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OPINION REVIEW

Multifaceted relationship between diabetes and kidney diseases: Beyond diabetes

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Abstract

Diabetes mellitus is one of the most common causes of chronic kidney disease. Kidney involvement in patients with diabetes has a wide spectrum of clinical presentations ranging from asymptomatic to overt proteinuria and kidney failure. The development of kidney disease in diabetes is associated with structural changes in multiple kidney compartments, such as the vascular system and glomeruli. Glomerular alterations include thickening of the glomerular basement membrane, loss of podocytes, and segmental mesangiolysis, which may lead to microaneurysms and the development of pathognomonic Kimmelstiel-Wilson nodules. Beyond lesions directly related to diabetes, awareness of the possible coexistence of nondiabetic kidney disease in patients with diabetes is increasing. These nondiabetic lesions include focal segmental glomerulosclerosis, IgA nephropathy, and other primary or secondary renal disorders. Differential diagnosis of these conditions is crucial in guiding clinical management and therapeutic approaches. However, the relationship between diabetes and the kidney is bidirectional; thus, new-onset diabetes may also occur as a complication of the treatment in patients with renal diseases. Here, we review the complex and multifaceted correlation between diabetes and kidney diseases and discuss clinical presentation and course, differential diagnosis, and therapeutic opportunities offered by novel drugs.

Key Words: Diabetes; Diabetic kidney disease; Nondiabetic kidney disease; Biomarkers; Glomerular disease; Kidney biopsy; Sodium-glucose cotransporter-2 inhibitors

Core Tip: The relationship between diabetes and kidney disease is complex. Indeed, in patients with diabetes beyond the development of diabetic kidney disease, other forms of kidney disorders not directly correlated with diabetes may occur. Distinguishing between these conditions is essential to guide clinical management. Additionally, de novo diabetes may complicate the treatment of patients with kidney disease. Finally, growing evidence indicates that new drugs, such as sodium-glucose cotransporter-2 inhibitors, may be effective under both conditions. Herein, we discuss the multifaceted correlation between diabetes and kidney diseases, focusing on clinical presentation, differential diagnosis, and new therapeutic opportunities.

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INTRODUCTION

Diabetes mellitus (DM) is one of the most common causes of renal disorders and chronic kidney disease (CKD) and the leading cause of end-stage kidney disease (ESKD) in high-income countries[1]. Kidney involvement may be found in up to 30%-40% of diabetes patients[2] and is characterized by a wide spectrum of possible clinical entities, such as diabetic kidney disease (DKD), nondiabetic kidney disease (NDKD), and association of DKD together with NDKD[3]. Consequently, the clinical presentation may range from mild urinary alterations and low-grade proteinuria to overt proteinuria and kidney failure[4].

DKD is usually diagnosed in patients with a long history of DM (> 10 years) who present with albuminuria and/or reduced estimated glomerular filtration rates (eGFR). However, recent epidemiological studies have highlighted that it may also present with non-albuminuric renal impairment[5]. Clinical experience and studies have found that not all cases of CKD and urinary alterations in patients with diabetes are direct consequences of DM. Indeed, studies of kidney biopsies have shown that up to 40% of patients with a clinical diagnosis of DKD present a form of NDKD[6]. These nondiabetic lesions include focal segmental glomerulosclerosis, IgA nephropathy, and other primary or secondary glomerular diseases. Therefore, it appears clear that an approach based exclusively on clinical evaluation is insufficient to properly classify and manage patients with DM with renal damage, whereas renal biopsy remains essential for acquiring both diagnostic and prognostic information[7]. Interestingly, the relationship between DM and kidney disease is bidirectional. Therefore, although patients with diabetes may be affected by various kidney diseases, developing *de-novo* DM in patients with nephropathies is possible, particularly in those undergoing immunosuppressive treatment[8]. Therefore, in this opinion review, we discuss the multifaceted relationship between kidney disease and DM. Moreover, we explored new therapeutic opportunities provided by the introduction of sodium-glucose cotransporter-2 (SGLT2) inhibitors, which were first used for their antidiabetic effects and have been shown to be potentially effective in kidney disease management[9].

WHAT ARE THE CAUSES OF CKD IN PATIENTS WITH DIABETES?

DKD

DKD is a complex and heterogeneous disease with overlapping etiological pathways. Understanding the molecular mechanism of DKD onset and progression may help optimize diagnosis and treatment. However, a full discussion of the precise pathogenesis is outside the scope of the present study; rather, it may be found in focused reviews[10,11].

Briefly, the mechanisms of DKD can be classified into changes in glomerular hemodynamics, inflammatory responses, and oxidative stress. In the early stages of DKD, one of the most characteristic alterations is glomerular hyperfiltration, which is also influenced by lifestyle factors, such as diet, body weight, and hyperglycemia[12,13]. In particular, hyperglycemia stimulates sodium-glucose cotransporters to increase the reabsorption of glucose and sodium in the proximal tubules, reducing sodium chloride delivery to the macula dense[14]. As a result, activation of the so-called tubuloglomerular feedback occurs, resulting in the dilatation of afferent arterioles and the release of angiotensin II[15]. These mechanisms contribute to increased glomerular perfusion, increased intraglomerular pressure, and glomerular hyperfiltration.

Regarding inflammatory responses, experimental and clinical evidence demonstrated changes in circulating leukocytes that may induce alterations in the levels of specific pro-inflammatory molecules[16]. Accordingly, increased expressions of inflammatory cytokines, chemokines, and growth factors have been observed in kidney biopsies from patients with DKD[17].

Instead, what concerns oxidative stress, hyperglycemia leads to the production of reactive oxygen species, which activates inflammasomes and induces epithelial-to-mesenchymal transition and apoptosis, thus contributing to the progression of kidney damage[18-20].

Recent mechanistic models highlight the importance of chronic subclinical inflammation as a key promoter of kidney injury in diabetes[21,22]. Indeed, inflammation may constitute a link between biochemical stimuli, immune cell recruitment, oxidative stress, and renal cell alterations, ultimately leading to glomerular and vascular damage with interstitial fibrosis and tubular atrophy[23,24].

Moreover, several individual and demographic factors may influence the development, presentation, and natural history of DKD. For example, epidemiological studies have shown that DKD occurs more frequently in African Americans, Asian Americans, and Native Americans than in Caucasians[25]. These differences may be explained by genetic backgrounds and economic and social factors.

Less consistent data are available on the effects of sex on DKD. While sexual dysmorphism may influence the metabolic and molecular mechanisms underlying DKD, the extent of these effects and the characterization of high-risk subjects (men and pre-or postmenopausal women) remain under debate[26].

Estimating the incidence and prevalence of CKD and kidney failure in patients with DM is challenging because kidney biopsies are infrequently performed[27,28]. Indeed, patients with a long history of DM who present with albuminuria and/or a reduced eGFR are presumed to have DKD without histological confirmation.

