associations between maternal FPG with birth weight **(A)**, birth length **(B)** and the estimated probability for LGA stratified by pre-pregnancy BMI **(C)**.

fasting plasma samples to investigate fetal growth trajectories during pregnancy. In the current study, per-unit increases in maternal FPG were associated with slowed mid pregnancy fetal growth. This suggests that hyperglycemia affects embryonic development and is a risk factor for fetal growth retardation in the first half of pregnancy. The underlying biological mechanisms may be attributed to a combination of glucose-mediated effects mediated by mitochondrial function, epigenetic modification, and oxidative stress (25–28). Experimental data have indicated that trophoblast cell exposure to hyperglycemia limits migration and invasion, often with dose–response patterns, which further impedes the normal function of the placental villi and interferes with the placentation process (29). These findings suggest that decreased fetal growth may be associated with the worsening of FPG within the respective normal reference range. Alternatively, other studies also demonstrated that hyperglycemia induced upregulation of the C-X3-C motif chemokine ligand 1 (CX3CL1)/C-X3-C motif chemokine receptor 1 (CX3CR1) signaling pathway, which is known to disturb placental perfusion (30, 31). This notion is supported by a study by Stridsklev et al. (32) showing that higher FPG concentrations during early pregnancy positively correlated with the mid pregnancy pulsatility index of the uterine artery. All of these factors triggered a lower chance of efficient glucose flux on the maternal side.

Although the placenta development as a whole is affected by exposure to hyperglycemia, the role of the fetal compensatory response specific to gestational age cannot be ignored. Human fetal glucose availability relies completely on transplacental glucose from mothers (1). The rate of glucose flux to the fetus is controlled by the maternal-to-fetal glucose concentration gradient across the placenta (33). Hyperglycemia-induced apoptosis of non-proliferative syncytiotrophoblast cells leaves incomplete holes in the placenta, which will cause a large flux of glucose into the fetal blood circulation (34). Data have demonstrated that women with higher FPG levels at baseline had a greater risk of developing GDM at approximately 26 weeks, which coincides with the period of elevated maternal endogenous glucose production and reduced insulin sensitivity (35, 36). Stimulation of fetal insulin secretion by maternal hyperglycemia lowered fetal glycemia, which, in turn, increased the maternal–fetal glucose gradient, resulting in rapid fetal growth and excess fat deposition (33). This might be the biological process of accelerated fetal growth in late pregnancy triggered by maternal FPG. In line with these theories, a study among 184 Asian women observed an intrauterine "catch-up" in GDM-exposed fetuses in late pregnancy (32). Furthermore, the exaggerated maternal–fetal glucose gradient by hyperinsulinemic fetuses further attenuates maternal glucose levels, providing an explanation for our study why women who did not develop

GDM also share phenotypic characteristics with obesogenic fetopathy. In another study conducted in the UK, Ong et al. (4) reported that FPG levels assessed in the second trimester in non-GDM mothers independently contributed to neonatal macrosomia. However, due to a lack of data about FPG from periconception or early pregnancy, they were unable to explain the potential biological mechanisms. More challenging is whether early exposure to elevated glucose and subsequently accelerated maturation of fetal beta cells will predispose offspring to metabolic diseases in adulthood. Further study in this population is certainly warranted.

We found that the influences of FPG on accelerated AC and EFW in late pregnancy could be explained by pre-pregnancy BMI but that on birth weight could not. However, the discrepancy is not necessarily contradictory. Body composition in neonates includes but is not limited to those measured in our study (i.e., the head, abdomen, and femur), as well as the trunk and limbs. It is likely that FPG may act preferentially in fetal extremities and the thoracic truncus. As stated in another study by Ong et al. (4), elevated maternal glycemia contributed to offspring fat deposition in the arms and the subscapular and suprailiac regions at birth. The positive relationship with femoral growth from late pregnancy in our study may also provide some clues. It has been well documented that fetal adipocyte proliferation occurs primarily in the third trimester and that AC is a good indicator of fetal fat deposition (37). The subgroup analyses showed that a significantly positive association between FPG and AC was robust to adjustment for BMI among individuals with advanced age, multiparity, and positive family history of diabetes. One possible explanation is that maternal conditions with these traditional risk factors might be profoundly involved in fetal programming through modification of oocyte metabolism, predominantly of their mitochondria, leading to increased susceptibility to or aggravated physiological insulin resistance during pregnancy (38, 39). We further stratified continuous BMI values into categories. AC and EFW in late pregnancy reflected changes in FPG concentrations to a lesser extent in lean women than in normal or obese women. This may be attributed to adiponectin, an antidiabetic adipokine that is richly expressed in lean women to regulate glucose metabolism and therefore attenuate fetal growth (1). Similarly, a study conducted in the UK showed that fetuses exposed to GDM mothers combined with obesity showed the greatest AC growth rates at 28 weeks (40). An unexpected observation was that the effects of FPG on the risk of LGA were strongest in underweight women when FPG levels were at high level. This might partly be explained by the fact that more attention might be given to overweight mothers, and interventional management effectively offsets the adverse pregnancy. In contrast, underweight women were regarded as overlooked. Differential DNA methylated regions might be a potential mechanism linking maternal glucose metabolism and offspring outcomes in different BMI subgroups (41).

In this study, we observed positive associations of first-trimester FPG with FL and BL, even after full adjustment. Both FL and BL are predictors of offspring height. However, few studies have investigated the effect of blood glucose on FL, BL, and height, and more studies are needed to replicate our observations.

The interventions of physical activity and diet counseling have not remarkably benefited those diagnosed with GDM at 24–28 weeks' gestation. In this regard, the IADSPG recommended that early FPG ≥5.1 mmol/L should be considered to define early GDM and supported immediate intervention of maternal glycemic control. To date, whether women with early-onset GDM could benefit from surveillance and management remains controversial due to lack of evidence from large randomized controlled trials (RCTs) (13), and they only observed the outcomes at birth and ignored the process of intrauterine growth. This finding in our study provides potential clinical implications to encourage future large-scale RCTs to pay extra attention to the fetal growth pattern during the management process.

Some limitations of our study should be considered. First, we cannot exclude bias in the selection of the population, since some of the information was based on the medical records and not all participants provided blood samples. It should be noted that self-reported pre-pregnancy weight was applied to calculate BMI, which may cause bias because women tended to underreport their initial weight and it should be used with caution. Second, this study was a hospital-based cohort, and the homogeneous ethnicity of the cohort may increase the internal validity and weaken the generalizability of our findings to other ethnicities. Third, we did not adjust for gestational weight gain (GWG), as fetal growth is a major component of GWG, and additional adjustment of GWG would thus lead to overadjustment. Last, among Caucasians, the Hadlock equation for estimated fetal weight based on FL, AC, and HC has been more widely employed. Although INTERGROWTH-21st has been used less, it is based on a large number of healthy women from eight countries including China. The INTERGROWTH-21st method had strictly defined protocols for conducting of the ultrasound scans, and the statistical analysis was rigorous. Further research is needed to repeat our study with performance of the Hadlock equation.

CONCLUSION

In conclusion, the current findings suggest significant glycemia-related fetal growth deviation and an increased risk of LGA infants, highlighting a potentially imperative need for recognition and management in early pregnancy. This is a first step toward emphasizing that the first trimester is a potentially key window of pregnancy for intervention studies. Additional studies including prospective cohorts or RCTs are needed to confirm a feasible strategy to improve fetal growth and birth outcomes.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the International Peace Maternity and Child Health Hospital (GKLW 2019-58). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FG designed the study, performed the statistical analysis, and wrote the initial manuscript. YL contributed to the study design and revision of the manuscript. ZD and YZ collected and interpreted the data. CZ critically validated the data. JF reviewed, revised, and approved the submitted version. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by a grant from the National Key Research and Development Program of China (2018YFC1004602).

ACKNOWLEDGMENTS

We especially thank the staff and pregnant women at the International Peace Maternity and Child Health Hospital for their support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.666194/full#supplementary-material

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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.

frontiers in Endocrinology

SYSTEMATIC REVIEW
published: 26 August 2021
doi: 10.3389/fendo.2021.668447

Prevalence of Gestational Diabetes Mellitus in the Middle East and North Africa, 2000–2019: A Systematic Review, Meta-Analysis, and Meta-Regression

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OPEN ACCESS

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

Received: *16 February 2021*
Accepted: *30 July 2021*
Published: *26 August 2021*

Citation:
Al-Rifai RH, Abdo NM, Paulo MS, Saha S and Ahmed LA (2021) Prevalence of Gestational Diabetes Mellitus in the Middle East and North Africa, 2000–2019: A Systematic Review, Meta-Analysis, and Meta-Regression. Front. Endocrinol. 12:668447. doi: 10.3389/fendo.2021.668447

Women in the Middle East and North Africa (MENA) region are burdened with several risk factors related to gestational diabetes mellitus (GDM) including overweight and high parity. We systematically reviewed the literature and quantified the weighted prevalence of GDM in MENA at the regional, subregional, and national levels. Studies published from 2000 to 2019 reporting the prevalence of GDM in the MENA region were retrieved and were assessed for their eligibility. Overall and subgroup pooled prevalence of GDM was quantified by random-effects meta-analysis. Sources of heterogeneity were investigated by meta-regression. The risk of bias (RoB) was assessed by the National Heart, Lung, and Blood Institute's tool. One hundred and two research articles with 279,202 tested pregnant women for GDM from 16 MENA countries were included. Most of the research reports sourced from Iran (36.3%) and Saudi Arabia (21.6%), with an overall low RoB. In the 16 countries, the pooled prevalence of GDM was 13.0% (95% confidence interval [CI], 11.5–14.6%, I^2, 99.3%). Nationally, GDM was highest in Qatar (20.7%, 95% CI, 15.2–26.7% I^2, 99.0%), whereas subregionally, GDM was highest in Gulf Cooperation Council (GCC) countries (14.7%, 95% CI, 13.0–16.5%, I^2, 99.0%). The prevalence of GDM was high in pregnant women aged ≥30 years (21.9%, 95% CI, 18.5–25.5%, I^2, 97.1%), in their third trimester (20.0%, 95% CI, 13.1–27.9%, I^2, 98.8%), and who were obese (17.2%, 95% CI, 12.8–22.0%, I^2, 93.8%). The prevalence of GDM was 10.6% (95% CI, 8.1–13.4%, I^2, 98.9%) in studies conducted before 2009, whereas it was 14.0% (95% CI, 12.1–16.0%, I^2, 99.3%) in studies conducted in or after 2010. Pregnant women in the MENA region are burdened with a substantial prevalence of GDM, particularly in GCC and North African countries. Findings have implications for maternal health in the MENA region and call for advocacy to unify GDM diagnostic criteria.

Systematic Review Registration: PROSPERO CRD42018100629

Keywords: gestational diabetes mellitus, MENA region, prevalence, meta-analysis, systematic review

INTRODUCTION

Gestational diabetes mellitus (GDM) (1) is usually diagnosed during the second and third trimesters of pregnancy (2). Risk factors of GDM include excessive body weight, low level of physical activity, consanguineous marriage, previous history of GDM, glycated hemoglobin >5.7%, and history of cardiovascular disease (3). As the toll of overweight and obese reproductive-age females soars, the risk of developing hyperglycemia in pregnancy increases (4).

GDM has a global public health burden (5) with both short- and long-term consequences on health. The short-term ramifications of GDM include adverse perinatal outcomes for the affected women (e.g., preeclampsia, polyhydramnios, and increased cesarean section ["C-section"] risk) and their neonates (e.g., macrosomia and shoulder dystocia) (1, 6), whereas the long-term complications of GDM incorporate the risk of type 2 diabetes mellitus (T2DM) for the mother and the risk of childhood obesity, impaired glucose tolerance, and/or metabolic syndrome for their neonates (6). Since increased blood glucose levels are associated with certain perinatal complications, gestational blood glucose control is vital (7).

Understanding population-specific healthcare needs at specific points of time is essential, and prevalence estimates are ideal for such purposes (8). Unfortunately, the global GDM prevalence estimates (<1%–28%) show a wide variation due to ethnicity, ethnic variation among various populations, and inconsistent use of screening and diagnostic criteria (4, 9). To precisely estimate the burden of GDM of a particular geographic area, it is essential to determine the region-specific prevalence estimate. There is scant literature on the prevalence of GDM in the Middle East and North Africa (MENA) region, although two of the main risk factors [physical inactivity and above-normal body mass index (BMI)] are identified as being highly prevalent in this region (10). Moreover, three of the world's top ten most prevalent countries for diabetes mellitus belong to this region: Saudi Arabia (24%), Kuwait (23%), and Qatar (23%) (11). For the entire Eastern Mediterranean region, the existing prevalence estimate of GDM is 14.5%, although this includes only cases diagnosed according to the World Health Organization (WHO) 1999 criteria (4). One previous survey showed that physicians and hospitals in this region use different criteria to diagnose GDM (12).

A systematic review and meta-analysis of prevalence studies is considered to be an ideal method to understand the burden of GDM at regional and national levels. In this systematic review, meta-analysis, and meta-regression, we estimated the weighted pooled prevalence of GDM in the MENA region, at the regional, subregional, and national levels, based on literature published between January 2000 and December 2019.

METHODS

This review follows the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2009 guidelines (13). The PRISMA checklist is provided elsewhere (**Supplementary File 1**). Following our published protocol, we report here "systematic review 2" (14). We implemented minor amendments whenever needed, including an updated database search.

Data Source and Searches

To identify eligible studies reporting the prevalence of GDM in the MENA countries, we conducted a comprehensive search of five electronic databases (MEDLINE, EMBASE, Web of Science, SCOPUS, and Cochrane library) from January 1, 2000, to December 31, 2019, using variant Medical Subject Headings and free-text terms. Restricting the literature search to 2000 was to estimate changes in the GDM prevalence over the past two decades (before and after 2010), at national, sub-regional, and regional levels, whenever enough data is available for the meta-analysis. The literature search strategy was developed in consultation with an expert librarian at the National Medical Library at the United Arab Emirates University. The full search strategy available in the published protocol (14). Retrieved references were imported to the Covidence software (Covidence, Melbourne, Australia) (15). Deduplication of similar references was performed automatically by the Covidence software.

Study Selection

To identify and select studies for inclusion, we followed the PECO(T) framework: participants, exposure, comparator, outcome(s), and type of study (16). However, we considered only participants and outcomes because the focus of this review was on studies reporting the prevalence of GDM. Study eligibility criteria are presented in **Table 1**.

Identifying Eligible Studies

Titles and abstracts were screened by RHA, NMA, and MSP to detect eligible research reports on the prevalence of GDM. For studies that appeared eligible, the full text was reviewed (RHA, NMA, and MSP). Screening of all titles and abstracts and full text articles was performed independently by two reviewers. Disagreements among reviewers were resolved by discourse. We also searched the reference lists of eligible studies for studies that might have been missed. **Figure 1** shows the PRISMA flowchart of study selection.

In this review, the term "research report" is used to refer to a full published research document. The term "study" is used to refer to a single study on a specific population group. One big observational study (one research report) provides GDM data stratified into four age groups (four studies). Hence, one research report could contribute several studies on GDM prevalence.

Data Extraction and Quality Assessment

Relevant data from eligible studies were extracted into a predesigned Excel sheet using a predefined list of numerical and string variables. The outcome of interest was the weighted prevalence of GDM in pregnant women in the MENA countries, according to various characteristics including, but not limited to, age, BMI, trimester, and time period. We extracted author names, publication year, country, city, and study setting.

TABLE 1 | Study eligibility criteria.

Criteria	Inclusion	Exclusion
Population	Pregnant women regardless of their age, parity, or any maternal or sociodemographic characteristics	Non-pregnant women
Outcome	Studies reported quantitative or calculable GDM prevalence estimate (s) regardless of the GDM diagnostic criteria/guidelines or pregnancy trimester	Studies on pregnant women with no information related to GDM prevalence
Sample size	Studies with at least ten pregnant women tested for GDM	Studies with less than ten pregnant women tested for GDM
Study design	Cross-sectional, cohort studies, case–control studies comparing no-GDM with no-GDM subpopulations, and trials with nonpharmaceutical interventions	Case–control studies comparing GDM with no-GDM populations, qualitative studies, modeling studies, case reports and case series regardless of the number of cases, narrative and systematic reviews, conference abstracts with no full information, editorials, commentaries, letters to the editor, author replies, and other publications that did not include quantitative data on the prevalence of GDM
Geographical region	Any of the 18 Arab countries (Algeria, Bahrain, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Saudi Arabia, Syria, Tunisia, United Arab Emirates, West Bank and Gaza, and Yemen) in addition to Iran and Malta in the MENA region, according to the definition of the World Bank Country and Lending Groups (17).	All other countries
Publication period	January 2000 to December 2019	Studies conducted before January 2000 or after December 2019 and studies for which the time period of the GDM tests in pregnant women was unclear
Language	English language	Non-English studies
Setting	No limitations. Hospital based, population based, or clinic based.	No limitations
Duplicate studies	–	Studies duplicating or potentially duplicating GDM ascertainment in the same population. In the case of duplicate publications, we included only the study containing the most relevant information in the context of the prevalence of GDM

In addition, data on the implemented methodology (design, data collection period, sampling strategy, and GDM diagnosis and ascertainment methodology) and characteristics of the studied pregnant women (age, pregnancy trimester, sample size, number of women with GDM and GDM prevalence) were extracted whenever available.