Currently, only a complete examination of the kidney biopsy may lead to the accurate definition of DKD versus NDKD [29]. The histological picture of DKD may vary, with pathological alterations in glomeruli, renal tubular cells, and vascular tissue[30]. The initial alteration in classical diabetic glomerulopathy is the thickening of the glomerular basement membrane[31]. Other glomerular changes include mesangial expansion, which can be diffuse or nodular (often termed "Kimmelstiel-Wilson nodules"), podocyte injury, and glomerular sclerosis[32,33] (Figure 1). A substantial number of patients with type 2 diabetes and DKD have mild or no glomerulopathy, with tubulointerstitial and/or arteriolar abnormalities[34,35]. Tubulointerstitial fibrosis usually occurs after the initial glomerular lesions and is the final pathway mediating progression to advanced CKD and ESKD. Patients with type 1 DM (T1DM) predominantly develop classical diabetic glomerulopathy, whereas pathological abnormalities in type 1 DM (T2DM), particularly in patients without albuminuria, are more heterogeneous[34,36,37].

The heterogeneity of DKD is also clinically evident. Some differences between T1DM and T2DM are as follows: The former generally presents more conspicuously, while T2DM can be asymptomatic for years before diagnosis. The most common clinical features are persistently elevated urine albumin excretion (defined as a urine albumin excretion > 30 mg/d or > 30 mg/g) and persistently decreased eGFR (defined as an eGFR < 60 mL/min using a creatinine-based formula). In severe cases, albumin levels can exceed the nephrotic threshold of 3.5 g per 24 h, resulting in nephrotic syndrome[38,39].

The early phases of DKD are often asymptomatic; thus, manifestations are detected through routine testing. Therefore, patients with DM should undergo annual testing for kidney complications using the serum creatinine-based estimated glomerular eGFR and urine tests for abnormal levels of albumin excretion[40,41]. The urine sediment in DKD is usually bland; however, patients with severely increased albuminuria may have microscopic hematuria[42,43], and those with nephrotic-range proteinuria often have oval fat bodies or lipid droplets. Dysmorphic red blood cells and red blood cell casts are uncommon in patients with DKD and, if present, may suggest NDKD[44].

In addition to the classical phenotype of albuminuria with or without eGFR reduction, clinical experience and epidemiological studies have observed an increased incidence of reduced eGFR without albuminuria[45,46]. Being aware of this occurrence is necessary as the non-albuminuric phenotype is present in both T1DM and T2DM patients and includes patients progressing toward ESKD independently of developing albuminuria[47,48].

From a prognostic point of view, whether the natural history and rate of progression of DKD differ according to DM type remains unclear. In T2DM, disease onset usually occurs after the age of 40 years, and factors such as age-related senescence of the kidney and hypertension can contribute to the decline in kidney function to varying degrees. In addition, T2DM can be asymptomatic for years, which could lead to delayed diagnosis; therefore, the true time of onset of hyperglycemia is usually unknown[48,49]. Moreover, owing to the obesity pandemic[50], T2DM is progressively increasing compared with T1DM among youths, resulting in earlier development of complications, including CKD[51-53].

NDKD

NDKD includes various renal diseases diagnosed in patients with diabetes who may benefit from specific therapies. Therefore, distinguishing between DKD and NDKD is of paramount relevance because their prognosis and treatment differ.

However, the epidemiology of DKD and NDKD remains unclear. The reported prevalence of DKD and NDKD varies among centers regarding indications for renal biopsy in patients with diabetes[54]. Selection bias is possible for two reasons. First, the prevalence of NDKD may be overestimated, as the criteria for kidney biopsy are generally represented by an atypical presentation with clinical elements highly suggestive of NDKD. Second, because diabetic patients with CKD are often clinically diagnosed with DKD, the diagnosis of NDKD or NDKD superimposed on DKD is often missed [3].

In 328 patients with T2DM enrolled between 2001 and 2014, Li *et al*[55] identified a histological diagnosis of pure DKD in 57.3%, NDKD in 36.9%, and mixed forms in 5.8% of cases. Similarly, Zeng *et al*[56] observed the diagnosis of DKD in 48.4% out of 244 patients with T2DM. The diagnoses of NDKD and a mixed form were made in 45.9 and 5.7% of the patients, respectively. In 2017, in a meta-analysis of 48 studies, Fiorentino *et al*[27] found that the prevalence of DKD, NDKD, and overlapping forms was extremely variable, ranging from 6.5 to 94%, 3.0 to 82.9%, and 4.0 to 45.5%, respectively. More recently, Tong *et al*[57] found prevalence of 41.3% for DKD, 40.6% for NDKD, and 18.1% for mixed forms.

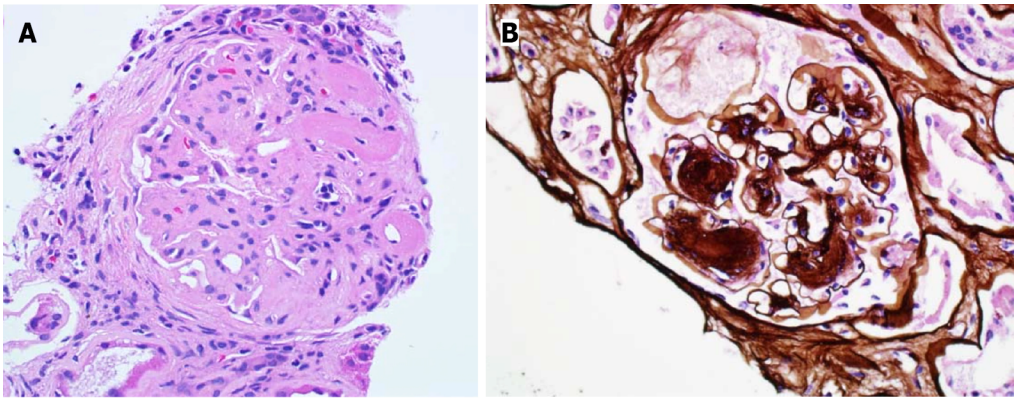

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Figure 1 Pure diabetic glomerulopathy. A: The glomerulus shows nodular expansion of the mesangial matrix and segmental sclerosis with hyalinosis (H&E 40 ×); B: Nodular mesangial matrix expansion with peripheralized capillaries (Jones methenamine silver 40 ×).

While the prevalence of DKD exceeded that of NDKD in Europe and Oceania, NDKD was more prevalent in North America, Asia, and Africa[57].

The pathological entities diagnosed on the kidney biopsies of patients with NDKD may also be influenced by ethnic and epidemiological factors. For example, while focal segmental glomerulosclerosis (FSGS) was the most prevalent diagnosis among patients in a North American cohort study, membranous nephropathy (MN) represented the most common pathological type of NDKD in Asia, Africa, and Europe[58].

Furthermore, it should be highlighted that patients affected by DM may also be at high risk of developing rare glomerulopathies, such as IgA-dominant acute postinfectious glomerulonephritis (APIGN). This is a subtype of APIGN first reported in the early 2000s and characterized by specific clinical and pathological elements[59]. From a clinical perspective, patients with IgA-dominant APIGN usually have severe and rapidly progressive renal failure with various degrees of hematuria, proteinuria, hypocomplementemia, and ongoing or recent staphylococcal infections. Patients with DM have a high prevalence of staphylococcal skin infections, which explains why DM is a major risk factor for glomerulonephritis[60,61].

Moreover, mounting evidence suggests that the intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors used to treat diabetic retinopathy (DR) may be associated with glomerular diseases. Once injected intravitreally, VEGF inhibitors are systemically absorbed, leading to nephrotoxicity in podocytes and endothelial cells[62,63].

Finally, even when a kidney biopsy shows NDKD, the coexistence of DM could impact its presentation, management, and prognosis. In a cohort of patients with various glomerular diseases, Freeman *et al*[64] found that patients with versus without diabetes had a significantly higher rate of proteinuria and a higher rate of progression to ESKD regardless of diagnosis.

However, despite the potentially high clinical impact of these conditions, beyond some epidemiological findings, no prospective data are available. This is the rationale for designing CureGN-Diabetes, an ongoing multicenter prospective cohort study that aims to understand how diabetes influences the diagnosis, treatment, and outcomes of glomerular disease[65].

WHAT ELEMENTS MAY GUIDE DIFFERENTIAL DIAGNOSIS BETWEEN DKD AND NDKD?

The clinical and histological heterogeneity of kidney damage in patients with diabetes highlights the importance of a proper differential diagnosis of DKD and NDKD. A correct diagnosis may impact clinical and therapeutic management. Even if some measures, such as optimizing glycemic and blood pressure control, and prescribing renin-angiotensin system inhibitors are strictly recommended for all diabetic patients with kidney disease, other treatments may differ significantly according to the diagnosis[66].

The main example is provided by immunosuppressive drugs (*e.g.*, steroids, mycophenolate, cyclosporine, *etc.*), which are not indicated for DKD; otherwise, they may constitute the treatment of choice for patients with non-diabetes-related glomerular disease. In this case, the histological diagnosis of NDKD is essential to support the use of these drugs, considering their potential side effects, such as infections, leukopenia, and metabolic alterations[67].

Moreover, distinguishing between DKD and NDKD may affect long-term clinical management. Some forms of glomerular disease may recur after kidney transplantation[68]. Therefore, for diabetic patients who develop ESKD, it may be useful to determine the exact cause of kidney disease.

Given these considerations, many authors have attempted to characterize the most relevant factors for differentiating between DKD and NDKD (Table 1).

Currently, the most widely used approaches in clinical practice are based on evaluating clinical elements and histological findings.

Table 1 Elements for the differential diagnosis between diabetic kidney disease and nondiabetic kidney disease

	DKD	NDKD	Ref.
Clinical characteristics			[57,71,72]
	Diabetic retinopathy	Microhematuria; active urinary sediment	
	Longer diabetes duration (> 5 yr)	Acute onset of nephrotic proteinuria	
		Acute kidney injury	
		Positive autoimmunity	
Histopathological elements			[27,29]
Light microscopy			
Diffuse glomerulosclerosis	Thickening of the GBM; mesangial expansion; mesangiolysis	Reduced vascular involvement and arteriolar hyalinosis	
Nodular glomerulosclerosis	Mesangial expansion with nodular glomerular sclerosis ("Kimmelstiel-Wilson nodules")		
	Nodules are PAS-positive, silver and Congo red negative	Amyloidosis: Congo red positive staining	
Immunofluorescence	Linear staining of the GBM and tubular basement membrane for IgG and albumin; no other specific stainings	MIDD: Light-chain and/or heavy-chain deposits; IgAN: Predominant or codominant mesangial staining for IgA with or without C3; Cryoglobulinaemia and MPGN: Mesangial and GBM staining for IgM, IgG and C3	
Electron microscopy	Diffuse GBM thickening; diabetic fibrillosis; podocytopenia	Fibrillar and Immunotactoid glomerulonephritis: Microfibrillar and microtubules deposition; cryoglobulinaemia and MPGN: Mesangial, subendothelial and subepithelial electron-dense deposits, intracapillary thrombi and leucocytic infiltrate	
Radiological features	Higher renal arterial resistance index (> 0.66)		[78]
Biomarkers	Higher uNGAL/creatinine ratio (cutoff = 60.85 ng/mg)		[75]
Omic sciences	Specific biomolecular signatures in urine and plasma; proteomic analysis of extracellular vesicles		[79,80,81,83]
Other techniques	Evaluation of urine samples by Raman spectroscopy and chemometric analysis		[82]

DKD: Diabetic kidney disease; NDKD: Nondiabetic kidney disease; MIDD: Monoclonal immunoglobulin deposition disorder; IgAN: IgA nephropathy; GBM: Glomerular basal membrane; MPGN: Membranoproliferative glomerulonephritis; uNGAL: Urinary neutrophil gelatinase-associated lipocalin.

The main clinical elements guiding the differential diagnosis are DM duration (shorter duration is more consistent with NDKD), microhematuria as a clinical indicator of NDKD, and evidence of DR as a clinical predictor of DKD[69]. Indeed, available data suggest that the absence of DR may predict NDKD; however, DKD cannot be excluded, whereas DR may occur in patients with mixed forms[70]. Moreover, a history of poor glycemic and blood pressure control is another factor that orients DKD[71,72]. Regarding the clinical presentation, rapid-onset severe albuminuria and/or a rapid eGFR decline (sometimes presenting as acute kidney injury), such as active urinary sediment, should be considered possible alternative etiologies.

Given the clinical limitations of reaching a proper diagnosis, renal biopsy remains an essential tool for differential diagnosis. However, even if a renal biopsy is performed, drawing a definite conclusion is not always straightforward. As mentioned previously, glomerulopathies may overlap with DKD. Moreover, some diseases may exhibit histological features resembling those of DKD. For example, both diffuse and nodular diabetic glomerulosclerosis are common diseases; in these cases, immunofluorescence and thorough ultrastructural examination using electron microscopy is required[30]. Diffuse diabetic glomerulosclerosis includes the differential diagnosis of IgAN, MN, and membranoproliferative glomerulonephritis (Figure 2). Alsaad *et al*[29] emphasized that these glomerulopathies frequently exhibit reduced vascular involvement and less severe arteriolar hyalinosis than diabetic nephropathy. Nodular diabetic glomerulosclerosis poses great concerns in terms of its differential diagnosis. For example, as their appearance on light microscopy may overlap, amyloidosis may only be distinguished from DKD by red-positive Congo staining, while non-amyloidotic monoclonal immunoglobulin deposition disease presents a typical light-chain and/or heavy-chain deposition on immunofluorescence. Fibrillar and immunotactoid glomerulonephritis may have various histological patterns, including nodular glomerulosclerosis, and when these entities are suspected, diagnostic certainty is obtained only with ultrastructural evaluation using electron microscopy. The most challenging differential diagnosis is idiopathic nodular glomerulosclerosis, a rare glomerulopathy that is not histologically distinguishable from nodular diabetic glomerulo-