In addition to the overall prevalence of GDM, some research reports also reported the prevalence of GDM stratified according to different characteristics, such as age, parity, comorbidity, pregnancy trimester, and BMI. In such reports, data extraction was performed for the stratified GDM prevalence, following the rule that the study had to have at least ten tested subjects per strata; otherwise, information on the entire tested sample was extracted. A predefined sequential order was established when extracting stratified GDM prevalence estimates as follows: GDM stratified first according to comorbidities followed by parity, age, and BMI. This prioritization was used to identify the strata with more information on the tested pregnant women. When there was no stratification for the prevalence of GDM, we extracted the overall GDM prevalence measured.

For each research report reporting the stratified prevalence of GDM according to more than one category (i.e., age and BMI), one category per research report was considered and included based on the aforementioned prioritization scheme, to avoid double counting. In studies in which GDM was ascertained using different guidelines, the most sensitive and reliable ascertainment assay was considered (i.e., prioritizing fasting blood glucose over self-reported) or was based on the most recent and updated criteria (i.e., prioritizing WHO 2010 over 2006 criteria).

The risk of bias (RoB) assessment was performed at the level of the research report rather than the study. The quality of each research report was evaluated according to criteria of the National Heart, Lung, and Blood Institute (18). Six of 14 items from the quality assessment tool for prevalence studies were used (18). The six quality-related items assessed the research question/objectives, studied population, sample size justification, and outcome measures and assessment. Eight items were not used because they are applicable only to follow-up cohort studies. For additional quality assessment, we also assessed the robustness of the implemented methodology using three additional quality-of-evidence criteria: sampling methodology, GDM ascertainment methodology, and precision of the estimate. Studies were considered to have "high" precision if at least 100 women were tested for GDM. We computed the overall proportion of research reports with potentially low RoB across each of these nine quality criteria and also computed the proportion (out of nine) of quality items with a potentially low RoB for each of the included research reports.

Data abstraction and quality assessment were performed independently by two reviewers (NA and MP) and cross-checked for disagreements. Any discrepancies in the extraction phase or in the quality assessment between the reviewers were discussed and resolved with a consultation of a senior reviewer (RA-R).

Data Synthesis and Analysis

To estimate the weighted pooled prevalence of GDM and the corresponding 95% confidence interval (CI), we performed meta-analyses of the extracted data. The Freeman–Tukey double arcsine transformation method was applied to stabilize the variances of the prevalence measures (19). The inverse variance method was used to weight the estimated pooled prevalence measures (20). Dersimonian–Laird random-effects model was used to estimate the overall pooled GDM

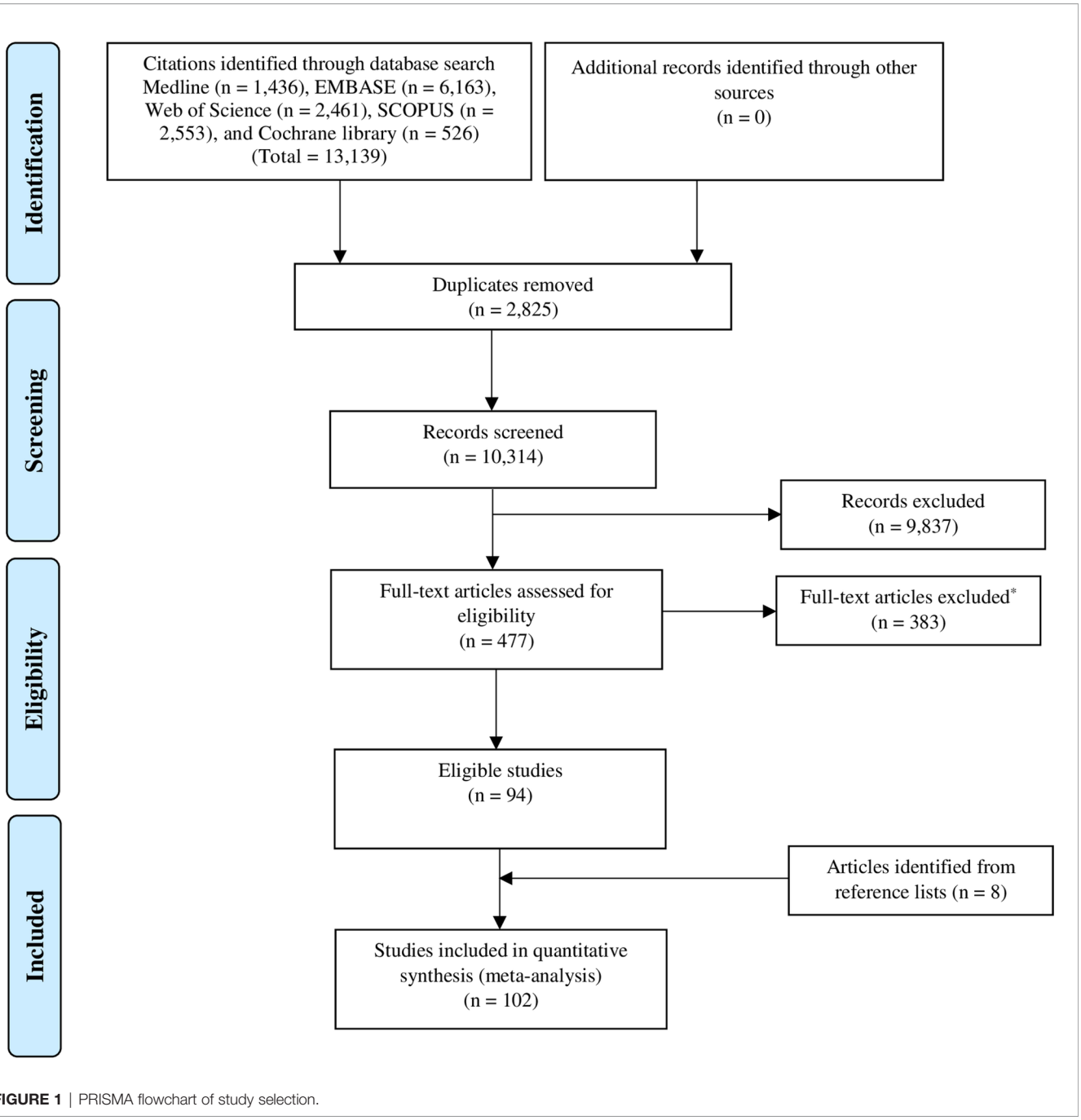

FIGURE 1 | PRISMA flowchart of study selection.

prevalence (21). Cochran's Q statistic and the inconsistency index, I^2, were calculated to measure heterogeneity (22). Along with the pooled estimates, ranges and median were also reported to describe the dispersion of the GDM prevalence measures reported in the literature. The prediction interval, which estimates the 95% interval in which the true effect size in a new prevalence study will lie, was also quantified and reported (22).

For the subgroup meta-analysis, country-level pooled estimates were generated overall and based on time period. In addition, to estimate the change in GDM both at the country level and overall, the data collection period was stratified into two time periods: 2000–2009 and 2010–2019. For studies in which the data collection period overlapped, the collection period was defined as "overlap" so as not to miss any important data when estimating country-level, subregional, and regional prevalence. The median (~2 years) was used in studies with an unclear data collection period. In these studies, the median was subtracted from the year of publication to estimate the year of data collection.

The weighted pooled prevalence, regardless of country, was also estimated according to the age of the pregnant women, trimester, BMI, study period, GDM ascertainment guidelines,

and sample size (<100 or ≥100). The provision of pooled estimates regardless of the ascertainment guidelines was justified by the fact that the women were defined and treated as GDM patients following each specific ascertainment guideline.

Accumulated evidence has shown that GDM is associated with an increased risk of C-section (23, 24) and maternal mortality (4). Independent of the research report and the characteristics of the tested pregnant women for GDM, we estimated the pooled GDM prevalence according to the C-section rate and maternal mortality ratio (MMR). Information on the C-section rate (25, 26) and MMR were retrieved from various resources (27). Depending on data availability, information on C-section rate and MMR was extracted in the same or the closest year to the estimated GDM prevalence. For every GDM study, the rate of C-section was then categorized as <15%, 15–29%, >30%, or unclear, whereas the MMR was categorized as either ≤100/100,000 live births, >100/100,000 live births, or unclear.

To provide prevalence estimates at a subregional level, we regrouped MENA countries into four subregions, namely, North Africa, Gulf Cooperation Council (GCC) countries, Levant, and Iran/Iraq region. We estimated the overall pooled prevalence in these subregions and according to patient age, trimester, BMI, study period, GDM ascertainment guidelines, rate of C-section, and MMR.

Random-effects univariate and multivariable meta-regression models were implemented to identify sources of between-study heterogeneity and to quantify their contribution to variability in the prevalence of GDM. In univariate meta-regression models, analysis was performed by country, age, pregnancy trimester, BMI, and sample size. All variables with a p-value <0.1 in the univariate models were included in the multivariable model. In the final multivariable model, a p-value ≤0.05 was considered statistically significant, which contributed to the heterogeneity in prevalence estimates.

Publication Bias

A funnel plot was generated to explore the small-study effect on the pooled GDM prevalence estimates. The funnel plot was created by plotting each GDM prevalence measure against its standard error. The asymmetry of the funnel plot was tested using Egger's test (28).

All analyses were performed using the *metaprop* (29) and *metareg* packages in Stata/SE v15 (30).

The study is registered with PROSPERO, number CRD42018100629.

RESULTS

Database Search and Scope of the Review

Of the 13,139 citations retrieved from the 5 databases, 102 research reports were deemed eligible and included in this review (**Figure 1**).

The research reports were from 16 countries in the MENA region: Algeria (one), Bahrain (two), Egypt (four), Iraq (three), Iran (37), Jordan (four), Lebanon (two), Libya (one), Morocco (one), Oman (five), Qatar (six), Saudi Arabia (22), Sudan (two), Tunisia (one), United Arab Emirates (UAE) (eight), and Yemen (one). The prevalence data for both decades (time periods) were available from six countries (Bahrain, Iran, Oman, Qatar, Saudi Arabia, and the UAE); for the other countries, data were available for the time period 2010–2019 (**Table 2**). Self-reported GDM status was documented in five research reports (31, 73, 83, 90, 119). The predominantly used GDM diagnostic criteria in the MENA region were from the American Diabetes Association and the International Association of Diabetes and Pregnancy Study Group (ADA/IADPSG; 48.5% of studies).

Crude GDM Prevalence

The 102 research reports (31–67, 69–132) yielded 198 GDM prevalence studies. Iran (32.3%) (41, 43–67, 69–77) and Saudi Arabia (24.2%) (97–118) contributed to most of the prevalence studies, followed by Qatar (9.7%). In these prevalence studies, a total of 279,202 pregnant women were tested for GDM between 2000 and 2019, and the crude GDM prevalence was estimated to be about 11.0%. The prevalence of GDM ranged from 0.0% in three studies (60, 98, 104) to 50.7% in pregnant women aged 40–49 years in Saudi Arabia tested between 2007 and 2009 (111). The GDM prevalence range was identical in studies reported in the two decades (**Tables 2** and **3**).

Regional and National Pooled GDM Prevalence

The overall pooled weighted GDM prevalence in the MENA region was 13.0% (95% CI, 11.5–14.6%, I^2, 99.3%; **Table 3**; **Figure 2**). The highest GDM prevalence was observed in Qatar (20.7%, 95% CI, 15.2–26.7%; 19 studies), followed by 15.5% in Saudi Arabia (95% CI, 12.6–18.8%; 48 studies) and 13.4% in the UAE (95% CI, 9.4–18.0%; 14 studies; **Table 3**). The lowest pooled GDM prevalence was 4.7% in Jordan (95% CI, 3.0–6.7%; six studies) reported between 2010 and 2019. In the studies conducted between 2000 and 2009, the prevalence estimates ranged from 3.2% in Oman (95% CI, 2.3–4.2%) to 22.3% in Qatar (95% CI, 15.9–29.4%), and in the studies conducted between 2010 and 2019, it ranged from 3.0% in Algeria (95% CI, 1.4–6.4%) to 23.0% in Sudan (95% CI, 3.3–45.2%; **Table 3**).

For the six countries reporting data on both decades, the overall GDM prevalence was estimated separately for each decade. There was a rise in the prevalence of GDM by 4% to 8% in Iran, Oman, and Saudi Arabia and a decrease of 2% to 4% in Bahrain, Qatar, and the UAE from 2000–2009 to 2010–2019 periods. The largest increase in prevalence occurred in Oman: from 3.2% in 2000 (95% CI, 2.3–4.2%) to 11.0% in 2019 (95% CI, 8.0–15.0%, I^2, 84.2%). An appreciable reduction in the prevalence of GDM was observed in the UAE: from 15.5% in 2000 (95% CI, 9.2–23.0%, I^2, 99.2%) to 11.3% in 2019 (95% CI, 7.6–15.69, I^2, 93.2%; **Tables 2** and **3**).

Subgroup Pooled GDM Prevalence

The prevalence of GDM in pregnant women aged ≥30 years was 2.26 times higher (21.9%, 95% CI, 18.5–25.5%, I^2, 97.1%) than that estimated in younger (15–29 years) pregnant women (9.7%, 95% CI, 6.7–13.2%, I^2, 98.0%). A trend was observed between GDM and pregnancy trimester. The weighted GDM prevalence

TABLE 2 | Summary of the included studies reporting the prevalence of GDM in pregnant women in the MENA region, 2000–2019, stratified by country (102 reports with 198 prevalence measures).

Author, year [Ref]	Duration of data collection	Country, city	Setting	Design	Sampling	Population	Strata	Ascertainment method	Tested sample	GDM	
										Positive	%
Tebbani F. et al. (31)	12/2013–12/2015	Algeria, Constantine	Maternities, antenatal and private gynecologists	PC	Unclear	Algerian pregnant women aged 19–41 years who entered prenatal care before 16 weeks of amenorrhea	All	Face-to-face interview	200	6	3.0
Rajab K. et al. (32)	2002–2010	Bahrain	Government central hospital that is responsible for approximately 80% of all births in Bahrain	CS	Whole population	Pregnant women	All 2002–2010	NDDG 1979 guidelines	49,552	4,982	10.1
Al Mahroos S. et al. (33)	1/2001–12/2002	Bahrain	ANC clinics at health centers and at Salmaniya Medical Complex	CS	All women during the study period	Nondiabetic pregnant women	All Bahraini Expatriate	Fourth International Workshop-Conference on GDM	10,495 7,575 2,920	1,394 1,175 219	13.7 15.5 7.5
Rakha S and El Marsafawy H (34)	01/2011 – 01/2019	Egypt, Mansoura	Pediatric cardiology unit in Mansoura University Children's Hospital	CS	Whole population	Pregnant with at least one high risk indication of fetal echocardiography	All	Unclear	458	57	12.5
Rezk M and Omar Z (35)	05/2012–05/2017	Egypt	Shibin El-Kom	PS	Whole Population	Pregnant women with chronic HCV infection Pregnant women with no HCV infection	All	Unclear	342 170	90 10	26.3 5.9
Maged AM. et al. (36)	01/2011–02/2013	Egypt, Cairo	Kasr El Aini Hospital	PS	Unclear	Pregnant women in their first trimester with a singleton living fetus, excluding women with preexisting type 1 or 2 diabetes mellitus, hypertension, liver disease, renal disease, or the presence of active infection	All	ADA 2002	269	27	10.0
Elkholi DGEY and Nagy HM (37)	3/2007–3/2013	Egypt, Tanta	Infertility Clinic, Tanta University Hospitals	CS	Unclear	Obese pregnant women (BMI ≥30 kg/m^2) with PCOS before treatment for infertility, attending 100 patients with android obesity and 100 patients with gynoid obesity	All	Fifth International Workshop Conference on Gestational Diabetes criteria	131	10	7.6
			Outpatient Clinic of Department of Obstetric			Non-PCOS pregnant women with android obesity were controls for group 1 and 100 non-PCOS pregnant women with gynoid obesity who were free of DM before pregnancy			177	14	7.9
Mohammed AK and Alqani VHA (38)	06/2016–07/2017	Iraq, Al-Diwaniyah	Child and Maternity Teaching Hospital	CS	Unclear	Pregnant women with a mean age of 30.02 ± 6.37 years	All	Unclear	49	12	24.5
Alawad ZM and Al-Omary HL (39)	09/2018–12/2018	Iraq, Baghdad	Baghdad teaching hospital	PC	Unclear	Women between 18 and 40 years of age, normal vaginal deliveries to live singletons with no congenital anomalies, women with normal thyroid function test	All	Unclear	35	7	20.0
Safari K et al. (40)	10/2017–01/2018	Iraq, Erbil	Hawler Maternity Teaching Hospital	CC	Unclear	Singleton Muslim pregnant women aged 18–35 years who fasted in Ramadan during the second trimester	All	Unclear	155 144	4 12	2.6 8.2
Maghbooli Z et al. (41)	2005	Iran, Tehran	Five university hospital clinics of the Tehran University of Medical Sciences	CS	Unclear	Pregnant women with no previous history of DM and who sought prenatal care during the first half of their pregnancies	All	Carpenter and Coustan criteria	741	52	7.0
Abolfazl M et al. (42)	2006	Iran, Shiraz	Shiraz Hospital	Unclear	Random	Pregnant women with a mean age of 31.2 years	All	Unclear	420	70	16.6
Keshavarz M et al. (43)	12/1999–01/2001	Iran, Shahrood	Fatemiyeh Hospital	PC	Consecutive	All pregnant women within the catchment area of the hospital were referred to this antenatal service; twin	All	Carpenter and Coustan criteria	1,310	63	4.8