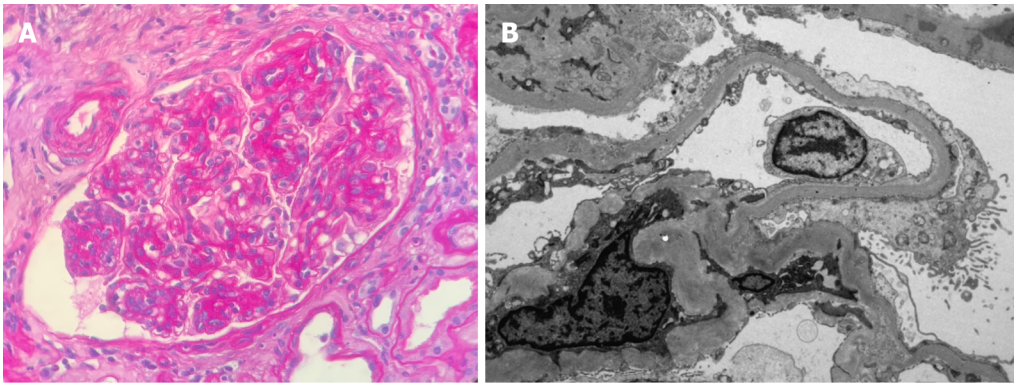

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Figure 2 Nondiabetic kidney disease. A: Membranoproliferative glomerulonephritis and diabetic nephropathy. Lobulated glomerulus due to nodular mesangial expansion and endocapillary hypercellularity in a patient with diabetes and proliferative glomerulopathy with monoclonal immunoglobulin deposition (PAS 40 ×); B: Severe effacement of the foot processes over thickened glomerular basement membranes in a patient with diabetic glomerulosclerosis with superimposed podocyte injury (electron microscopy, magnification 2000 ×).

sclerosis. In this case, the absence of DM was the only diagnostic element[30]. While kidney biopsy remains the gold standard method to obtain a differential diagnosis between DKD and NDKD, an advancement in precision medicine in the renal setting is the definition of novel noninvasive biomarkers[73]. Many studies have evaluated different molecules, such as urinary neutrophil gelatinase-associated lipocalin (NGAL), plasma copeptin, urinary liver-type fatty acid-binding protein, and, more recently, the omics platform-based approach, finding that these molecules may be correlated with kidney disease progression[74]. As tubulointerstitial involvement occurs frequently in DKD, some authors have attempted to clarify the role in the differential diagnosis between DKD and NDKD[75] of NGAL, a well-known tubulointerstitial biomarker[76,77]. Duan *et al*[75] recruited 100 patients with T2DM who were histologically diagnosed with DKD (n = 79) or NDKD (n = 21). Urinary NGAL levels were normalized to creatinine levels to obtain the uNGAL/creatinine ratio (uNCR). The uNCR was an independent risk factor for DKD in patients with DM and renal impairment, and patients with NDKD showed lower uNCR levels than patients with DKD. A uNCR value of 60.685 ng/mg was found as the best predictive cutoff for DKD. Interestingly, patients with DKD with a uNCR higher than 60.685 ng/mg showed a worse prognosis and a higher risk of developing proteinuria in the nephrotic range[75].

Confirming the vascular involvement in diabetic nephropathy, Li *et al*[78] described a higher renal arterial resistance index (RI) in patients with DKD than in patients with NDKD, with 0.66 being the optimal predictive cutoff for DKD, even after adjusting for serum creatinine levels. The authors also created a promising diagnostic tool: A RI-based prediction model for the differential diagnosis between DKD and NDKD.

Interestingly, some innovative solutions to early and proper diagnosis of kidney involvement in diabetic patients come from studies using omics sciences. The proteomic analysis of the urine (nowadays seen as a potential surrogate for the kidney biopsy) by multiple peptide panels, such as cell-free microRNAs and extracellular vesicles, has allowed to predict DKD development and progression[79-81].

In addition, very recently, it has been demonstrated that the evaluation of urine samples by Raman spectroscopy followed by chemometric analysis may be able to differentiate between DKD and NDKD with high specificity and sensitivity[82]. Similar results were also found in blood samples, in which the combination of traditional molecular biology and transcriptomic approaches has led to the identification of potential DKD biomarkers[83,84].

While these new approaches may improve the risk stratification of patients with diabetes and kidney disease, they have scarcely been studied in clinical trials[85].

Thus, although integrating biomarkers into the clinical management of patients with diabetes seems promising, the effective use of these tools remains to be defined, and longitudinal prospective studies are needed to validate these strategies.

HOW CAN THE TREATMENT OF KIDNEY DISEASES IMPACT GLYCEMIC CONTROL?

One of the least considered aspects of the relationship between DM and kidney disease is the possibility of developing DM during the treatment of glomerular diseases.

Although post-transplant DM has been the subject of extensive clinical and experimental research, data on epidemiology, pathogenesis, and risk factors of new-onset DM among patients with glomerular diseases (NODAG) are scarce[86].

Conversely, conceivable data extrapolated from transplant studies may not apply to patients with glomerulonephritis as immunosuppressive strategies in these patient populations are substantially different in terms of intensity and duration of treatment. Theoretically, patients with glomerular diseases may present with multiple causes for the development of DM and metabolic complications. Renal diseases, particularly inflammation, are associated with reduced glucose filtration, increased insulin resistance, hyperuricemia, and impaired tubular function, which predispose patients

to hyperglycemia[87]. Moreover, all the immunosuppressive drugs commonly used to treat glomerulonephritis may cause metabolic complications[88]. Apart from the well-known hyperglycemic effects of corticosteroids, calcineurin inhibitors, such as cyclosporine and tacrolimus, may promote DM through a direct effect on pancreatic β-islet cells[89]. Given these considerations, the scarcity of data regarding this issue is surprising. In 2017, Miyawaki *et al*[90] investigated the incidence of new-onset DM in a cohort of 95 patients at the first diagnosis of IgAN treated with tonsillectomy combined with steroid pulse therapy and evaluated them both during hospitalization and after 1 year of follow-up.

They found that DM occurred with an incidence of 20% (19 patients) only during the hospitalization, and no patients developed DM during the follow-up. Patients developing NODAG, compared with patients without DM, were older, with a higher prevalence of hypertension and family history of DM. In addition to steroid use, age and family history of DM have emerged as independent risk factors for DM development.

Lim *et al*[91] evaluated the epidemiology, risk factors, and outcomes of NODAG in 448 Asian patients with biopsy-proven glomerulonephritis. Among the evaluated patients, the most common diagnoses were lupus nephritis (24.6%), MCD, FSGS (27.7%), and IgAN (21.7%). The majority (72.1%) received immunosuppressants after diagnosis, mostly steroids, mycophenolate, cyclosporine, and cyclophosphamide. Moreover, patients also received non-immunosuppressant drugs such as diuretics and renin-angiotensin-aldosterone system inhibitors. NODAG occurred in 48 patients (10.7%); the time from biopsy to hyperglycemia was 9.1 wk. Methylprednisolone and cyclophosphamide are commonly administered to patients with NODAG. Hyperlipidemia, greater proteinuria, lower HDL-C levels, and methylprednisolone use were independently associated with NODAG risk. Looking at clinical outcomes, the authors noticed no differences in ESKD, time to ESKD, cardiovascular disease, or death among patients with NODAG compared with those who did not develop it. In 2020, the same group evaluated the prevalence of prediabetes and NODAG in a cohort of 229 nondiabetic adults diagnosed with glomerulonephritis[92]. The authors found that prediabetes was already present in approximately one-third of patients at the time of renal biopsy. After the biopsy and during the follow-up, 29 patients (12.7%) developed NODAG. Adjusted multivariate analysis confirmed that prediabetes and methylprednisolone use were independently associated with NODAG.

Overall, these data highlight that new-onset DM after the diagnosis of the glomerular disease is an early event with a significant incidence ranging from approximately 10% to 20% of glomerular patients. This variability may be due to the intensity of the immunosuppressive treatment and use of corticosteroids.