(Continued)

TABLE 2 | Continued

Author, year [Ref]	Duration of data collection	Country, city	Setting	Design	Sampling	Population	Strata	Ascertainment method	Tested sample	GDM	
										Positive	%
						pregnancies, miscarriages, terminations, and women with preexisting diabetes were excluded from our study					
Hadaegh F et al. (44)	3/2002–3/2004	Iran, Bandar Abbas	Obstetrics clinics in various parts of Bandar Abbas city in southern Iran	CS	All women during the study period	Pregnant women with a mean age of 24.9 years in the 24th to the 28th week of pregnancy excluding women with history of diabetes, using drugs that affect glucose metabolism, with chronic liver disease, endocrine disorders (such as hyperthyroidism), or connective tissue disorders, and with major medical conditions, such as persistent hypertension	All <20 years 20–24 years 25–29 years 30–34 years 35–≥45 years	Carpenter and Coustan criteria	700 93 279 184 103 41	62 2 15 22 13 10	8.9 2.2 5.4 12.0 12.6 24.3
Amooee S et al. (45)	2006–2008	Iran, Sheraz	Hafez and Zeinabieh Hospitals of Shiraz University of Medical Sciences	CS	Unclear	All singleton pregnancies with and without minor β-thalassemia	With minor β-thalassemia Without minor β-thalassemia	Unclear	510 512	16 20	3.5 20.0
Lamyian M et al. (46)	08/2010–01/2011	Iran, Tehran	Prenatal clinics in five hospitals affiliated with universities of medical sciences in different districts	PS	Random	Singleton pregnant women age 18–45 years, excluding preexisting diabetes and smokers	All	ADA 2016	1,026	71	6.9
Soheilykhah S et al. (47)	2007–2009	Iran, Yazd	Two prenatal clinics in Yazd	PS	Unclear	Iranian pregnant women with a mean age of 27 years, excluding those with prepregnancy DM	All <25 years 25–29 years ≥30 years	ADA 2004	734 247 202 285	95 19 30 46	13.0 7.7 14.9 16.1
Pirjani R et al. (48)	2012–2013	Iran, Tehran	Dr Shariati and Arash Hospitals	PS	Convenience	Pregnant women with a mean age of 28.70 ± 5.57 years (range 17–44 years) excluding women with a history of diabetes (type 1 or 2), tested for GDM at the 24th–28th weeks of pregnancy	All	ADA 2012	256	78	30.5
Soheilykhah S et al. (49)	01/2010–02/2013	Iran, Yazd	Two prenatal clinics (Mojibian and Shahid Sadoughi Hospitals	CS	Unclear	Pregnant women tested for GDM at 24–28 weeks of pregnancy, excluding women with type 1 or 2 diabetes, malignancies, acute or chronic inflammatory or infective diseases, acute or chronic liver disease, and iron deficiency anemia	All	ADA 2013	1,279	281	21.9
Shahbazian H et al. (50)	08/2014–02/2015	Iran, Ahvaz	Prenatal clinic of a public medical hospital and four private prenatal clinics	PS	Unclear	Pregnant women tested for GDM between 24 and 32 weeks of gestation	All 15–24 years 25–34 years 35–44 years	IADPSG	750 190 452 108	224 32 145 47	29.9 16.8 32.1 43.5
Yassaee F et al. (51)	10/2008–2/2010	Iran, Tehran	Teaching hospital in the North of Tehran	PS	Unclear	Pregnant women with idiopathic thrombocytopenic purpura at a mean age of 28.9 years		Unclear	21	6	28.6
Ashrafi M et al. (52)	2012–2013	Iran, Tehran	Reproductive biomedicine research center, Royan Institute	CS	Unclear	Non-PCOS pregnant women who conceived spontaneously with a mean age of 26.4 years	All	Fifth International Workshop on GDM	234	17	7.3
						Non-PCOS pregnant women conceived with RT with a mean age of 30.7 years	All		234	70	29.9
						PCOS pregnant women with ART with a mean age of 29.6 years	All		234	104	44.4

(Continued)

TABLE 2 | Continued

Author, year [Ref]	Duration of data collection	Country, city	Setting	Design	Sampling	Population	Strata	Ascertainment method	Tested sample	GDM	
										Positive	%
Goshtasebi A et al. (53)	8/2010–1/2011	Iran, Tehran	Prenatal clinics in five hospitals affiliated with universities of medical sciences	CS	Consecutive	Pregnant women aged 18–45 years, singleton pregnancy, gestational age ≤6 weeks, gestations ≤2, and nonsmokers	All	ADA 2016	1,026	71	6.9
Ashrafi M et al. (54)	11/2011–10/2012	Iran, Tehran	Reproductive Biomedicine Research Centre of the Royan Institute,	CS	Unclear	Pregnant women who conceived after fresh IVF/ICSI or intrauterine insemination at a mean age of 31.3 years with no history of DM, family history of DM, GDM	All	ADA 2005	145	54	15.7
			Akbarabadi Women's Hospital, affiliated with Tehran University of Medical Science	CS	Unclear	Pregnant women with singleton spontaneous pregnancies at a mean age of 26.6 years and with no history of DM, family history of DM, or GDM	All		215	22	25.1
Jamali S et al. (55)	4/2012–10/2015	Iran, Jahrom	Paymaneh Hospital Jahrom, Iran	CS	Unclear	Inclusion criterion was all women aged 15–45 years; incomplete and doubtful data were excluded; the study compared 154 women in the first group (teenage group), 400 women in the second group (control group), and 196 women in the third group (adult women)	All	Medical Records			
							15–45 years		750	16.2	2.1
							15–19 years		154	1	0.6
							20–34 years		400	7	1.8
							35–45 years		196	8	4.1
Pourali L et al. (56)	7/2009–7/2014	Iran, Mashad	Ghaem Hospital	CS	Convenience	Women with dichorionic spontaneous twin pregnancy with a mean age of 27.1 years	All	Medical records	96	8	8.3
						Women with dichorionic pregnancy following ART with a mean age of 28.9 years			31	8	25.8
Mehrabian F and Rezae M (57)	1/2009–3/2013	Iran, Isfahan	Shahid Beheshti Hospital	CS	Unclear	Pregnant women who were infertile due to PCOS with an age range of 18–42 years	All	ADA 2011	180	50	27.8
Mehrabian F and Hosseini SM (58)	2011–2012	Iran, Isfahan	Isfahan University of Medical Sciences	CS	Convenience	Pregnant women without preexisting diabetes, mean age 27.6 years	All	Unclear	944	72	7.6
Hosseini E et al. (59)	10/2015–01/2017	Iran, Isfahan	10 community health care centers	CS	Consecutive	Women 18–45 years old with singleton pregnancy	All	IADSPG two-step approach	929	93	10.0
Hantoushzadeh S et al. (60)	2/2012–3/2015	Iran, Tehran	Maternal, Fetal and Neonatal Research Center, Vali-asr Teaching Hospital	CS	Unclear	Pregnant women aged 20–32 years with singleton pregnancies screened for GDM at 28 weeks. excluding women with a history of type 1 or type 2 diabetes mellitus, missing information about prepregnancy diabetes status or BMI, incomplete data on glucose tolerance testing or weight gain during pregnancy	All	ACOG	1,279	100	7.8
							Underweight		27	0	0.0
							Normal weight		751	45	3.3
							Overweight		381	35	9.2
							Obese		120	20	16.7
Niromanesh S et al. (61)	2008–2010	Iran, Tehran	Tehran Women General Hospital	CS	Consecutive	Normal pregnant women 20–35 years of age with gestational age 16–20 weeks, gravid >2, BMI of 20–25 kg/m² were included in the study, excluding women with a history of PTB, preeclampsia, diabetes, GDM, primigravida, those with a BMI >25, and high maternal age (>35 years)	High triglyceride level (>195 mg/dL)	Unclear	45	9	20.0
							Normal triglyceride level (<195 mg/dL)		135	8	5.9
Vaezi A et al. (62)	2009–2012	Iran, Tehran	Akbarabadi Hospital	RC	Convenient	Medical records of pregnant women aged between 18 and 50 years admitted to the hospital to obtain prenatal care	All	Unclear	580	56	9.6
							With asthma		274	37	13.5
									306	19	6.2

(Continued)

TABLE 2 | Continued

Author, year [Ref]	Duration of data collection	Country, city	Setting	Design	Sampling	Population	Strata	Ascertainment method	Tested sample	GDM	
										Positive	%
							Without asthma				
Hossein–Nezhad A et al. (63)	Unclear	Iran, Tehran	Five teaching hospitals affiliated with Tehran University of Medical Sciences	CS	Consecutive	Pregnant women referred to ANC visits with no known history with known diabetes were excluded from the study	All	Carpenter and Coustan	2,416	114	4.7
							15–45 years		1,209	27	2.2
							15–24 years		1,001	56	5.6
							25–34 years		206	31	15.0
							35–45 years				
Nastaran SA et al. (64)	10/2009–8/2010	Iran, Tehran	Milad Hospital	PS	Convenience	Pregnant woman referred to the pregnancy care clinics with a single fetus, aged 18–35 years with a gestational age of 1–13 weeks, a parity of 3 or less, lack of known systemic diseases, and lack of gestational diabetes during previous pregnancies	All	Carpenter and Coustan	600	49	8.2
Talebian A et al. (65)	2/2007–12/2012	Iran, Kashan	Shabihkhani, Shahid Beheshti and Milad hospitals	CS	Unclear	Pregnant women with normal pregnancies and with neural tube defects	All	Unclear	300	21	7.3
Kouhkan A, et al. 2018 (66)	11/2014–1/2017	Iran, Tehran	Royan Institute and maternity teaching hospital located in Tehran	PC	Whole population	Singleton pregnant women aged 20–42 years, who conceived via ART or SC	All	ADA/IAPDSG	574	287	50
Abedi P et al. (67)	08/2013–10/2014	Iran, Ahfav	Four centers from the east and three centers from the west of Ahvaz	CS	Unclear	Pregnant women	All	Medical records	700	43	6.1
Pezeshki B et al. (68)	04/2015–04/2016	Iran, Zanjan	Seven health care centers affiliated with Zanjan University of Medical Sciences	PC	Whole population	Pregnant women between the ages of 18 and 35 years, gestational age of equal or less than 12 weeks at first visit, a BMI of between 30 and 18.5 kg/m^2, and a blood pressure of less than 140/90 mm Hg during first visit, tested for GDM in the first trimester	All	ADA 2016	356	25	7.0
Heydarpour F et al. (69)	2015–2017	Iran, four cities were selected from each province	One rural and one urban health clinic were selected in each city	RC	Multistage	Pregnant women with: a hemoglobin level less than 11 g/dL during the first trimester	All	Medical records	1,038	27	2.6
						a hemoglobin level more than 11 g/dL during the first trimester			2,463	106	4.3
						a hemoglobin level less than 11 g/dL during the third trimester			756	28	3.8
						a hemoglobin level more than 11 g/dL during the third trimester			1,986	68	3.4
Fazel N et al. (70)	08/2014–04/2015	Iran, Sabzevar	From 18 obstetric clinics associated with Mobini Hospital	PC	Cluster random sampling	Pregnant women in gestational week 24 or less	All	Medical records	1603	30	1.87
Nouhjah S. et al. (71)	03/2015–01/2016	Iran, Ahvaz	25 urban and public and private prenatal care clinics	PC	Unclear	Pregnant women	All	IADPSG	800	176	22.0
Maghbooli Z et al. (72)	04/2016–03/2017	Iran, Tehran	Prenatal care clinics in two regions in Tehran, Iran	CC	Unclear	Pregnant women living in nonpolluted areas	All	Unclear	44	3	6.8
Salehi-Pourmehr H et al. (73)	12/2012–01/2016	Iran, Tabriz	All health centers in Tabriz (65 centers and subcenters)	PC	Unclear	Obese (BMI ≥ 35 kg/m^2) pregnant women in the first trimester of pregnancy, aged 18–35 years	All	Self-reported	62	7	11.0

(Continued)

TABLE 2 | Continued

Author, year [Ref]	Duration of data collection	Country, city	Setting	Design	Sampling	Population	Strata	Ascertainment method	Tested sample	GDM	
										Positive	%
Zargar M et al. (74)	2011–2016	Iran, Ahvaz	Pregnant women referring to three infertility centers in Ahvaz city	CC	Randomly	All women undergoing ART	All	Unclear	318	33	10.4
Mojtahedi SY et al. (75)	04/2010–05/2016	Iran, Tehran	Ziaeean and Imam Khomeini hospitals in Tehran	CS	Random	Mothers of neonates (<15 days) with hyperbilirubinemia (> 15 mg/dL)	All	Medical records	163	41	25.2
Eslami E et al. (76)	07/2016–04/2016/ 12/2017–02/2017	Iran, Tehran	12 health centers of Tehran	RCTs	Unclear	Singleton pregnant females with BMI greater than 25 aged 18 and older, gestational age of 16–20 weeks	All	Unclear	70	17	24.3
						Singleton pregnant females with BMI greater than 25, aged 18 and older, gestational age of 16–20 weeks receiving lifestyle training	All		70	15	21.4
Mardani M et al. (77)	2015–2016	Iran	Health care centers	CC	Whole population	Pregnant women with severe acute respiratory illness	All	Medical records	24	3	12.5
					Randomly	Living pregnant women with severe acute respiratory illness	All		100	4	4.0
Basha S et al. (78)	01/2015–01/2016	Jordan	Jordan University Hospital	CS	Consecutive	Women with singleton pregnancies tested for GDM at 24–28 weeks of pregnancy	All	IADPSG	644	87	13.5
							15–49 years				
							15–29 years		301	24	8.0
							30–39 years		302	50	16.5
							40–49 years		41	13	31.7
Abdel Razeq NM et al. (79)	2012/2013	Jordan	Nationwide in 18 maternity hospitals	CS	Unclear	All women who gave birth to dead or live neonates at 20 or more weeks of gestation	All	Medical records	21,075	253	1.2
Clouse K et al. (80)	04/2015–05/2015	Jordan, Amman	Al-Bashir Hospital	CS	Unclear	Pregnant women	All	Medical records and interviews	200	3	1.5
Khader YS et al. (81)	03/2011–04/2012	Jordan, nationwide	18 hospitals with maternity departments in three regions of Jordan (South, Middle, and North)	CS	Whole population	Deliveries with a gestational age ≥20 weeks	All	Medical records and interviews	21,928	261	1.2
Zein S et al. (82)	12/2012–11/2013	Lebanon, Beirut	Bahman hospital	CS	Unclear	Singleton pregnancies, nonanemic, having first prenatal visit before 12 weeks	All	IADPSG	104	16	15.4
Ghaddar N et al. (83)	09/2016–08/2017	Lebanon, Beirut and South Lebanon	Outpatient clinic of obstetrics and gynecology department of different hospitals and peripheral clinics in Lebanon	CS	Consecutive	Pregnant women, at 35–37 weeks of gestation	All	Self-reported or reported by physician	107	7	6.5
Khalil MM and Alzahra E (84)	1/2009–12/2010	Libya, Tripoli	Al-Jalaa Maternity Hospital	CS	Consecutive	Pregnant women with singleton pregnancies who completed 28 weeks of gestation excluding stillbirths, neonatal deaths, and infants with congenital anomalies	All	Medical records	28,140	405	1.4
Utz B et al. (85)	12/2016–03/2017	Morocco, Marrakech-Safi	10 health centers per district; two districts, Marrakech and Al Haouz	CS	Whole population	Pregnant women attending ANC with GDM screening and management intervention	All	WHO 2013	846	155	18.3
						Pregnant women attending ANC with GDM screening and initial management			1034	138	13.4

(Continued)

TABLE 2 | Continued

Author, year [Ref]	Duration of data collection	Country, city	Setting	Design	Sampling	Population	Strata	Ascertainment method	Tested sample	GDM	
										Positive	%
Abdwani R et al. (86)	01/2007–12/2013	Oman, Seeb	Sultan Qaboos University Hospital	RS	Consecutive	Mothers with systemic lupus erythematosus	All	Medical Records	56	15	26.8
						Healthy mothers			91	9	9.9
Al-Hakmani FM et al. (87)	3/2011–4/2012	Oman, Seeb	All primary health care centers	PS	Consecutive	Pregnant women without preexisting diabetes or chronic disease tested in their second trimester	All	WHO 1999	638	100	15.7
							BMI: 18.5–24.9 kg/m^2		229	27	11.8
							BMI: 25–29.9 kg/m^2		197	35	17.8
							BMI: ≥30 kg/m^2		212	38	17.9
Abu-Heija AT et al. (88)	09/15/2013–09/14/2014	Oman, Muscat	Sultan Qaboos University Hospital	CS	Whole population	Healthy singleton Omani nondiabetic pregnant women attending the antenatal clinic at SQUH were studied	All	Unclear	306	23	7.5
							BMI: 18–20 kg/m^2		32	1	3.1
							BMI: 21–25 Kg/m^2		74	3	4.1
							BMI: 26–30 kg/m^2		102	8	7.8
							BMI: 31–35 kg/m^2		47	5	10.6
							BMI: >35 kg/m^2		51	6	11.8
Zutshi A et al. (89)	11/2011–04/2012	Oman, Muscat	Royal Hospital in Muscat	RC	Whole population	All pregnant Omani women with available weight/height or BMI data at <12 gestational weeks (obese and normal weight)	All	Medical records	1813	221	12.2
							Normal weight		912	69	7.6
							Obese		901	152	16.9
Islam M et al. (90)	2000–2000	Oman	National Health household survey	CS	Multistage sampling	15–49-year-old pregnant women	All	Self–reported	1,345	44	3.3
							20–34 years		1,030	30	2.9
							≥35 years		315	14	4.4
Al–Kuwari MG et al. (91)	1/3–30/6/2010	Qatar	Sixteen primary health care centers that offer ANC care services	CS	Unclear	All pregnant women attending ANC clinics with a mean age of 28.3 years	All	ADA 2003	4,295	275	6.4
							<24 years		1,140	27	2.4
							25–29 years		1,537	89	5.8
							30–34 years		1,007	70	7.0
							≥35 years		611	89	14.6
Bener A et al. (92)	1/2010–4/2011	Qatar	Women's Hospital in Doha	CS	Whole population	All pregnant women who attended the ANC clinics, excluding women with diabetes before pregnancy	All	Unclear	1,608	262	16.3
							BMI: <25 kg/m^2		513	35	6.8
							BMI: 25–30 kg/m^2		601	72	12.0
							BMI: >30 kg/m^2		494	155	31.4
Abu Yaacob S et al. (93)	01/2001–06/2001	Doha, Qatar	Women's Hospital	CS	Random	Postnatal women at the Women's Hospital; multiple pregnancies were not included	All	Medical records	150	35	23.3
							BMI: >30 kg/m^2		75	26	34.7
							BMI: 20–28 kg/m^2		75	9	12.0

(Continued)

TABLE 2 | Continued

Author, year [Ref]	Duration of data collection	Country, city	Setting	Design	Sampling	Population	Strata	Ascertainment method	Tested sample	GDM	
										Positive	%
Bashir M et al. (94)	03/2015–12/2016	Qatar, Doha	Women's Hospital of Hamad Medical Corporation	CS	Whole population	Pregnant women	All	Medical records, FBG at first trimester and OGTT at second trimester according to WHO	2,221	801	36.1
Shaukat S and Nur U (95)	06/01/2016–11/10/2017	Qatar	Primary Healthcare Corporation Database	RC	Whole population	Nulliparous women with singleton pregnancies who had their first antenatal visit at the Primary Healthcare Corporation	All	Medical records	1,134	407	35.9
							BMI: <25 Kg/m^2		404	118	29.2
							BMI: 25–29.99 Kg/m^2		399	140	35.1
							BMI: ≥30 kg/m^2		230	108	47.00
							Missing		101	41	40.6
Soliman A et al. (96)	01/2017–08/2017	Qatar, All Qatar	Perinatal registry	CS	Whole population	Women with singleton births and completed record abstraction	All	IADPSG	12,255	3027	24.7
							≤19 years		256	35	13.7
							20–24 years		2,075	332	16.0
							25–29 years		4,035	909	22.5
							30–34 years		3,641	964	26.7
							≥35 years		2,275	787	34.6
Kurdi AM et al. (97)	07/01/2010–06/30/2013	Saudi Arabia, Riyadh	The Prince Sultan Military Medical City (PSMMC) is a tertiary teaching institution	PC	Random	Healthy pregnant women	All	IADPSG	1262	188	14.9
					Whole population	Pregnant women with congenital anomalies	All		1179	187	15.9
El–Gilany AH and Hammad S (98)	2007	Saudi Arabia, Al–Hassa	Primary health care centers	PS	Unclear	Pregnant women initiated into ANC in the first month of pregnancy, excluding any prepregnancy chronic medical disease (e.g., hypertension, diabetes, renal or cardiac disease, and sickle cell disease) and multiple pregnancies	All	Unclear	787	30	3.8
							BMI: 18.5–24.99 kg/m^2		307	3	1.0
							BMI: <18 kg/m^2		67	0	0.0
							BMI: ≥25–29.99 kg/m^2		187	8	4.3
							BMI: ≥30 kg/m^2		226	19	8.4
Lasheen AE et al. (99)	1/2011–11/2011	Saudi Arabia, Riyadh	Security Forces Hospital	CS	Unclear	Pregnant women	All	Unclear	601	153	25.5
Wahabi HA et al. (100)	2013–2015	Saudi Arabia, Riyadh	Three hospitals, part of RAHMA study	CS	Random	Saudi mothers	All	WHO 2013			
							<20–≥45 years		9,723	345	3.5
							<20 years		216	38	17.6
							20–24 years		1,625	271	16.7
							25–29 years		2,850	596	20.9
							30–34 years		2,603	688	26.4
							35–39 years		1,769	537	30.4
							40–44 years		601	208	34.6

(Continued)

TABLE 2 | Continued

Author, year [Ref]	Duration of data collection	Country, city	Setting	Design	Sampling	Population	Strata	Ascertainment method	Tested sample	GDM	
										Positive	%
							≥45 years		59	16	27.1
Wahabi HA et al. (101)	1/1/–31/ 12/2008	Saudi Arabia, Riyadh	King Khalid University Hospital	RS	Unclear	Women who were admitted to the labor ward in King Khalid University Hospital	All	IADPSG	3,157	569	18.0
Wahabi HA et al. (102)	1/1–31/ 12/2010	Saudi Arabia, Riyadh	King Khalid University Hospital	RS	Unclear	Pregnant women with singleton pregnancies at gestational age of at least 24 months excluding women with preexisting diabetes	All	IADPSG	3,041	569	18.7
Wahabi HA et al. (103)	1/7/2011– 30/6/2012	Saudi Arabia, Riyadh	King Khalid University hospital	RS	All subjects during the study period	Women booked for ANC care services who were with singleton pregnancies and with no history of T1DM or T2DM	All	Carpenter and Coustan	2,701	415	15.4
							Obese		1,185	260	21.9
							Not obese		1,516	155	10.2
Al-Rowaily MA and Abolfotouh MA (104)	7/2005–7/ 2006	Saudi Arabia, Riyadh	ANC clinic of King Fahd hospital, part of the National Guard Health Affairs services	CS	Consecutive	All pregnant women who had no previous history of diabetes without pregnancy excluding women who suffered an abortion before reaching 24–28 weeks gestation; 50.1% of pregnant women were grand multiparas	All	WHO 1985	633	79	12.5
							<20 years		21	0	0.0
							20–29 years		180	10	5.6
							30–39 years		379	54	14.2
							≥40 years		53	15	28.3
Almarzouki AA (105)	1/11/ 2007–30/ 4/2008	Saudi Arabia, Makkah	Department of endocrinology, Al-Noor Specialist Hospital	RS	All pregnant women during the study period	All singleton pregnant women excluding pregnant women known to have DM before pregnancy or who have OGTT positive in first trimester of pregnancy with unknown prepregnancy DM status were also excluded	All	O'Sullivan and NDDG	1,550	94	6.1
Al–Shaikh G et al. (106)	2014– 2014	Saudi Arabia, Riyadh	Labour ward of King Khaled University Hospital	CS	Consecutive	17–47-year-old pregnant women who were admitted for delivery	All	Unclear	1,000	111	11.1
Al-Daghri N et al. (107)	Unclear	Saudi Arabia, Riyadh	Patients recruited from homes and invited to visit primary healthcare centers.	CS	Random	18–45-year-old pregnant women attending clinics	All	WHO 1999	2,373	33	1.4
Wahabi H et al. (108)	2013– 2015	Saudi Arabia, Riyadh	Large tertiary care public hospitals	CS	Whole population	Women delivered at participating hospitals with a mean age of 29.1 years	<20–≥40 years	WHO 2013	9,723	2,354	24.2
Alfadhli E et al. (109)	2011– 2014	Saudi Arabia, Medina	Maternity and Children hospital	PC	Consecutive	Singleton Saudi pregnant women without DM and with mean age 30.5 years	All	ADA 2010	573	93	16.2
Al Serehi A et al. (110)	2011– 2013	Saudi Arabia, Riyadh	Single-center study conducted at King Fahad Medical City	CS	Whole population	Pregnant women with a mean age of 29.9 years; trimester not mentioned	All	Medical records	1,718	238	13.8
Al–Rubeaan K et al. (111)	2007– 2009	Saudi Arabia, Nationwide	SAUDI–DM national level household survey.	CS	Random	Pregnant women in different trimesters, recruited from general population with an age range of 18–49 years	All	IADPSG criteria			
							18–49 years		549	201	36.6
							18–29 years		264	79	29.9
							30–39 years		212	85	40.1
							40–49 years		73	37	50.7
Gasim T et al. (112)	2001– 2008	Saudi Arabia	King Fahad Hospital	CC	Matched random sampling	Pregnant women in their second trimester with a mean age of 32.4 years	All	IADPSG	8,075	220	2.7
Kurdi MA et al. (113)	01/2000– 12/2001	Saudi Arabia, Riyadh	Armed Forces Hospital and King Khalid University Hospital	CS	Consecutive	Pregnant women with multiple pregnancies	All	Unclear	375	60	16.0
Abdelmola AO et al. (114)	11/2014	Saudi Arabia, Jazan	Sabya, Jazan, and Abuarish hospitals	CS	Random	Pregnant women aged 15–49 years in the second and third trimester tested for GDM at 24–28 weeks	15–20 years	Medical records	48	6	12.5
							21–25 years		145	3	2.1
							26–30 years		136	13	9.6

(Continued)

TABLE 2 | Continued

Author, year [Ref]	Duration of data collection	Country, city	Setting	Design	Sampling	Population	Strata	Ascertainment method	Tested sample	GDM	
										Positive	%
							31–35 years		76	10	13.2
							36–50 years		35	4	11.4
Al-Shaikh GK et al. (115)	11/2013-11/2014	Saudi Arabia, Riyadh	King Khaled University Hospital	CS	Whole population	Women who had singleton births	All	Medical records	3,327	415	12.5
							Primipara		1,889	174	9.3
							Multipara		1,097	156	14.4
							Grand multipara		341	85	25.2
Fayed AA et al. (116)	11/2013–03/2015	Saudi Arabia, Riyadh	Multicenter Mother and Child Cohort Study RAHMA, three hospitals in Riyadh	CS	Systematic	RAHMA study recruited more than 14,000 pregnant women and their newborns from three hospitals representing the ministry of health, military and university hospitals; all Saudi women were eligible to participate, and 14,568 consented	All	WHO 2013	9,022	2,124	23.5
							15–39 years		181	32	17.7
							15–20 years		4,469	867	19.4
							20–29 years		2,606	688	26.4
							30–34 years		1,766	537	30.4
							35–39 years				
Subki AH et al. (117)	01/2015–06/2017	Saudi Arabia, Jeddah	King Abdulaziz University Hospital, a teaching hospital and tertiary health center located in the city of Jeddah in the western province of Saudi Arabia	CS	Whole population	All patients diagnosed with HDP	All	Medical records	244	59	26.3
							Primigravida		97	18	18.6
							Multigravida		127	41	32.3
Al Shanqeeti SA et al. (118)	01/2016–08/2016	Saudi Arabia, Riyadh	King Abdulaziz Medical City	CS	Whole population	Pregnant women attending the antenatal clinic at the tertiary hospital as well as those admitted for OB/GYN care and women attending the antenatal clinic at the primary care center were invited to participate in this study	All	Unclear	384	35	9.1
Dafa Elseed EB and Khougali HS (119)	01/01/2016–06/01/2017	Sudan Omdurman	Outpatient clinical at Omdurman Maternity Hospital, Omdurman, Sudan	CS	Unclear	Women with diabetes aged 18–45 years	All	Self-reported	119	55	46.2
Naser W et al. (120)	01/2015–11/2015	Sudan, Khartoum	ANC clinic of Saad Abualila Hospital	PC	Whole population	Singleton pregnant, started ANC follow-up in the first trimester (≤14 weeks of gestation)	All	IADPSG and ADA	126	19	15.0
Alshareef SA et al. (121)	07/01/2017–01/31/2018	Sudan, Khartoum	Saad Abuelela hospital	CS	Unclear	Pregnant women	All	IADPSG	166	20	12.0
Mallouli M et al. (122)	01/01–31/12, 2013	Tunisia, Sfax	University Hospital, HediChaker	CS	Whole population	Mothers of macrosomic newborn	All	ADA 2015	821	76	9.3
Radwan H et al. (123)	6/2016	UAE, Sharjah, Dubai and Ajman	Three main public governmental hospitals and seven rimary health care (PHC) clinics and mother and child centers (MCH)	PC	Convenient	Singleton Arab aged 19–40 years within the third trimester of pregnancy (27–42 weeks of gestation)	All	NICE	256	49	19.2
Agarwal MM et al. (124)	1/1998–12/2002	UAE, Al Ain	Obstetric clinics at the Al Ain Hospital	RS	Unclear	Pregnant women attending routine obstetric clinics at the Al Ain Hospital with a mean maternal age of 32 years	All	ADA 1997	5,347	1,641	30.7

(Continued)

TABLE 2 | Continued

Author, year [Ref]	Duration of data collection	Country, city	Setting	Design	Sampling	Population	Strata	Ascertainment method	Tested sample	GDM	
										Positive	%
Agarwal MM et al. (125)	1/1/2012–31/12/2012	UAE, Al Ain	Tawam Hospital	CS	Unclear	Pregnant women attending the routine ANC clinics	All	ADA 2003	2,337	310	13.2
Agarwal MM et al. (126)	2003–2008	UAE, Al Ain	Antenatal clinics of two tertiary care hospitals	PC	Whole population	Pregnant women attending antenatal clinics	All	ADA 2010	10,283	1328	12.9
Agarwal MM et al. (127)	1/07/2007–30/06/2008	UAE, Al Ain	Al Ain Hospital	CS	Unclear	Pregnant women attending routine antenatal clinics tested for GDM at 24–28 weeks' gestation	All	ADA 2007	1,465	196	13.4
Mirghani MH et al. (128)	01/2002–05/2004	UAE, Al Ain	Al-Ain Hospital, Al Ain District	CS	Consecutive	Healthy pregnant women fasting in the month of Ramadan	All	WHO 1999	168	34	20.2
						Healthy pregnant women not fasting in the month of Ramadan			156	11	7.1
Agarwal MM et al. (129)	1/5/2003–31/7/2003	UAE, Al Ain	Tawam Hospital, Al Ain	CS	Consecutive	All pregnant women undergoing one-step universal screening protocol for GDM between 24–28 weeks gestation	All	ADA 2004	442	49	11.1
Vaswani PR et al. (130)	12/2010–10/2011	UAE, Abu Dhabi	Mafraq hospital	CS	Consecutive	Pregnant women except the ones with multiple pregnancies or BMI less than 18.5 kg/m^2 or preexisting hypertension or diabetes	All	Medical records	1,985	171	8.6
							Overweight		635	36	5.6
							Obese class I		520	53	10.1
							Obese class II		280	42	1.0
							Obese class III		130	23	17.6
							Normal weight		420	17	4.0
Abdel–Wareth OL et al. (131)	11/1999–04/2001	UAE, Abu Dhabi	Mafraq Hospital	CS	Consecutive	Women delivering at Mafraq Hospital during the time period were included; women who could not perform the test due to vomiting were excluded from the study	<25–≥35 years	ADA criteria	877	143	16.3
Ali AD. et al. (132)	08/2013–03/2014	Yemen, Dhamar	Antenatal care clinics associated with several hospitals	CS	Systematic	Pregnant women visiting antenatal clinics with a mean age of 25.1 years	Obese	ADA criteria	18	3	16.7
							Others		293	13	4.4

ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; ANC, antenatal care; ART, assisted reproductive technology; BMI, body mass index; CC, case control; CS, cross-sectional; DM, diabetes mellitus; FIGO, Federation of Gynecology and Obstetrics; GDM, gestational diabetes mellitus; HCV, hepatitis C virus; HDP, hypertension disorder in pregnancy; IADPSG, International Association of Diabetes and Pregnancy Study Groups; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; NDDG, National Diabetes Data Group; OGTT, oral glucose tolerance test; PC, prospective cohort; PCOS, polycystic ovary syndrome; PS, prospective; PTB, preterm birth; RC, retrospective cohort; RS, retrospective; SC, spontaneous conception; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

TABLE 3 | Weighted national prevalence of GDM in pregnant women in 16 MENA countries by study period and overall.