MAY ANTIDIABETIC DRUGS INFLUENCE THE COURSE OF KIDNEY DISEASES? THE EXAMPLE OF SGLT2 INHIBITION

Recent evidence suggests that novel antidiabetic drugs may exert significant nephroprotective effects resulting in a reduction of albuminuria and a slower decline in eGFR in patients with CKD, even in the absence of diabetes[93]. An example is provided by the case of SGLT2 inhibitors (SGLT2i), recently introduced to the market.

In the kidneys, the reabsorption of filtered glucose occurs through SGLTs, a family of membrane proteins expressed in the renal proximal tubule. SGLT2, a high-capacity, low-affinity transporter, accounts for approximately 90% of glucose reabsorption in the kidneys. Thus, the pharmacological inhibition of SGLT2 may reduce glucose and sodium reabsorption by inducing glycosuria[94]. This mechanism of action offers potential promise for the treatment of patients with T2DM; consequently, early research focused on the effects of SGLT2i in improving glucose control and metabolic parameters [95]. However, in recent years, SGLT2i have arisen from antidiabetic drugs to cardiorenal protective treatments. The first trials exploring the cardiovascular effects of SGLT2i were EMPA-REG OUTCOME, testing empagliflozin; CANVAS, testing canagliflozin; and DECLARE-TIMI 58, testing dapagliflozin[96-98]. Briefly, these trials showed that in patients with T2DM, the addition of SGLT2i to standard care reduced the incidence of cardiovascular events and mortality. Interestingly, although not specifically designed to the scope, both secondary and post-hoc analyses in subgroups of patients with CKD showed that SGLT2i treatment was correlated with a slower progression of kidney disease and a reduced number of renal events, defined as increased proteinuria, eGFR reduction, ESKD, or death from renal disease [99].

Theoretically, several plausible mechanisms of action for SGLT2i are present in the kidneys[100]. The first effect is lowering the threshold for glucose excretion, normally 180 mg/dl to approximately 40 mg/dl, causing glycosuria and consequently reducing serum glycemia and HbA1c (0.6%-1.0%) and improving insulin secretion and sensitivity. However, other factors may be implicated. For example, limiting the passage of glucose through proximal cells can reduce glycolysis, which can be related to renal fibrosis[101]. The reabsorption of glucose is coupled with Na^+ in the proximal tubule; inhibition of SGLT2 leads to increased delivery of NaCl to the macula densa, activating tubule-glomerular feedback and reducing intraglomerular pressure[102]. Moreover, this mechanism, associated with decreased activity of the Na^+-H^+ antiporter, may exert a natriuretic effect with a subsequent reduction in blood pressure and hypervolemia. Previous effects allow SLGT2i to reduce kidney ATP consumption and prevent kidney hypoxia. Other effects are being studied, such as the possibility of weakening fibrosis, oxidative stress, endothelial dysfunction, and podocyte loss, stimulating uricuria and autophagy, and improving metabolic flexibility and weight loss[103,104]. Based on these considerations and the results of early trials, additional studies have been specifically designed to test the renal effects of SGLT2i in patients with kidney disease with or without DM. The CREDENCE trial (canagliflozin), which included only patients with T2DM with an eGFR of 30-90 mL/min and albuminuria, showed that patients with kidney disease who received canagliflozin had a lower risk of death from renal or cardiovascular causes, ESKD, or doubling of the serum creatinine level than those who received a placebo[105]. Instead, in the DAPA-CKD enrolling patients with eGFR 25-75 mL/min and albuminuria > 200 mg/g, approximately one-third of the patients had no prior DM. In this

cohort, the diagnoses of kidney diseases included IgAN in 17%, FSGS in 2%, MN, and other glomerular diseases. Nonetheless, even in patients affected by T2DM, approximately 3% of patients with coexistent GN exist (1% IgAN, 1% FSGS, < 1% MN)[106]. In addition to the renal protective effects of dapagliflozin reported in the entire study population, sub-analyses were performed on 270 patients with IgAN and 104 patients with FSGS. These studies indicated that while dapagliflozin was effective in slowing kidney disease progression in IgAN, in patients with FSGS, the reduction in eGFR decline was not statistically significant compared with the placebo[107,108]. Finally, in the more recent EMPA-KIDNEY trial enrolling patients with eGFR > 20 mL/min with or without albuminuria, only 46% of the patients had a history of DM, including 6% of patients with a biopsy-proven concomitant glomerular disease (3% IgAN). In 54% of the patients without DM, the most prevalent diagnosis was IgAN (21%) and FSGS (5%)[109]. In agreement with previous results, in this trial, the use of an SGLT2i, empagliflozin, was associated with significant clinical benefits in renal outcomes regardless of basal eGFR and the presence/absence of DM. The importance of this evidence is highlighted by the fact that the European Medicines Agency recently approved the first SGLT2i, dapagliflozin, as a nephroprotective drug for the treatment of CKD in nondiabetic patients[110].

Plausibly, in the future, this indication will be expanded to other molecules in the SGLT2i class and patients affected by systemic diseases, such as erythematous systemic lupus and vasculitis, who were excluded from all large renal outcome trials[111].

The development and clinical application of sGLT2i offer just an example of successful translational research, underlying how the individuation of new molecular mechanisms linking kidney disease and diabetes.

Similar considerations could be made for other antidiabetic drugs, such as metformin and glucagon-like peptide-1 receptor agonists, that have shown nephroprotective effects[93,112,113]. However, research on the pathogenesis of DM and kidney damage is an extremely active field[114]. So, both experimental findings and clinical scenarios of kidney disease in diabetes are rapidly evolving, and significant innovations are expected in the next future.

CONCLUSION

Here, we overviewed the complex bidirectional relationship between diabetes and renal disease. Regarding kidney involvement in patients with diabetes, we underline the necessity of an appropriate diagnostic workup to define a precise diagnosis, as many conditions other than DKD may cause renal impairment. Accurate diagnosis has important clinical implications and may guide therapeutic approaches.

In this view, although the potential utility of new biomarkers, kidney biopsy remains an irreplaceable tool for acquiring crucial information on the diagnosis and severity of renal damage. Furthermore, we discuss the risk of developing new-onset DM as a complication of immunosuppressive treatment in patients with immune-mediated renal disease. Available data reveal that about 10%-20% of patients treated for glomerulonephritis may develop DM, but it is unclear if *de-novo* DM may affect renal or general outcomes. Therefore, while waiting for proper longitudinal prospective studies, it appears reasonable to devote more attention to the early recognition of DM in patients with glomerular diseases.

Finally, the case of SGLT2i, first tested as an antidiabetic drug and then showing glucose-independent nephroprotective effects, suggests that both experimental and clinical research may have practical implications. This example demonstrates how efforts to improve our understanding of the complex pathophysiology of diabetes and kidney diseases may translate into novel therapeutic approaches[115].