Country/study period	No. of studies	Tested sample	GDM	GDM prevalence				Heterogeneity measures			p–value[4] (fixed model)
				Range (%)	Median (%)	Weighted prevalence %	95% CI	Q (p–value)[1]	I^2 (%)[2]	95% prediction interval (%)[3]	
Algeria											—
2010–2019	1	200	6	—	—	3.0	1.4–6.4	—	—	—	
Bahrain											<0.001 (<0.001)
2000–2009	2	10,495	1,394	7.5–15.5	11.5	13.0	12.4–13.7	—	—	—	
2010–2019	9	49,552	4,982	6.9–13.3	9.5	9.7	8.1–11.6	352.4 (p<0.001)	97.7	4.2 – 17.2	
Overall	11	60,047	6,376	6.9–15.5	9.5	10.0	8.3–11.9	572.3 (p<0.001)	98.3	4.0–18.3	
Egypt											0.21 (0.002)
2010–2019	4	1,239	184	5.9–26.3	11.2	13.5	6.2–21.8	49.9 (p<0.001)	94.0	0.0–63.8	
Overlapping	2	308	24	7.6–7.9	7.8	7.8	5.0–11.1	—	—	—	
Overall	6	1,547	208	5.9–26.3	9.0	11.2	6.2–17.4	59.7 (p<0.001)	91.6	0.0–37.7	
Iran											0.07 (<0.001)
2000–2009	16	7,343	492	2.2–24.4	7.4	8.2	5.9–11.0	215.3 (p<0.001)	93.0	0.8–21.9	
2010–2019	39	21,028	2,235	0.0–50.0	9.2	12.3	9.0–16.0	2,135 (p<0.001)	98.2	0.0–41.0	
Overlapping	9	1,388	166	5.9–28.6	13.5	13.5	8.2–19.7	67.8 (p<0.001)	88.2	0.3–38.4	
Overall	64	29,759	2,893	0.0–50.0	8.8	11.4	9.2–13.9	2,491 (p<0.001)	97.5	0.1–35.8	
Iraq											—
2010–2019	4	383	35	2.6–24.5	14.2	11.5	3.3–23.3	24.5 (p<0.001)	87.8	0.0–76.6	
Jordan											—
2010–2019	6	43,847	604	1.2–31.7	4.7	4.7	3.0–6.7	193.7 (p<0.001)	97.4	0.4–12.5	
Lebanon											—
2010–2019	2	211	23	6.5–15.4	11.0	10.5	6.7–15.1	—	—	—	
Libya											—
Overlapping	1	28,140	405	–	–	1.4	1.3–1.6	—	—	—	
Morocco											—
2010–2019	2	1,880	393	13.3–18.3	15.8	15.5	13.9–17.2	—	—	—	
Oman											<0.001 (<0.001)
2000–2009	2	1,345	44	2.9–4.4	3.7	3.2	2.3–4.2	—	—	—	
2010–2019	10	2,757	344	3.1–17.9	11.2	11	8.0–15.0	59.2 (p<0.001)	84.8	1.9–25.8	
Overlapping	2	147	24	9.9–26.8	18.3	15.5	10–21.9	–	–	–	
Overall	14	4,249	412	2.9–26.8	10.3	10.1	6.5–14.3	184.5 (p<0.001)	93.0	0.2–29.7	
Qatar											0.65 (0.59)
2000–2009	2	150	35	12.0–34.7	23.3	22.3	15.9–29.4	–	–	–	
2010–2019	17	21,513	4,772	2.4–47.0	22.5	20.5	14.8–26.9	1,869.0 (p<0.001)	99.1	1.6–52.6	
Overall	19	21,663	4,807	2.4–47.0	22.5	20.7	15.2–26.7	1,880.3 (p<0.001)	99.0	1.7–52.4	
Saudi Arabia											0.02 (<0.001)
2000–2009	16	17,499	1,286	0.0–50.7	7.2	10.8	6.2–16.5	1,330.5 (p<0.001)	98.9	0.0–41.1	
2010–2019	32	44,918	9,331	2.1–34.6	17.6	18.2	15.9–20.6	1,116.5 (p<0.001)	97.2	7.1–32.9	

(Continued)

TABLE 3 | Continued

Country/study period	No. of studies	Tested sample	GDM	GDM prevalence				Heterogeneity measures			*p*–value[4] (fixed model)
				Range (%)	Median (%)	Weighted prevalence %	95% CI	Q (*p*–value)[1]	I^2 (%)[2]	95% prediction interval (%)[3]	
Overall	48	62,417	10,617	0.0–50.7	16.1	15.5	12.6–18.8	4,989.3 (*p*<0.001)	99.1	1.0–41.9	
Sudan											—
2010–2019	3	411	94	12.0–46.2	15.1	23.0	3.3–45.2	47.2 (*p*<0.001)	95.8	—	
Tunisia											—
2010–2019	1	821	76	—	—	9.3	7.5–11.4	—	—	—	
United Arab Emirates											0.3 (<0.001)
2000–2009	7	18,738	3,402	7.1–30.7	13.4	15.5	9.2–23.0	736.7 (*p*<0.001)	99.2	0.2–46.9	
2010–2019	7	4,578	530	4.0–19.1	13.3	11.3	7.6–15.69	87.8 (*p*<0.001)	93.2	1.3–28.8	
Overall	14	23,316	3,932	4.0–30.7	13.3	13.4	9.4–18.0	945.1 (*p*<0.001)	98.6	1.1–35.6	
Yemen											
2010–2019	2	311	16	—	—	—	—	—	—	—	—
Overall[5]	**198**	**279,202**	**30,797**	**0.0–50.7**	**12.3**	**13.0**	**11.5–14.6**	**28,154 (p<0.001)**	**99.3**	**0.1–40.6**	—

CI, confidence interval calculated using the exact binomial method; GDM, gestational diabetes mellitus; MENA, Middle East and North Africa.

[1]Q: Cochran's Q statistic is a measure assessing the existence of heterogeneity in estimates of GDM prevalence.

[2]I^2 is a measure assessing the percentage of between-study variation due to differences in GDM prevalence estimates across studies rather than chance.

[3]Prediction intervals estimate the 95% confidence interval in which the true GDM prevalence estimate in a new study is expected to fall.

[4]Heterogeneity between subgroups using random-effects model (fixed-effect model).

[5]Overall pooled estimates in the 16 countries regardless of the tested population, sample size, and data collection period, using the most updated criteria when GDM is ascertained using different criteria in the same population.

increased by 45.0%, from 8.9% in the first trimester to 12.9% in the second trimester, and by 55.0% in the third trimester (20.0%, 95% CI, 13.1–27.9%, I^2, 98.8%) compared with the second trimester. It was also noticeable that, as the BMI increased, the prevalence of GDM increased by 54% in overweight (12.0%, 95% CI, 5.7–20.1%, I^2, 96.7) and by 120% in obese (17.2%, 95% CI, 12.8–22.0%, I^2, 93.8%) compared with normal-weight pregnant women (7.8%, 95% CI, 4.1–12.4%, I^2, 95.0%). No GDM cases were reported in two studies that included underweight women (**Table 4**).

From the 137 studies conducted between 2010 and 2019, the pooled GDM prevalence (14.0%, 95% CI, 12.1–16.0%) was 32.0% higher than that reported in the 45 studies conducted in the previous decade (2000–2009; 10.6%, 95% CI, 8.1–13.4%). The pooled GDM prevalence was relatively higher in 32 studies with a sample size of <100 pregnant women (14.8%, 95% CI, 10.7–19.5%) compared with that in 164 studies with a sample size of ≥100 pregnant women (12.8%, 95% CI, 11.2–14.8%; **Table 4**).

The prevalence of GDM was 25.2% higher in countries with a C-section rate of 15–29% (weighted estimate of 14.4%, 95% CI, 12.3–16.6%, I^2, 99.5%) than countries with a C-section rate of <15% (weighted estimate of 11.5%, 95% CI, 5.36–19.0%, I^2, 97.9%; **Table 4**). In addition, in four studies in countries with high MMR (i.e., >100 per 100,000 live births), the prevalence of GDM was 25.0% higher than in countries with MMR ≤100 per 100,000 live births (weighted estimates of 16.5%, 95% CI, 3.4–36.3%, and 14.4%, 95% CI, 12.3–16.6%, respectively; **Table 4**).

Subregional Specific Pooled GDM Prevalence

In Sudan, one of the North African countries with a C-section rate of 15–29%, a lower GDM prevalence (weighted prevalence of 7.9%) was observed compared with countries with a C-section rate of <15% (weighted prevalence of 23.0%). In North African countries with an MMR of >100/100,000 live births, the prevalence of GDM was 32.0% higher than in countries with an MMR of ≤100/100,000 live births (**Supplementary File 2**).

The highest weighted GDM prevalence was in the GCC countries (14.7%, 95% CI, 13.0–16.5%, I^2, 99.0%), followed by North African countries (13.5%, 95% CI, 7.4–20.9%, I^2, 98.9%) and Iran/Iraq 11.2% (95% CI, 9.0–13.5%, I^2, 97.4%), whereas the lowest prevalence was estimated in the Levant region countries (5.8%, 95% CI, 3.9–7.9%, I^2, 97.1%; **Supplementary File 3**).

In GCC countries, the prevalence of GDM rose from 11.9% to 15.9% over the two successive decades. Overweight (12.5%) and obese (18.5%) pregnant women and pregnant women with a C-section rate of 15–29% (15.5%) were burdened with high GDM prevalence (**Supplementary File 3**). In these countries, pregnant women aged ≥30 years were burdened with higher GDM prevalence than the other subregions. As compared with the first decade, the weighted GDM prevalence in the subsequent decade increased by almost 4% in Iraq.

Tables 2–4 in the appendix provide additional weighted GDM prevalence estimates in each subregion according to different measured characteristics (**Supplementary Files 2–5**).

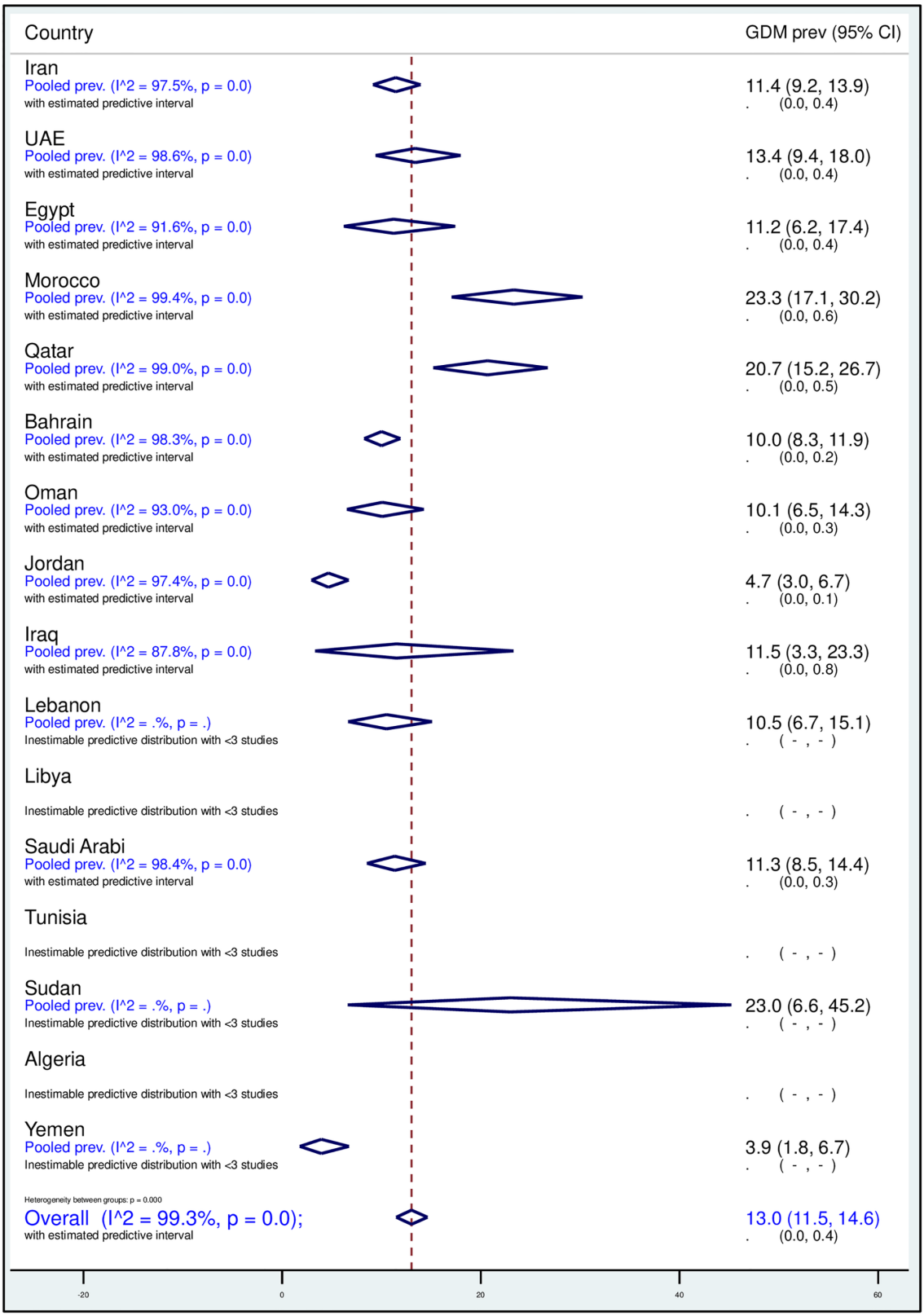

FIGURE 2 | Forest plot of the meta-analyses of the studies on GDM from 16 MENA countries.

TABLE 4 | Subgroup weighted prevalence of GDM in pregnant women in 16 MENA countries by age, pregnancy trimester, body mass index, study period, ascertainment methodology, tested sample, C-section, and maternal mortality ratio.

	No. of studies	Tested sample	GDM	GDM prevalence				Heterogeneity measures			*p*–value[4] (fixed model)
				Range (%)	Median (%)	Weighted prevalence %	95% CI	Q (*p*–value)[1]	I^2 (%)[2]	95% prediction interval (%)[3]	
Age											<0.001 (<0.001)
15–29 years	24	19,187	2,883	0.0–29.9	10.8	9.7	6.7–13.2	1,140.7 (p<0.001)	98.0	0.0–31.4	
≥30 years	26	22,186	5,617	4.1–50.7	25.4	21.9	18.5–25.5	868.6 (p<0.001)	97.1	7.0–42.0	
Unclear age	148	237,518	22,281	0.0–50.0	11.2	12.3	10.6–14.0	20,967.2 (p<0.001)	99.3	0.1–37.6	
Trimester											0.06 (<0.001)
First	11	5,807	387	2.2–37.2	7.6	8.9	5.3–13.3	272.5 (p<0.001)	96.3	0.0–29.7	
Second	85	134,792	14,378	0.0–50.0	12.0	12.9	10.9–15.0	9,687.2 (p<0.001)	99.1	0.6–36.3	
Third	18	14,146	1,354	2.7–50.7	18.5	20.0	13.1–27.9	1,428.2 (p<0.001)	98.8	0.0–60.6	
Not reported	84	124,457	14,678	0.0–47.0	12.5	12.5	9.8–15.5	16,618.8 (p<0.001)	99.5	0.0–46.1	
BMI											<0.001 (<0.001)
Underweight	2	94	0	0	0	0	—	—	—	—	
Normal weight	11	3,822	335	1.0–29.2	6.0	7.8	4.1–12.4	200.8 (p<0.001)	95.0	0.0–29.5	
Overweight	7	2,502	334	4.3–35.1	9.2	12.0	5.7–20.1	182.2 (p<0.001)	96.7	0.0–47.5	
Obese	17	4,8459	941	7.6–47.0	15.8	17.2	12.8–22.0	241.5 (p<0.001)	93.8	2.6–40.2	
Unclear	161	267,6925	29,187	0.0–50.7	12.8	13.4	11.7–15.2	27,066.0 (p<0.001)	99.4	0.1–41.2	
Study period											0.14 (<0.001)
2000–2009	45	55,570	6,653	0.0–50.7	11.1	10.6	8.1–13.4	4,118.0 (p<0.001)	98.9	0.0–34.2	
2010–2019	139	193,3649	23,527	0.0–50.0	12.7	14.0	12.1–16.0	19,613.9 (p<0.001)	99.3	0.2–42.2	
Overlapping	14	29,983	619	1.4–28.6	9.1	12.0	6.5–18.7	414.1 (p<0.001)	96.9	0.0–45.3	
GDM ascertainment[5]											<0.001 (<0.001)
WHO guidelines											
WHO 1985	4	633	79	0.0–28.3	9.9	10.4	3.2–20.5	25.4 (p<0.001)	88.2	0.0–67.5	
WHO 1999	6	3,335	178	1.4–20.2	14.8	11.4	3.6–22.8	228.9 (p<0.001)	97.8	0.0–62.4	
WHO 2013	14	30,348	7,125	13.3–34.6	22.6	22.8	20.2–25.5	344.5 (p<0.001)	96.2	13.0–34.5	
WHO year not mentioned	1	2,221	801	—	—	36.1	34.1–38.1	—	—	—	
ADA guidelines				—	—			—	—	—	
ADA 1997	1	5,347	1,641	—	—	30.7	29.5–31.9	—	—	—	
ADA 2002–2010	16	19,604	2,269	2.4–37.2	12.0	11.7	9.0–14.7	364.6 (p<0.001)	96.4	2.6–25.9	
ADA 2011–2013	4	3,180	605	13.4–30.5	24.9	22.7	15.4–30.9	67.5 (p<0.001)	95.6	0.2–65.0	
ADA 2015–2016	4	3,229	243	6.9–9.3	7.0	7.5	6.4–8.7	4.435 (p=0.218)	32.4	4.2–11.7	
ADA year not mentioned	1	877	143	—	—	16.3	14.0–18.9	—	—	—	
ADA/IADPSG	2	700	306	15.1–50.0	32.5	43.1	39.4–46.8	—	—	—	

(Continued)

TABLE 4 | Continued

	No. of studies	Tested sample	GDM	GDM prevalence				Heterogeneity measures			*p*–value[4] (fixed model)
				Range (%)	Median (%)	Weighted prevalence %	95% CI	Q (*p*–value)[1]	I^2 (%)[2]	95% prediction interval (%)[3]	
Self-reported	6	1,833	119	2.9–46.2	5.5	9.6	2.7–19.8	148.2 (p<0.001)	96.6	0.0–56.2	
Medical records	45	70,833	2,803	0.6–47.0	11.4	11.5	9.1–14.2	3,588.1 (p<0.001)	98.8	0.4–33.1	
Unclear	36	31,541	1,319	0.0–31.4	8.4	9.3	6.2–12.9	1,770.5 (p<0.001)	98.0	0.0–36.9	
IADPSG	23	32,911	5,577	2.7–50.7	18.0	20.9	15.6–26.6	3,071.8 (p<0.001)	99.3	1.5–53.5	
Carpenter and Coustan	13	8,468	755	2.2–24.4	8.2	8.8	5.6–12.7	356.1 (p<0.001)	96.6	0.1–27.4	
NDDG	10	51,102	5,076	6.1–13.3	8.7	9.4	7.8–11.1	382.7 (p<0.001)	97.6	4.0–16.7	
Fourth International Workshop–Conference	2	10,495	1,394	7.5–15.5	11.5	13.0	12.4–13.7	—	—	—	
Fifth International Workshop–Conference	5	1,010	215	7.3–44.4	7.9	17.4	5.6–33.9	149.9 (p<0.001)	97.3	0.0–85.6	
ACOG	4	1,279	100	0.0–16.7	7.6	7.7	3.7–12.9	18.11 (p<0.001)	83.4	0.0–36.8	
NICE	1	256	49	—	—	19.1	14.8–24.4	—	—	—	
Sample size											0.25 (<0.001)
<100	32	1,779	300	0.0–50.7	12.8	14.8	10.7–19.5	198.8 (p<0.001)	84.4	0.0–44.3	
≥100	166	277,423	30,497	0.6–50.0	12.0	12.8	11.2–14.5	27,873.7 (p<0.001)	99.4	0.1–40.1	
C-section rate											<0.001 (<0.001)
<15%	7	10,206	481	2.7–46.2	12.0	11.5	5.6–19.0	285.6 (p<0.001)	97.9	0.0–44.2	
15–29%	118	235,106	27,222	0.0–50.7	13.5	14.4	12.3–16.6	24,307.1 (p<0.001)	99.5	0.2–43.3	
>30%	69	29,101	3,010	0.0–50.0	9.2	11.6	9.4–14.1	2,461.8 (p<0.001)	97.2	0.1–36.1	
Unclear	4	4,789	147	1.4–15.0	3.9	4.8	1.8–9.0	89.2 (p<0.001)	96.6	0.0–34.3	
Maternal mortality ratio											<0.001 (<0.001)
≤100/100,000	188	273,491	30,534	0.0–50.7	12.5	13.2	11.6–14.9	27,551.7 (p<0.001)	99.3	0.1–40.8	
>100/100,000	6	922	1116	3.0–46.2	13.6	16.5	3.4–36.3	97.1 (p<0.001)	96.9	0.0–100.0	
Unclear	4	4,789	147	1.4–15.0	3.9	4.8	1.8–9.0	89.2 (p<0.001)	96.6	0.0–34.3	
Overall[6]	**198**	**279,202**	**30,797**	**0.0–50.7**	**12.3**	**13.0**	**11.5–14.6**	**28154 (p<0.001)**	**99.3**	**0.1–40.6**	—

CI, confidence interval calculated using the exact binomial method; ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; GDM, gestational diabetes mellitus; IADPSG, International Association of Diabetes and Pregnancy Study Groups; NDDG, National Diabetes Data Group; NICE, National Institute for Health and Care Excellence; WHO: World Health Organization.

[1]Q: Cochran's Q statistic is a measure assessing the existence of heterogeneity in estimates of GDM prevalence.

[2]I^2 is a measure assessing the percentage of between-study variation due to differences in GDM prevalence estimates across studies rather than chance.

[3]Prediction intervals estimate the 95% confidence interval in which the true GDM prevalence estimate in a new study is expected to fall.

[4]Heterogeneity between subgroups using random-effects model (fixed-effect model).

[5]Regardless of the year of the guidelines for the most updated criteria when GDM was ascertained, based on different criteria in the same population.

[6]Overall pooled estimates in the 16 countries regardless of the tested population, sample size, and data collection period, using the most updated criteria when GDM was ascertained using different criteria in the same population.

Predictors of Heterogeneity in GDM

In the univariate meta-regression models, country, age, pregnancy trimester, BMI, and sample size were associated with variability in the prevalence of GDM at $p<0.1$. In the multivariate meta-regression model, only pregnancy trimester was retained, with no significant association with the prevalence of GDM at $p<0.05$. Compared with Saudi Arabia, the adjusted GDM prevalence was 135% (adjusted odds ratio [aOR],

2.35, 95% CI, 1.39–3.95) and 122% (aOR, 2.22, 95% CI, 1.30–3.76) higher in Qatar and Morocco, respectively, but lower in Libya (aOR, 0.09, 95% CI, 0.02–0.52) and Jordan (aOR, 0.38, 95% CI, 0.18–0.80). Pregnant women aged ≥30 years had a 152% higher prevalence of GDM (aOR, 2.52, 95% CI, 1.51–4.21) relative to younger pregnant women. Obese pregnant women were burdened with a 192% higher prevalence of GDM relative to normal-weight pregnant women (aOR, 2.92, 95% CI, 1.50–5.69; **Supplementary File 6**).

Publication Bias in GDM Prevalence

Both the visual (funnel plot asymmetry) and statistical assessment (Egger's test, $p<0.001$) of publication bias suggested the role of a small-study effect (**Supplementary File 7**).

Quality Assessment of the GDM Research Reports

Supplementary Figure 2 presents the findings of the research report-specific quality assessment for relevant GDM prevalence studies. In all 102 research reports, the research question(s) and/or objective(s) were clearly stated, and the study population group was clearly specified and defined. Half of the research reports (49.5%) did not provide information on the sample size calculation or justification. Most (79.2%) of the research reports used biological assays or extracted data from medical records to ascertain GDM, whereas the GDM status was self-reported in only five reports. In more than half (58.4%) of the 102 research reports, the tested sample size was at least 100 pregnant women. Overall, the research reports were judged to be of potentially low RoB, with an average of seven of the nine measured assessment items. Four (4.0%) of the reports (70, 85, 105, 120) were of low RoB in all of the assessed RoB items (**Supplementary File 8**).

DISCUSSION

Main Findings

A total of 102 eligible research reports comprising 198 GDM prevalence studies were reported in 16 countries in the MENA region between 2000 and 2019. Most of these reports (58.41%) were from Iran and Saudi Arabia. The pooled prevalence of GDM in the 16 MENA countries was appreciably high (13.0%, 95% CI, 11.5–14.6%, I^2, 99.3%), particularly in the GCC and North African countries. The prevalence of GDM increased with maternal age, gestational age, and BMI. It was also high in countries with a C-section rate of 15–29% and an MMR of >100/100,000 live births.

The pooled GDM prevalence (13.0%) was alarmingly higher than that of European countries (2–6%) (133) but was similar to the sub-Saharan Africa region (14.0%). In contrast to the pooled prevalence estimates of Asia (11.5%) (134), the prevalence estimated in the present meta-analysis was slightly higher. The Asian meta-analysis included prevalence estimates from Saudi Arabia, Iran, and Qatar, and when compared with our estimates, they were 3.5% and 7.4% lower for Iran and Saudi Arabia, respectively, and 7.4% higher for Qatar (134). Such variations might be due to the differences in the literature search dates and languages, eligible sample size, GDM ascertainment criteria, and differences in the type of observational studies used for the prevalence estimation.

Our overall weighted GDM prevalence estimate depicted substantial heterogeneity (I^2, 99.3%). This could be attributable to the less restrictive inclusion criteria in this review. In addition, the prevalence estimates of GDM can significantly differ with the variation in the GDM diagnostic criteria (135, 136). We noted clinical inconsistency in GDM diagnostic criteria used in the prevalence studies we reviewed (**Table 4**). This corresponds to the common use of existing nonuniform GDM diagnostic criteria in different countries (12, 134). Given the importance of the prevalence of GDM in meaningful intervention development, its estimation can be affected by the inclusion of studies that use different GDM diagnosing criteria (137, 138). The prevalence of GDM estimated based on the IADPSG criteria is usually high due to the low threshold for fasting blood glucose level relevant to other criteria. In our study, more than 25% of the studies used IADPSG criteria. To obtain homogenous and comparable prevalence estimates and to avoid confusion in practices of screening, diagnosis, and follow-up of GDM, health authorities should consider implementing uniform GDM diagnostic criteria nationally and across the MENA region.

The GDM prevalence estimates in our analysis suggested an increasing trend, parallel to the increase in BMI, correlating with the known fact that overweight and obesity are risk factors of GDM (139, 140). Although this does not prove a causal link between these parameters, it inevitably might significantly reflect the impact of the high burden of overweight and obesity in several countries in the MENA region, such as Egypt and the six GCC countries (141). This highlights the importance of investigating dietitians' role in ensuring the appropriate caloric intake of GDM patients based on their BMI as per the recommendations of the ADA (142) and promoting exercise, especially among those with increased BMI (143).

GDM can have devastating maternal and birth consequences. Mothers with GDM are at higher risk of developing T2DM, dying, and undergoing C-section (23, 24, 144). Children born to mothers with untreated GDM face an increased risk of neonatal death and long-term disability (145, 146). Notably, diabetes in pregnancy is a neglected cause of maternal mortality globally, affecting one of every sixth pregnancy in the world, and some of the known GDM morbidities that may cause maternal death are postpartum hemorrhage, obstructed labor, and preeclampsia (147). In our analysis, although the prevalence of GDM was higher (16.35%) in countries with high MMR (>100/100,000 live births), it was also substantial in countries with lower MMR (≤100/100,000 live births). Although this does not prove temporality, it highlights the importance of researching complications of GDM (if any) leading to maternal deaths, to help healthcare providers in the MENA region establish protocols to prevent these anticipated adversities. GCC countries with the highest GDM prevalence, as presented in this study, are also burdened with high T2DM (148). There is no doubt that controlling GDM would have multiple benefits in

avoiding unfavorable health consequences for both mothers and their babies.

Strengths, Implications, and Limitations

The strengths of our review included its comprehensive characterization of the burden of GDM among pregnant women in several MENA countries. The review provides several weighted estimates in different population groups of the pregnant women at national, subregional, and regional levels that could be used, in addition to future work, to guide the planning, implementation, and evaluation of programs to prevent and control GDM. The overall and national-based pooled prevalence estimates might help policy makers of the respective MENA countries to contrast and quantify the local burden of GDM and introduce better policy initiatives regarding the flow of resources and funds for GDM care and management. Moreover, the finding of higher GDM prevalence corresponding to higher BMI categories might help in developing BMI-specific dietary and exercise guidelines. Furthermore, health authorities and organizations in the region are encouraged to review and consider standardizing the GDM diagnostic criteria at least at the national levels to improve the measurability and comparability of GDM rates and burden across the country and over time. Since we found a wide range of GDM diagnostic criteria used in the MENA region, health organizations across this region might consider moving toward the use of uniform GDM diagnostic criteria to produce better comparable statistical estimates in the future. For instance, in the UAE, different hospitals within the country use different GDM screening and ascertainment criteria (12). Having different GDM diagnostic criteria will preclude understanding the exact burden of the GDM.

Limitations included that our review did not provide any prevalence estimate for about 29% of the MENA region countries, as no prevalence data were available. This might have compromised the comprehensiveness of our prevalence estimates at the regional level. Since we believe that this study is the first to determine the prevalence of GDM in the MENA region, a comparison with previous similar estimates was not possible. This study offers scarce help regarding the prevalence of GDM with its associated comorbidities, such as gestational hypertension, preterm birth, and traumatic vaginal delivery (149), and separate review articles are warranted. The prevalence of GDM can also vary depending on several sociodemographic and maternal characteristics as well as within [urban or rural setting (150, 151)] and between countries and regions; however, our study does not provide such distinction on the prevalence data. In some of the reviewed studies, detailed information on the methodology and GDM measurement procedures was missing, and this limits the category-based generalizability of the measured pooled GDM prevalence. For instance, the 3.35-times increase in the prevalence of GDM in studies reported before 2009 compared with studies reported after 2009 should be cautiously interpreted, as there was an overlap in the time period in 14 studies that tested 29,983 women. The various thresholds for fasting blood glucose level to diagnose GDM, applied on the several criteria considered from the studies, might suggest a bias in the estimated GDM prevalence. Unless estimated by rigorous comparable survey and testing methodology in individual population-based studies, the burden of GDM at the country, subregional, or regional level should not be interpreted as the burden of the measured outcomes at the population level. Moroever, this review did not explore the associations between various maternal and neaonatal characterstics and GDM. Therefore, future systematic reviews and meta-analyses studies focusing on the burden of GDM according to different maternal and neonatal characteristics as well as on the strength of association between various maternal characteristics and GDM are warranted.

CONCLUSIONS

Pregnant women in the MENA region are burdened with a relatively high GDM prevalence. Particularly, in the GCC and North African countries, the observed high burden of GDM may be mainly driven by the high prevalence of several risk factors for DM including overweight and obesity, parity, and late maternal age. To avoid maternal and newborn consequences, vigilant risk factor prevention programs and screening and management programs are necessary in the context of GDM. Moreover, unifying the GDM screening and diagnostic criteria, at least at the country level, is warranted to understand the precise burden of GDM. In countries that lack GDM burden data, high-quality research and surveillance programs are also warranted.

DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed in the current study and the supplementary information files are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Conceptualization, RHA. Methodology, RHA, NMA and MSP. Software, RHA. Validation, RHA. Formal analysis, RHA, NMA, and LAA. Resources, RHA. Writing—original draft preparation, SS and MSP. Writing—review and editing, NMA, MSP, SS, and LAA. Supervision, RHA. Project administration, RHA. Funding acquisition, RHA. All authors contributed to the article and approved the submitted version.