FOOTNOTES

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REVIEW

Partners in diabetes epidemic: A global perspective

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Abstract

There is a recent increase in the worldwide prevalence of both obesity and diabetes. In this review we assessed insulin signaling, genetics, environment, lipid metabolism dysfunction and mitochondria as the major determinants in diabetes and to identify the potential mechanism of gut microbiota in diabetes diseases. We searched relevant articles, which have key information from laboratory experiments, epidemiological evidence, clinical trials, experimental models, meta-analysis and review articles, in PubMed, MEDLINE, EMBASE, Google scholars and Cochrane Controlled Trial Database. We selected 144 full-length articles that met our inclusion and exclusion criteria for complete assessment. We have briefly discussed these associations, challenges, and the need for further research to manage and treat diabetes more efficiently. Diabetes involves the complex network of physiological dysfunction that can be attributed to insulin signaling, genetics, environment, obesity, mitochondria and stress. In recent years, there are intriguing findings regarding gut microbiome as the important regulator of diabetes. Valid approaches are necessary for speeding medical advances but we should find a solution sooner given the burden of the metabolic disorder — What we need is a collaborative venture that may involve laboratories both in academia and industries for the scientific progress and its application for the diabetes control.

Key Words: Diabetes; Diabetes mellitus; Endocrinology; Genes; Gut microbiota;

Environment; Insulin signaling; Metabolic disorder; Mitochondria; Obesity

Core Tip: We have read through the references, gathered information and then summarized the literature focusing on the complex physiological networks that play important roles in diabetes. This review highlight that how impairment of insulin signaling, mitochondrial dysfunction can bring about changes in energy balance resulting in diabetes epidemic. We have covered studies from laboratory experiments, clinical trials, epidemiological, and several review articles making this review is a good reference point for further understanding and control of diabetes epidemic in human population.

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INTRODUCTION

Diabetes mellitus is a widespread endocrine disorder. A dysfunctional carbohydrate, lipid, and protein metabolism lead to diabetes mellitus which is identified by prolong hyperglycemia, resulting from insufficient insulin secretion, insulin action or both. Prolonged hyperglycemia in partner with other metabolic abnormalities in patients with diabetes mellitus can cause a significant negative impact on many organs, leading to a life-threatening health problem, including retinopathy, nephropathy, and neuropathy and can also lead to an increased risk of cardiovascular diseases. Karamanou *et al*[1] gathered information from published research and review articles and presented a notable story of Diabetes mellitus in a review article in 2016.

Diabetes mellitus is largely classified into insulin dependent Type 1 Diabetes (T1D) and non-insulin-dependent, Type 2 Diabetes (T2D). In addition, there is also Gestational diabetes, a common medical complication that arises in women during pregnancy[2,3]. Several lines of evidence support the view that both genetic and the environmental risk factors act cooperatively in the pathogenesis of diabetes[4].

There is a recent increase in the worldwide prevalence of both obesity and diabetes [the International Diabetes Federation (IDF) Diabetes Atlas 9th edition 2019]. According to IDF report the diabetes prevalence in 2019 was 463 million people, will rise to 578 million by 2030 and 700 million by 2045. The global incidence of impaired glucose tolerance was around 374 million in 2019 and projected to reach 454 million by 2030 and 548 million by 2045. According to a World Health Organization (WHO) report, diabetes will become one of the most significant diseases or major diseases in the future[5]. A relatively recent WHO global reports (2016) stated that the number of diabetic adults ages between 40 and 59 escalated to 422 million in 2014. Although most countries are experiencing dramatic increase in diabetes, it appears to be more prevalent in middle- and low-income countries. Diabetes is not transmissible however risk factors including impaired glucose tolerance, insulin resistance, genetics, environment, and stress can cause the disease. Mitochondria are also important in many phases of diabetes disorder; however, their role in the pathophysiology of the disease is much dispersed involving both insulin sensitivity and secretion. The human microbiome including both the oral and gut microbiota are linked with diabetes and therefore, in recent years the world scientific communities and medical professionals are beginning to focus attention on the relationship between human microbiome and diabetes. The recent microbiome studies have linked gut microbiome to diabetes. For instance, Li *et al*[6] have assessed auspicious studies which allow a better understanding of the probable mechanism of microbiota in diabetes epidemic in 2020.

To protect the population from diabetes a number of approaches can be adopted by which it can be treated and its effects eluded with balanced diet, physical activity, and medication. Recent technological advancement has offered unique opportunities for the development of strategies to minimize or control the spread of diabetes. What we need is a collaborative venture that may involve laboratories both in academia and industries to understand the mechanism and control of diabetes. This review aims to assess literatures providing insights into factors associated with diabetes.

METHODS

Data sources and search strategy

The initial search was performed in September 2019, the search was restricted to articles published in English focusing on the factors associated with diabetes. Then an updated search was performed in July 2023. In both searches we used the medical and biological databases (PubMed, MEDLINE, EMBASE, Google scholars and Cochrane Controlled Trial Database) using the search terms (diabetes, insulin resistance, insulin secretion, obesity, genetics-diabetes, environment-diabetes, mitochondria-diabetes and gut microbe-diabetes).

Data extraction

The authors of this review were consulted for the inclusion of appropriate articles. EndNote was used to manage references. We examined each article according to the following inclusion and exclusion criteria: The study: (1) Described the factors linked with diabetes; (2) be an original study; and (3) have key information from laboratory experiments, epidemiological evidence, clinical trials, experimental models, meta-analysis and review articles. We included a wide range of study designs used in laboratory studies, cross-sectional, prospective studies and clinical trials. The following studies were excluded: Irrelevant to our main objective and low-quality articles. All abstracts and full-text articles were assessed independently and in duplicate according to pre-defined inclusion/ exclusion criteria. Articles that met all criteria were selected for data extraction. In this review, we followed The Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. The studies used in this review were published between 1981 and 2021.

RESULTS

We identified studies that discussed diabetes including T1D, T2D and gestational diabetes, and then the data were extracted by two authors who focused on first author name, year of publication, title of study, study design, study location and duration and the journals in which articles were published. The selected articles were discussed and then final decision was made for the inclusion in this systematic review. The quality of articles was assessed by three authors on the basis of relevance to the topic. Two authors independently evaluated the characteristics of the study population, as well as the quality of the methods, results and the discussion used in the selected studies.

We recognized 3376 possibly pertinent papers in our initial search as well as 18 published articles from reference lists, assessed the title and abstracts of all 3376 articles and then selected 144 full-length articles that met our inclusion and exclusion criteria for complete assessment (Figure 1). Studies have shown a possible association of genetics, environment, mitochondria, obesity and insulin resistance with diabetes. As identified in 144 publications; 26 articles evaluated the relationship between diabetes and insulin signaling; 16 articles evaluated the link between diabetes and environmental factors; 9 articles linked diabetes with lipid dysfunction; 52 articles assessed the link between diabetes and genetics; 14 articles evaluated the relation between diabetes and mitochondria; 10 articles evaluated the relation between diabetes and gut microbiota; 17 articles presented general description of diabetes (Figure 1).

Diabetes can cause long-term damage to individuals suffering from this disease. It may cause impairment of heart, damages to kidneys. Adults with diabetes confers greater risk of cardiovascular complications including heart attack and strokes[7]. The elevated blood glucose levels can result in fat deposits in blood vessel walls, causing obstruction in blood flow and may increase the possibility of developing atherosclerosis. Diabetes complication can lead to diabetic retinopathy; an estimated 2.6% of blindness reported from around the world is related to diabetes[8]. Apparently, severe diabetic condition can also result in diabetic nephropathy[9]. T1D is the result of pancreatic beta cell damage, by autoimmune mechanisms which may lead to poor or no insulin production and hence the individuals need exogenous insulin to regulate blood glucose levels[10]. T2D results from the body's resistance to insulin as well as inefficient secretion of insulin involving muscle, adipocytes, hepatocytes and may also involve the central nervous system. T2D is usually the result of excess body weight. Ordinarily, diabetes starts at or around the age of 40, but now there are reports of T2D in many children[11]. Gestational diabetes develops during pregnancy; it causes high blood glucose that can affect pregnancy and baby' s health[12].