FUNDING

This systematic review was funded by the Summer Undergraduate Research Experience (SURE) PLUS-Grant of the United Arab Emirates University, 2017 (research grant 31M348). The funding source had no role in the study design, collection, analysis, or interpretation of the data, nor in writing or the decision to submit this article for publication.

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.668447/full#supplementary-material

Supplementary File 1 | PRISMA checklist.

Supplementary File 2 | Overall weighted prevalence of GDM in pregnant women in North African countries (Morocco, Algeria, Tunisia, Libya, Egypt) by pregnancy trimester, body mass index, study period, ascertainment methodology, rate of cesarean section deliveries, and maternal mortality.

Supplementary File 3 | Overall weighted prevalence of GDM in pregnant women in GCC countries and Yemen (the UAE, Qatar, Saudi Arabia, Kuwait, Yemen, Oman, Bahrain) by pregnancy trimester, body mass index, study period, ascertainment methodology, rate of cesarean section deliveries, and maternal mortality.

Supplementary File 4 | Overall weighted prevalence of GDM in pregnant women in Iran/Iraq by pregnancy trimester, body mass index, study period, ascertainment methodology, rate of cesarean section deliveries, and maternal mortality.

Supplementary File 5 | Overall weighted prevalence of GDM in pregnant women in the Levant region (Jordan, Syria, Palestine, Lebanon) by pregnancy trimester, body mass index, study period, ascertainment methodology, rate of cesarean section deliveries, and maternal mortality.

Supplementary File 6 | Univariate and multivariable meta-regression analyses to identify sources of heterogeneity in studies reporting on the prevalence of GDM in pregnant women by different measured characteristics.

Supplementary Figure 7 | Funnel plots **(A)** and Egger's publication bias plot **(B)** examining small-study effects on the pooled GDM prevalence among pregnant women in the MENA region, 2000–2019.

Supplementary Figure 8 | Risk of bias assessment of the 102 reviewed research reports on GDM.

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frontiers in Endocrinology

REVIEW
published: 17 September 2021
doi: 10.3389/fendo.2021.630032

Non-Coding RNA as Biomarkers for Type 2 Diabetes Development and Clinical Management

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OPEN ACCESS

Edited by:
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Putra Malaysia University, Malaysia

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

Received: *16 November 2020*
Accepted: *10 August 2021*
Published: *17 September 2021*

Citation:
Chi T, Lin J, Wang M, Zhao Y, Liao Z and Wei P (2021) Non-Coding RNA as Biomarkers for Type 2 Diabetes Development and Clinical Management. Front. Endocrinol. 12:630032. doi: 10.3389/fendo.2021.630032

Diabetes, a metabolic disease characterized by high blood glucose and other complications, has undefined causes and multiple risk factors, including inappropriate diet, unhealthy lifestyles, and genetic predisposition. The two most distinguished types of diabetes are type 1 and type 2 diabetes, resulting from the autoimmune impairment of insulin-generating pancreatic β cells and insulin insensitivity, respectively. Non-coding RNAs (ncRNAs), a cohort of RNAs with little transcriptional value, have been found to exert substantial importance in epigenetic and posttranscriptional modulation of gene expression such as messenger RNA (mRNA) silencing. This review mainly focuses on the pathology of type 2 diabetes (T2D) and ncRNAs as potential biomarkers in T2D development and clinical management. We consolidate the pathogenesis, diagnosis, and current treatments of T2D, and present the existing evidence on changes in multiple types of ncRNAs in response to various pathological changes and dysfunctions in different stages of T2D.

Keywords: ncRNAs, miRNAs, lncRNAs, circRNAs, diabetes, biomarker

1 INTRODUCTION

Diabetes is a kind of metabolic disease characterized by a high level of blood glucose with multiple complications, including macrovascular complications (cardiovascular disease) and microvascular complications (e.g., diabetic kidney disease, diabetic retinopathy, and neuropathy), and higher risks of developing several types of cancer, which subsequently could result in decreased life quality and even death (1–8). Type 1 and type 2 diabetes are the two most common types of this disease. Type 1 diabetes (T1D) presents an absolute insulin deficiency resulting from the autoimmune impairment of insulin-generating β cells, while type 2 diabetes (T2D) displays a relative insulin deficiency due to metabolic dysfunction (9). According to the estimation of International Diabetes Federation, the prevalence of diabetes increases dramatically; by 2045, diabetes is projected to affect approximately 700 million people worldwide, up from the previous estimation of 463 million in 2019. Moreover,

approximately one in every two persons living with diabetes is undiagnosed. In 2019, diabetes causes over 4 million deaths globally in the 20–79 years age range (10, 11). To be diagnosed as diabetic, one's blood glucose should be equal to or above certain values. According to the classification and diagnosis of diabetes by the American Diabetes Association (12), the methods and criteria are as follows: fasting plasma glucose test [FPG ≥126 mg/dl (7.0 mm/L)] and fasting are defined as no caloric intake for the past 8 h at least; 2-h oral glucose tolerance test [OGTT ≥ 200 mg/dl (11.1 mmol/L)] and the test should be conducted strictly as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; glycated hemoglobin test [A1C ≥ 6.5% (48 mmol/mol)]; or random plasma glucose ≥ 200 mg/dl (11.1 mmol/L), coupled with classic symptoms of hyperglycemia or hyperglycemic crisis. In the absence of definitive hyperglucose, at least two of the abnormal test results are required for the diagnosis of diabetes, either from one same sample or two separate ones.

Non-coding RNA (ncRNA) refers to a type of RNA that is not involved in producing proteins but plays a key role in cellular function and development of different diseases. More than 90% of human genome RNAs consist of ncRNAs, and they can be divided into several types based on their size (13). The small ncRNAs such as microRNAs (miRNAs) and longer ncRNAs including long non-coding RNAs (lncRNAs) have been discovered that their up- or downregulation may regulate endothelial function in the vasculature, which is associated with the occurrence of diabetes (**Table 1**) (50). Moreover, the development of islet autoimmunity and dysfunction of β cells may result from the deregulation of immune-cell-specific T1D loci-associated lncRNAs and islet-specific lncRNAs, which leads to T1D (51). In addition, lncRNAs are linked to poor glycemic control, insulin resistance, senescence, and proinflammation in patients with T2D (45). Thus, the specificity that ncRNAs exert significant functions in adjusting cellular pathways and the development of diseases affects their expression patterns, which is reflected in various body fluids, make them ideal as biomarkers for diabetes. This review aims to consolidate the pathogenesis, diagnosis, and treatments of T2D, and the role of ncRNAs as biomarkers in progress and management of T2D.

TABLE 1 | Summary of different expressions of ncRNAs in various target cells of T2D and prediabetic patients.

	Differentially Expressed ncRNAs	Target Cells	Reference
Enhanced↑			
T2D Patients	miR-16	Pancreatic β cells	(14)
	CDR1	Pancreatic β cells	(15, 16)
	circRNA-HIPK3	Pancreatic β cells	(16)
	hsa_circ_0054633	Pancreatic β cells	(17)
	circANKRD36	Pancreatic β cells	(18)
Prediabetes Patients	miR-499-5p	Hepatic cells	(19, 20)
	hsa_circ_0054633	Pancreatic β cells	(17)
Reduced↓			
T2D Patients	miR-376	Pancreatic β cells	(21)
	miR-432	Pancreatic β cells	(21)
	miR-200	Pancreatic β cells	(22)
	miR-184	Pancreatic β cells	(23)
	miR-204	Pancreatic β cells	(24)
	miR-24, miR-26, miR-148, miR-182	Pancreatic β cells	(25)
	miR-9	Pancreatic β cells	(26)
	miR-130a, miR-130b, miR-152	Pancreatic β cells	(27)
	miR-187	Pancreatic β cells	(28)
	miR-7	Pancreatic β cells	(29)
	miR-708	Pancreatic β cells	(30)
	miR-34a, miR-146a	Pancreatic β cells	(31, 32)
	miR-182-5p, miR-33, miR-37	Pancreatic β cells	(33, 34)
	miR-802	Hepatic cells	(35, 36)
	miR-122-5p	Hepatic cells	(37)
	miR-106b	Skeletal muscle cells	(38, 39)
	microRNA let-7a, let-7d	Skeletal muscle cells	(40)
	miR-29	Skeletal muscle cells	(41)
	miR-192, miR-122, miR-27a-3p, miR-27b-3p	Adipocytes	(42)
	LncRNA H19	Pancreatic β cells	(43, 44)
	LncRNA MEG3	Pancreatic β cells	(45–47)
	LncRNA MALAT1	Pancreatic β cells	(48, 49)

2 TYPE 2 DIABETES

2.1 Current Pathogenesis

According to the American Diabetes Association (ADA) (12), diabetes can be classified into the following general categories: type 1 diabetes; type 2 diabetes; gestational diabetes mellitus; specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young) and diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis); and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation).

T2D is characterized by hyperglycemia, insulin resistance, and relatively impaired insulin secretion. Ever since the study of the impaired responsiveness to insulin of the diabetics opened by Berson and Yalow in the 1960s (52), insulin resistance has been proposed, investigated, demonstrated, and concluded as the initial defect in T2D. To compensate for the insufficient insulin functions due to the presence of insulin resistance, hyperinsulinemia occurs, consequent to increased β-cell insulin secretion. However, it is worth noting that patients with primary insulin resistance, characterized by marked hyperinsulinemia and genetically dysfunctional insulin receptor, namely, those with type A insulin resistance, Rabson–Mandenhall syndrome, or Leprechaunism, may have close to normal glucose tolerance, retain normal weight, and normotrygliceridemic, in spite of congenital significantly elevated plasma insulin concentrations (53). Therefore, it is the secondary insulin resistance that is being discussed here, which is remarkably associated with T2D. In a popular context of chronic energy surplus, usually caused by sedentary lifestyle, adipocyte dysfunction may arise as a result of fibro-inflammation process, when white adipose tissue fails to properly adapt and expand in response to positive energy balance, which is normally induced by insulin, liver, pancreas, and skeletal muscle, T2D occurs (54).

It is widely assumed that aside from the aged tendency of population, changes in diet and lifestyle are also responsible for the speedy boost in the global prevalence and incidence of type 2 diabetes in recent decades. These two factors also contribute largely to the ongoing global obesity epidemic, while obesity is tightly correlated with the incidence of T2D (55). Epidemiological studies have shown that the level of overall physical exercise is related to a decline in the relative risk of diabetes by roughly 30% (56). There are also some evidence that T2D may derive from infection. For example, *Chlamydia pneumoniae* may induce β-cell dysfunction in the case of systemic inflammation (57). Although lifestyle and overeating seem to be the activating factors, genetic factors also play an important role in the pathogenesis of T2D. GWAS published in 2007 identified six new diabetes susceptibility genes: SLC30A8, HHEX-IDE, CDKN2A/2B, IGF2BP2, CDKAL1, and FTO (58–62). The first GWAS (61) repeated the previously known correlation between TCF7L2 and type 2 diabetes, which has been found in Icelandic populations (63). TCF7L2 is the most replicated genetic variant related to T2D so far, with a relative risk of 1.4. Besides, epigenetic factors (such as DNA methylation) are particularly crucial as they may mediate the impact of environmental exposure to T2D (64).

3 DIFFERENT TYPES OF NCRNAS USED AS BIOMARKERS OF DIABETES

Non-coding RNA (ncRNA) is a functional RNA molecule that is not translated into a protein. The ncRNAs, making up more than 90% of human genome RNAs, were once labeled "molecular fossils" or "relics" due to their conserved nature and for being "useless" transcriptional products. However, countless significant functions have been unveiled during the past decades, including recruitment of epigenetic modifier proteins, control of mRNA decay and translation, and DNA sequestration of transcription factors, showcasing tremendous biological and medical potential with fast-gaining momentum (65). Categorized by size and length, members of ncRNA family include miRNAs, siRNAs, piRNAs, snoRNAs, snRNAs, exRNAs, scaRNAs, and the long ncRNAs, and the nonlinear circular RNAs. Furthermore, ncRNAs such as miRNAs, lncRNAs, and circRNAs have been proven to have tight links or direct participation in the pathogenesis, development, and prognosis of T2D. Due to their unique roles in modulating biological actions preceding the changes on glucose level and improved detectability and accuracy boosted by technological progression, ncRNAs are emerging as potent biomarkers in the diagnosis of the development and clinical management, utilized alone or complementary to the traditional yardsticks (**Figure 1**).

3.1 miRNA

miRNAs are a large group of small (15–22 nts), non-coding sequences with hairpin conformation, and are highly conserved among the species. Their major roles include direct posttranscriptional repression or cleavage of mRNA targets, resulting in the destabilization of the transcripts, functioning as a critical regulator of an overarching array of cellular processes such as cell development, proliferation, differentiation, apoptosis, and metabolism (66). miRNAs have underestimated potentials,

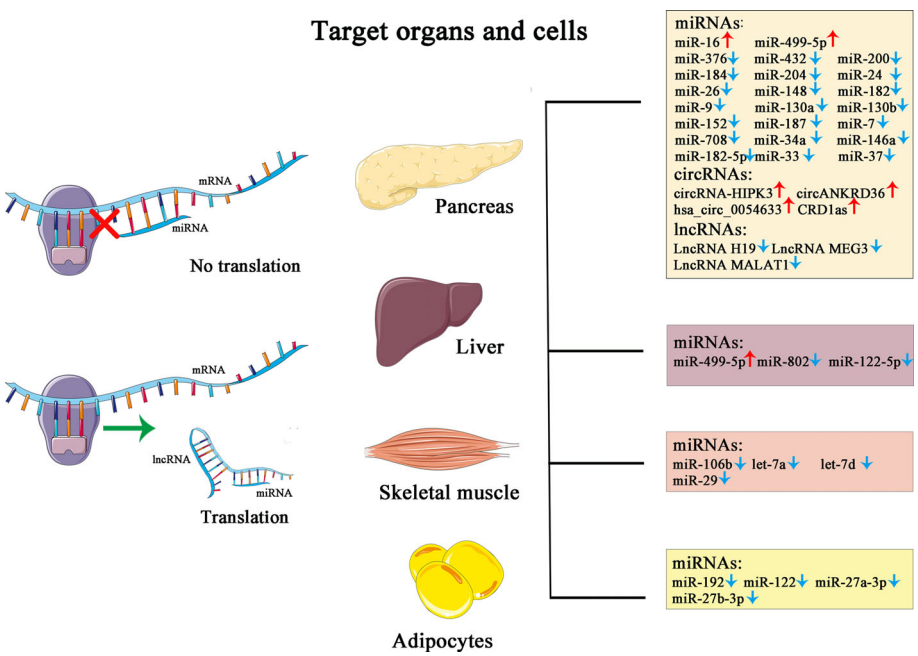

FIGURE 1 | This figure illustrates the simplified mechanism of miRNA and lncRNA in post-transcriptional modulation of gene expression, the target organs and cells, and their corresponding changes in the pathological state of diabetes.

owing to technological limitations. It is only until the discovery of two miRNAs, lin-4 and let-7, which occupies pivotal niches in the timing of development of *Caenorhabditis elegans*. There are over 2,000 miRNAs listed for *Homo sapiens*, and it is predicted that approximately 60% of protein-coding human genes possess miRNA target sites (67, 68).

3.1.1 miRNA and Pancreatic β Cells

The orchestra between pancreatic β cells, insulin, and peripheral recipient cells including hepatic cells, skeletal muscle cells, and adipocytes is key to the occurrence of T2D. Therefore, apart from the conventional focus on the insulin insensitivity of recipient cells where blood glucose fails to enter or being stored as glycogen, attention should also be placed on the secretion and transportation of insulin as well. It has been proven that defective insulin secretion shares association with both reduced β-cell mass and impaired β-cell function, where miRNAs exert effect on (69).

The secretory functions of β cell relies on its physical existence, with emphasis on the proliferation and apoptosis thereof. In human T2D islets, the incidence of methylation of the DLK1-MEG3 cluster is high. This region contains cell-specific histone modifications and is home to over 50 miRNAs, among whom miR-376 and miR-432 has been exemplified to control islet amyloid polypeptide (IAPP) level, which is involved in β-cell apoptosis (21). It has also been found that the expression of miR-200 is highly induced in the islets of diabetic mice, whose beta-cell-specific overexpression suffices to induce beta cell apoptosis and lethal T2D, while its ablation can rescue β cells against apoptosis (22). The downregulation of miR-184 has been witnessed both *in vitro* and *in vivo* in obese diabetic mice, and a decreased expression in the islets of T2D patients, which corroborates the inhibitory effect of miRNA on beta-cell proliferation (23). Another phenomenon concerning beta-cell survival worth mentioning is the extracellular miR-16, which is delivered to β cell by exosome-like vesicles released by skeletal muscles in insulin-resistant conditions. Probably as a compensatory effect, the upregulated expression of said miRNA is in favor of insulin-secreting cell expansion, which increases islet size (14).

Intact as the cell structure may be, pancreatic β cell loses its existential significance once the secretory function proves useless. Before reaching target cells, insulin has to be synthesized and transported out of β cells. In diabetic mice models and cultured beta cells, miR-204 expression has been demonstrated to be induced, which blocks insulin production by directly targeting and downregulating MAFA, a known insulin transcription factor (24). A similar effect has been witnessed in line with the downregulation of a cohort of miRNAs, namely, miR-24, miR-26, miR-148, and miR-182, in isolated islets and cultured β cells where insulin content has been shown to be decreased due to reduced insulin promoter activity (25). MiR-9, among the first detected islet miRNAs, is one of the modulators of insulin granule exocytosis. Its increased expression represses the transcription factor ONECUT2 and increases the expression of granuphilin, which negatively regulates of insulin exocytosis (26). Intracellular energy production also plays a role in the secretion of insulin granules. miR-130a, miR-130b, and miR-152 are found to have overexpression in T2D patient islets, where they each reduced the level of the common target pyruvate dehydrogenase E1 alpha 1 subunit (PDHA1), thereby reducing intracellular ATP and insulin secretion (27). According to a global profiling of islet miRNAs in cohorts of individuals with and without T2D conducted by Locke et al., a dramatic increase in the expression of miR-187 in the islets obtained from T2D donors was noticed. Its exact mechanism on insulin secretion remains to be precisely defined; however, certain relations with homeodomain-interacting protein kinase 3 (HIPK3) were suspected, a protein kinase that is required for normal insulin secretion and a direct target of this miRNA (28).

miR-7 is abundantly expressed in pancreatic islet cells. Studies showed that miR-7 directly regulates insulin granule exocytosis by controlling late stages of insulin granule fusion with the plasma membrane and ternary SNARE complex activity, with no effect on cell proliferation and apoptosis (29). Transgenic mice overexpressing miR-7a in β cells developed diabetes due to impaired insulin secretion and β cell dedifferentiation, while in human, its pattern of expression oscillates responding to the extent of insulin resistance: it is reduced under moderate insulin resistance conditions, contributing to improved insulin secretion; however, it raises progressively under severe diabetic conditions and can reach levels even higher than in healthy individuals (29). The abovementioned phenomenon has established itself as a major obstacle in applying the expression of miR-7 as an independent or complementary biomarker in determining the diagnosis of T2D. In addition to that, challenges for the clinical application of miRNAs as biomarkers also include but not limited to genetic background, treatment types, glycemic control quality, and disease duration.

Reactive oxygen species (ROS) has been placing a great threat to various tissues/cells, causing pathologies including inflammation, metabolic dysfunction, age-related degeneration, and diabetes. β Cells may be at higher risk of oxidative damage from ROS, as a consequence of excessive levels of mitochondrial ROS generation and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, failure of antioxidant defense, and endoplasmic reticulum (ER) stress (38). Chronic hyperglycemia and hyperlipidemia are characteristic of patients with T2D. Several studies have indicated that mammalian (human and murine) pancreatic islets cultured at high glucose concentration manifested miR-708 upregulation, treated with ER stress reliever, which was known to improve ER folding capacity; however, this upregulation is reversed (30). High levels of free fatty acids (FFAs) can be another trigger for beta-cell oxidative stress. Related miRNA such as miR-34a and miR-146a showed an increasing pattern after palmitate treatment on islet cells, in parallel with increased beta-cell apoptotic behaviors, whose inhibition rescued the viability of beta-cells but not their insulin secretory functions (31, 32). Other miRNA with negative regulation on β-cell survival include miR-182-5p, miR-33, and miR-370, whose effect could be corrected by thrombospondin 1 (THBS−1) and Glucagon Like Peptide-1 (GLP-1), respectively (33, 34).

3.1.2 miRNA and Peripheral Recipient Cells

Insulin resistance is the inability of the target tissues to orchestrate well-coordinated glucose-lowering processes, including the suppression of gluconeogenesis, lipolysis, net glycogen synthesis, and cellular glucose uptake in response to physiological blood insulin levels (70). The glucose-insulin balance is maintained through the liver, skeletal muscle, and white adipose tissue, with the liver exerting major effects as the metabolic center of an organism. Hence, once the hepatic insulin signaling cascade faces impairment resulting in hepatic insulin resistance, other metabolic symptoms occur, incurring hyperglycemia, inflammation, and *de novo* lipogenesis, and further, hepatic steatosis and nonalcoholic fatty liver disease (NAFLD) (67). Thus, it is beyond reasonable that tools for early diagnosis of hepatic insulin resistance is beneficial. miRNAs has been investigated for their potential as biomarkers for hepatic insulin resistance, and to qualify as one, whose circulating levels must correlate to corresponding hepatic states and must be crucial in the signaling cascade. miR-802, an intensively studied miRNA in the oncological field, has been demonstrated to be associated with oxidative stress and hepatic insulin resistance. In high-fat diet (HFD) mice, studies have shown that, along with increased expression of miR-802, ROS generation was significantly greater, and the expression of gluconeogenesis-related genes was significantly downregulated (35, 36), and its circulating levels were dramatically elevated in T2D patients, qualifying it as a biomarker. Other miRNAs with changed expression patterns include miR-499-5p, which affects insulin signaling cascade and glycogen synthesis by suppressing phosphatase and tensin homolog (PTEN), alongside the improvement of Akt/GSK activation, and is found to be reduced in prediabetic patients (19, 20), and miR-122-5p, which affects the hepatic gluconeogenesis process, whose circulating levels were significantly higher in cohorts with insulin resistance, T2D, or MetS (37).

Aside from liver cells, another important target of insulin is skeletal muscle, whose glucose uptake also substantially contributes to glucose and metabolic homeostasis. In an investigation on the antioxidant effects of berberine (BBR), an isoquinoline alkaloid, it was found that BBR could attenuate oxidative stress of diabetic mice partly through inhibiting miR-106b/SIRT1 pathway, an miRNA associated with skeletal muscle insulin resistance (38, 39). Interleukin (IL)-13 has been revealed having an autocrine role in the glucose metabolism of skeletal muscle according to Jiang et al., and its exposure increases skeletal muscle glucose uptake, oxidation, and glycogen synthesis *via* an Akt-dependent mechanism. In T2D patients, such bioactivities are found to be suppressed by the increased expression of miRNA let-7a and let-7d, which repress IL-13 genes on translational level (40). To put it simpler, insulin functions by combining to insulin receptor substrate 1 (IRS-1), subsequently triggering a signaling cascade consisting of phosphorylation of protein kinase B (PKB/AKT), translocation of glucose transporter-4 (Glut4) from the cytosol to the membrane, and glucose uptake. The overexpression of miR-29 was demonstrated to be capable of disrupting the glucose metabolism of skeletal muscle by inhibiting insulin signaling, expression of insulin receptor substrate 1 (IRS-1), and phosphoinositide 3-kinase (41).

Since obesity are getting more and more attention as a risk factor of T2D, the role white adipose tissues play in diabetes is receiving piling investigational highlights. Researchers have found that certain exosomes extracted from obese mice were able to induce glucose intolerance in lean mice transfected with certain exosomes, which was demonstrated to be viable through the miRNA content, namely, miR-192, miR-122, miR-27a-3p, and miR-27b-3p, the expression of all of which was increased in obese mice. Data further showed that the mechanism of induced diabetes in white adipose tissue was navigated by the targeting of peroxisome proliferator-activated receptor α (PPARα) (42, 71).

3.2 lncRNA

lncRNAs are a group of transcripts, with lengths extending 200 nucleotides, that also do not translate into proteins. Divided by functions, lncRNAs have three subtypes: the non-functional ones, which serve no purpose other than being by-products of transcriptions; the second type are those whose own transcription is of a self-sufficient manner; and the third type consists of those that are able to act in *cis* and/or *trans* orientations (72). lncRNAs interact intensively with miRNAs, acting as the molecular sponges or decoys of miRNAs to regulate their cytoplasmic level by binding specific miRNAs and actively sequestrate them from their target mRNAs. In turn, lncRNAs can be destabilized by miRNAs' direct targeting and posed as competitors on shared mRNA targets (67). With such intertwined involvement in gene expression regulation, lncRNAs have been presenting some potential in T2D development and management.

H19 is among the earliest-discovered lncRNAs, whose biofunctions have been relatively thoroughly investigated. A recent study conducted by Sanchez-Parra et al. found that H19 may act upstream of miRNA let-7 and the activation of Akt, whose silencing decreased β-cell expansion in newborns and re-expression promoted proliferation of β cells in adults (43). Moreover, the circulating levels of H19 have been demonstrated to be significantly increased in T2D patient cohorts, according to Fawzy et al., which indicates its potential as a biomarker in insulin resistance (44).

MEG3 is another lncRNA known to researchers for a long time as well, mostly indicated in cancer suppression. Its association has been noted with pancreatic cell apoptosis, insulin synthesis, and secretion, whose expression may function as a new regulator of maintaining beta cells identity (46). However, its overexpression, suggested by Zhu et al., may be a promoter for hepatic insulin resistance *via* increasing FOXO1 expression by acting as a sponge for miR-214 (47). It has also been reported that the competitive binding of MEG3 to miR-185-5p, acting as a competing endogenous RNA (ceRNA), promoted the expression of early growth response 2 (EGR2), which was reported to inhibit IRS. Clinical evidence also supported this hypothesis: its overexpression in T2D patients was significant (45).

Like its counterparts, lncRNAs are associated with oxidative stress-induced insulin resistance as well, according to studies.

lncRNA MALAT1, which has been shown to take part in regulation of cell proliferation and motility, has been found to partake in suppressing insulin signaling by inhibiting the phosphorylation of IRS and Akt, *via* the upregulation of the c-Jun N-terminal kinase (Jnk), a stress-sensitive kinase (48). This negative regulatory effect has been corroborated by its increased expression in GDM patients (49).

3.3 circRNAs

Circular RNAs (circRNAs) are a group of non-linear, naturally occurring ncRNAs with covalently closed circular structures. They are usually generated from precursor mRNA by a non-canonical event called backsplicing, displaying exceptional stability and evolutionary conservation, and tissue or development stage-specific expression patterns (73). Compared to miRNAs and lncRNAs, where many research results have been obtained, the biological functions discovered for circRNAs are relatively scarce, whereas a few associations have been made between them and glucose metabolism, insulin resistance, and T2D.

Certain circRNAs are capable of fulfilling various intracellular functions mainly by acting as sponges of miRNAs or RNA-binding proteins (RBPs). The best understood endogenous circRNA to this date has been CDR1as (also termed as ciRS-7). By potently binding to miR-7, it relieves the inhibitory effect of miR-7 on β-cell function, subsequently promoting islet β-cells proliferation and insulin secretion (15). Such phenomenon has also been observed *in vivo*, where the expression of CDR1as was reduced in diabetic mice (16). A similar effect has been witnessed in another circRNA, circRNA-HIPK3, whose regulation on islet cell function was mediated by sequestering miR-124-3p and miR-338-3p (16). Clinically, such effect could be potentially employed as a marker for therapeutic outcome evaluation. Reverse transcription polymerase chain reaction (RT–PCR) and quantitative polymerase chain reaction (qPCR) analyses were adopted for the screening of circRNAs related to T2D, and several circRNAs were detected to show statistical significance between T2D patients and healthy controls. Among them, there are hsa_circ_0054633 and circANKRD36, with the former being a potential diagnostic biomarker of prediabetes and T2D in peripheral blood cells and the latter displaying a potential in discerning the T2D-inflicted within cohorts with chronic inflammation (17, 18).

4 DISCUSSION

Early detection of diabetes mellitus is very useful for preventing onset and progression. Several biomarkers of diabetes mellitus have been reported, such as GDF-15, YKL-40, 2-aminoadipic acid, serum adipocyte fatty acid–binding protein, and urinary 8-oxo-7,8-dihydro-2′-deoxyguanosine (74–78). While many current biomarkers are based on proteins, ncRNAs have been recognized as a new sensitive, noninvasive biomarker for diagnosis, prognosis, and prediction to therapeutic responses in the recent years due to their high stability in body fluids (urine, plasma, exosomes, etc.) and the development of new detection techniques (79).

miRNAs are very stable and resistant to ribonucleases, freezing/thawing cycles, and other severe experimental conditions (80). Therefore, serum or plasma samples can be stored at −20°C or −80°C for several months without causing significant degradation of miRNAs, which serves as valid evidence to support the use of miRNAs as ideal biomarkers (81). lncRNAs are less stable than miRNAs, but compared to protein-coding mRNAs and miRNAs that are frequently expressed in multiple tissues, they show higher tissue specificity (82) and tend to show remarkable level of overexpression in diabetes. circRNAs are presumably more stable than most linear RNAs because they form a unique, circular, covalently closed continuous loop that is resistant to exonuclease-mediated degradation as they have no 5′ or 3′ ends. Recent evidence indicates that circRNAs usually regulate the transcription of miRNA-target genes by acting as miRNA sponges.

The extensive role of ncRNAs in physiological processes and deregulation in human diseases also makes them very attractive targets for new therapies. Several strategies that either silence overexpressed ncRNAs or reactivate downregulated ncRNAs are currently being investigated. Some of the ncRNAs have even shown encouraging therapeutic effects in animal models. For instance, MEG3 knockdown in STZ-induced diabetic mice resulted in increased levels of acellular capillary formation, microvascular leakage, and inflammatory proteins (83). MIAT knockdown in STZ-induced diabetic rats did not affect body weight or blood glucose levels but corresponded with improvements in visual function and partial reversal of a-wave, b-wave, and oscillatory potentials. MIAT downregulation also decreased the number of apoptotic retinal cells and attenuated retinal vessel impairment and retinal vascular leakage (84). In short, the therapeutic potential of ncRNA has been discovered, but the current findings are only the tip of the iceberg, and further research is still needed.

However, the pivotal issue is how to apply the molecular markers determined in the laboratory to the clinical environment. Currently, various limitations impede this research field and delay the clinical application of ncRNAs. On the grounds that ncRNAs are a quite novel area of research, most of the information obtained from the previous studies is only descriptive and correlational, and it is not possible to precisely infer the cause and effect. In particular, the deficiency of thorough understanding regarding the explicit origin, synthesis, modification, and regulatory pathways, and the interactions, cross-talk and coregulation of ncRNAs may hinder the clinical utilization of these ncRNAs. Hence, more edge leading and precise approaches in ncRNAs expression quantification and functional analysis are required.

According to association studies, prevalent assertion arises that ncRNAs can be used as biomarkers for diabetes. Nonetheless, as mentioned above, correlation does not imply causation; thus, pilot results still require large-scale clinical trials. Furthermore, it is strongly advocated to perform *in vitro*/*in vivo* verification of ncRNAs with candidate predictive functions and therapeutic targets since what occurs under physiological and pathophysiological conditions may

not necessarily be consistent with the results from pure calculation and analysis. Therefore, the current data should be regarded as exploratory data and illustrated discreetly before further experiments and comprehensive clinical verification can prove the biological effects of ncRNAs.

The tissue specificity of ncRNAs and their enhanced stability in body fluid also enable them to be a promising future antidiabetic therapy. However, ncRNA therapy that can be authentically applied in the clinics still faces considerable obstacles, including the development of reliable delivery systems, dosage regimens, and technologies to improve off-target effects. On top of these, just like any other therapies, it is expected that ncRNAs as drugs may cause adverse side effects or induce drug resistance.

5 CONCLUSION

ncRNAs have a role in regulation of cellular functions including development, proliferation, differentiation, and apoptosis. ncRNAs anomalies would be indicative as molecular signatures under disease states, which can be applied to arrive at different diagnoses and explore treatments. Considering the rawness of this research field, many ncRNAs functions are waiting to be discovered. In conclusion, studies combining ncRNAs and clinical, genetic, epigenetic, and classical markers could help direct the medical decisions on diabetic patients and show broad prospect in precision medicine.

AUTHOR CONTRIBUTIONS

Conceptualization: ZL and PW. Writing—original draft preparation: TC, JL, MW, and YZ. Writing—review and editing: ZL and PW. Supervision: ZL and PW. Funding acquisition: PW. All authors contributed to the article and approved the submitted version.

FUNDING

This work was funded by the National Natural Science Foundation of China (Grant No. 31800652), Young Scientist Program by Beijing University of Chinese Medicine (Grant No. BUCM-2019-QNKXJ-C014), and the "Double First Class" Construction Funds of Discipline of Integrated Traditional Chinese and Western Medicine of Beijing University of Chinese Medicine.

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