There is a strong link between human microbiome and diabetes and therefore, the world scientific communities are beginning to focus attention on the relationship between human microbiome and diabetes. It is critical to understand that how microbes interact with the fundamental mechanisms of diabetes in humans and how much close is the relationship? We have discussed this topic in the preceding paragraphs.

Most diabetes-related problems can be minimized by managing glucose, triglycerides and cholesterol levels within normal range. Although the molecular mechanisms of diabetes are not fully understood, it may result from defects in diverse molecular pathways or from genetic defects that cause both insulin resistance and insulin deficiency (Figure 2). The multidimensional interventions involving organizational changes including a change in the structure of health care system which is one step forward that can provide a positive effect on patient's care. Such as develop strategies to improve treatment of diabetes by managing hyperglycemia and hyperlipidemia in patient as well as physician's faithfulness to ensure a monitoring system.

Insulin signaling

Insulin is the key hormone frequently produced by pancreatic β cells regulates the fat storage from absorbed nutrients while acting as adiposity signal to the brain for regulation of energy balance[13], affecting skeletal muscle, liver, and adipose tissue. Insulin secretion from β-cells is fueled by high glucose levels, maintains the normal levels of blood glucose [14]. The presence of insulin receptors on muscle and adipose tissues allows insulin-dependent uptake of glucose into these tissues and thus lowers blood glucose levels by taking away the excess glucose from the blood[15-17]. A fall in blood glucose results in lowering insulin release from β-cells and augmenting glucagon release from α-cells, thereby stimulating the glycogen to glucose conversion.

A lack of insulin and hyperglycemia intensify insulin resistance and affects insulin secretion. In insulin resistance state, high insulin level creates a reduced biological response; weekend sensitivity to insulin mediated glucose removal[18]. Most diabetic patients are obese, which is believed to be an important causal factor in the development of insulin resistance. During the disease development there seems to be a gradual injury to beta cells and finally, the insulin resistant becomes evident in liver resulting in hyperglycemia. A high blood glucose levels that may arise due to dysfunc-

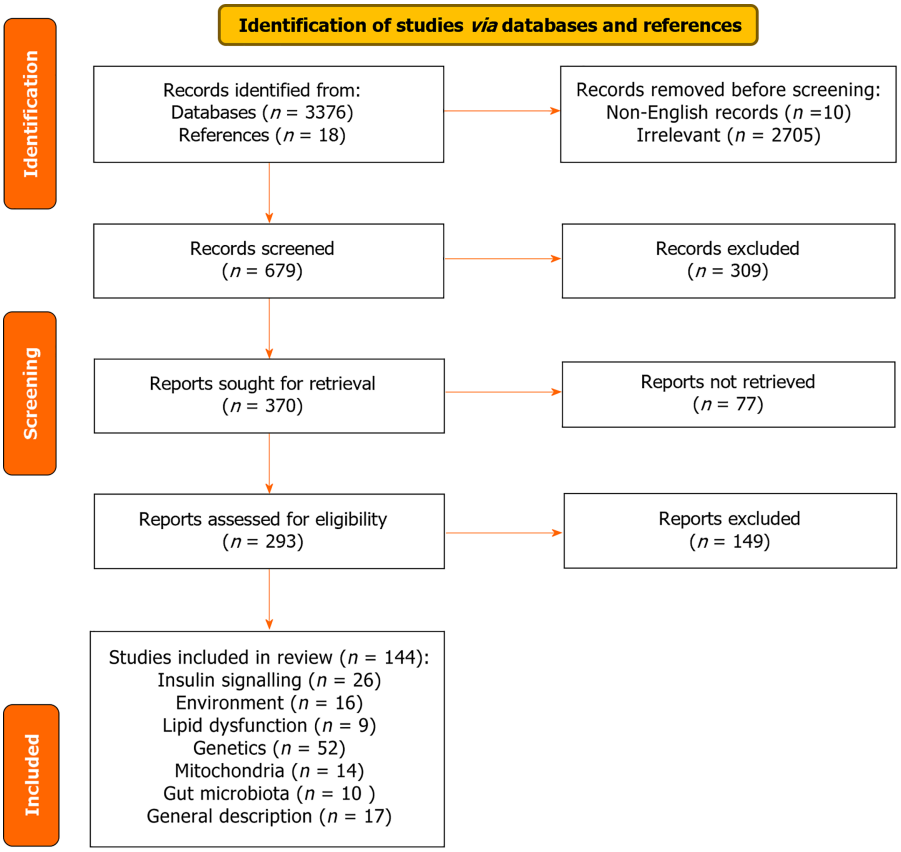

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Figure 1 A flow chart for article selection criteria.

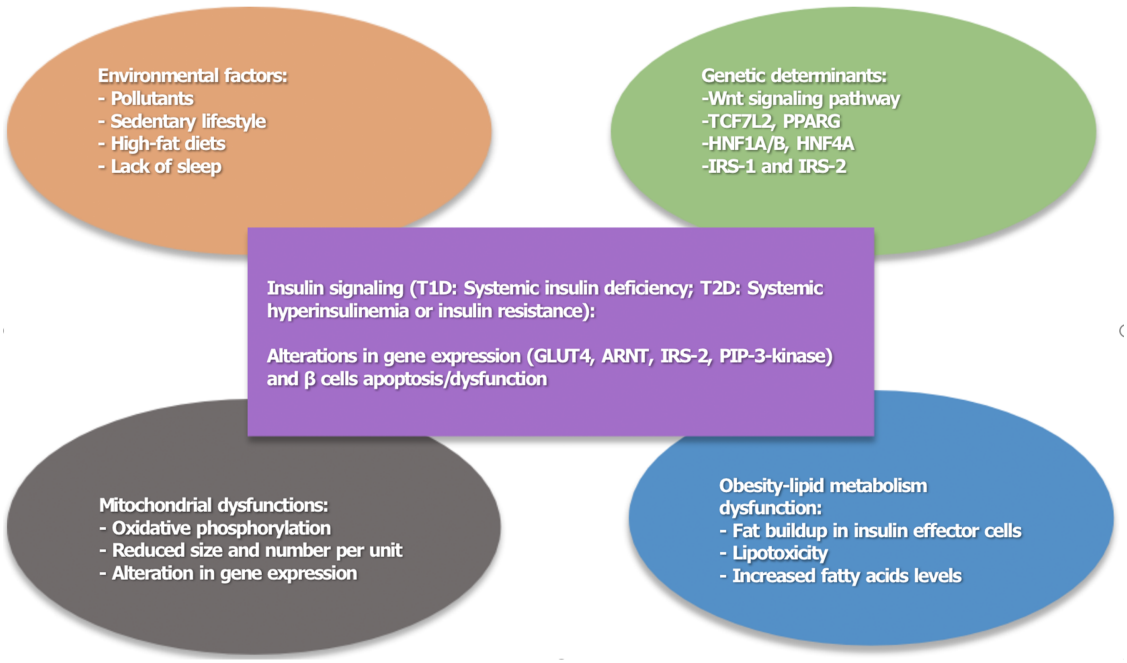

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Figure 2 Factors responsible for Type 1 Diabetes and Type 2 Diabetes incidence. T1D: Type 1 Diabetes; T2D: Type 2 Diabetes.

tional insulin action and/or insulin secretion[19] is a prime factor causing diabetes (Table 1).

The progressive failure of β cells in making up for insulin resistance results in reduced glucose tolerance and diabetes [20] and with a rise in glucose levels and a further decline in β cell function leads to low glucose sensitivity. Although there is genetic predisposition to insulin resistance, physical inactivity, fatty foods, stress[21] and sleep deficiency[22] are other risk factors. The detailed mechanism of insulin resistance is not clear but the general belief is that insulin resistance begins in the adipose tissue playing a critical part in initiating insulin resistance in the muscles and the liver. Adipocytes from T2D patients have been reported to do poor GLUT 4 translocation, reduced insulin's intracellular signaling activities including low insulin receptor substrate (IRS)-1 expression, as well as reduced insulin-stimulated PIP-3-kinase and PKB/Akt activities[23,24]. Insulin stimulates glucose and free fatty acids uptake, suppresses lipolysis, and perhaps stimulates *de novo* fatty acid synthesis[25]. An elevated plasma free fatty acid is generally associated with insulin-resistant states, and T2D[26,27]. Perseghin *et al*[28] performed a cross-sectional study of young, normal-weight offspring of T2D patients and found an inverse relationship between fasting plasma fatty acid levels and insulin sensitivity, consistent with the premise that changes in fatty acid metabolism add to insulin resistance in T2D patients in 1997[29]. Later, Perseghin *et al*[30] studied 18 patients with T1D in 2003, 7 older and overweight/obese patients with T2D, and 15 nondiabetic, and insulin-resistant offspring of T2D parents. They reported an increased adiponectin levels in insulin-resistant patients with T1D, and a reduced levels in patients with T2D. The increased adiponectin levels in insulin-resistant patients with T1DM, in contrast to the reduced levels found in patients with T2DM showed an undefined relationship of adiponectin to insulin resistance in humans[30].

Acting as a neuropeptide, insulin also functions in satiety, appetite and olfaction[31]. Whereas angiotensinogen and leptin increase insulin resistance, adiponectin reduces insulin resistance suggesting that both leptin and insulin are possibly a part of a common signaling system in the hypothalamus.

It is generally believed that impairment of glucose transporter GLUT4 in adipose tissue is responsible for insulin resistant, obesity, and diabetes[32] and its key sites of expression are white and brown adipocytes, skeletal muscle, and cardiac muscle, but it is also present in some isolated areas of brain and kidney[33]. Study with tissue-specific targets have identified the specific insulin responsive organs to glucose homeostasis[34]. In 2003, Minokoshi *et al*[35] reported data from tissue-conditional knock-out mice showing that while suppression of muscle-specific insulin receptor activity did not affect glucose tolerance regardless of insulin resistance, the suppression of muscle specific GLUT4 activity caused insulin resistance and T2D. In addition, suppression of GLUT4 expression in white adipose showed insulin resistance, glucose intolerance, T2D and a deficiency in glucose uptake[35]. Surprisingly, knockout of insulin receptor in adipocyte did improve insulin sensitivity suggesting a fundamental role of adipocytes in diabetes. Many groups have shown that the suppression of insulin receptor activity in the liver resulted in hyperinsulinemia along with peripheral insulin resistance[34,36-38]. In 2003, Fisher and Kahn[36] performed high-dose hyperinsulinemia-euglycemic clamps using [3-(3)H]-glucose in liver-specific insulin receptor knockout (LIRKO) mice, and LIRKO mice treated with streptozotocin (STZ) (LIRKO + STZ) and found that in LIRKO mice, both direct and indirect effects of insulin required an intact insulin-signaling pathway in the liver, primary hepatic insulin resistance led to hyperinsulinemia and secondary extrahepatic insulin resistance.

Adipocyte-targeted GLUT4 knockout mice developed insulin resistance comparable to that shown by muscle-specific GLUT4 knockout mice would suggest that GLUT4 deficient adipocyte may release molecules involved in organ cross-talk [39,40]. Later, Yang *et al*[41] (2005) noted that retinol binding protein-4 (RBP4) could be involved in the organ cross-talk in the adipose tissue of adipose-specific Glut4 deficient mice. Not only, they found elevated serum RBP4 protein levels in insulin resistant mice but also found this protein in obese and diabetic individuals. Mice injected with recombinant RBP4 protein showed the sign of insulin resistance, whereas *Rbp4* knockout mice increased insulin sensitivity[41]. Both visceral and peripheral adipocytes secrete multiple cytokines and hormone-like molecules such as adiponectin, leptin, cytokines interleukin-6 and tumor necrosis factor-α, visfatin, RBP4, and free fatty acids which may produce significant effect on insulin action and hepatic glucose production[42-44]. High fat deposits and increased levels of cytokine secretion give rise to inflammatory response that leads to insulin resistance[44-46].

While gene expression profiling of pancreatic islets obtained from T2D individuals, Gunton *et al*[47] (2005) observed major reduction in the expression of hepatocyte nuclear factor 4 alpha, insulin receptor, IRS-2, Akt2, and several glucose-metabolic-pathway genes. They also found a very high reduction in the transcription factor, aryl hydrocarbon nuclear receptor translocator (ARNT) in T2D islets compared with nondiabetic individuals. Basic helix-loop-helix Per/AhR/ARNT/Sim family ARNT and its partner proteins form heterodimers acting as transcription factors[48] and in association with other transcription factors show hypoxic stress response, may bring about the negative effects of both genetics and environment in T2D pathology[49], chronic hyperglycemia[50], hyperlipidemia[51] and oxidative stress[52]. Rhodes[53] (2005) argued that the failure of β-cell mass to compensate for insulin resistance is caused by a significant increase in β-cell apoptosis, stimulated by chronic hyperglycemia, hyperlipidemia, or specific cytokines affecting pathways responsible for maintaining healthy β-cell. Insulin receptor substrate, IRS-2 is fundamental and necessary for maintaining the adult β-cell in its normal state, and is a key factor in keeping the balance between β-cell and insulin resistance. The mechanisms pertinent to T2D pathogenies is possibly boost IRS-2 serine/threonine phosphorylation that leads to IRS-2 ubiquitination and proteasomal loss[54,55].

Consistent evidence has shown that the wide spread incidence of T2D is in part due to obesity, none or reduced physical activity and aging. However, many individuals exposed to these risk factors do not develop diabetes suggest that genetics may be involved in diabetes pathology. Obesity prompts T2D in individuals with susceptibility alleles in T2D associated genes acting at several points on the diabetes pathway[56].

Table 1 The important physiological dysfunction negatively affect insulin synthesis and secretion

Defect	Phenomenon	Ref.
β cells failure	Insulin resistance, hyperglycaemia	Kahn[20]
↓ GLUT 4 translocation in adipocytes	↓ IRS-1 expression, ↓ PIP-3-kinase and PKB/Akt activities	Wilcox[23], Smith[24]
↑ Plasma free fatty acid	Insulin resistance, ↓ lipoprotein lipase activity, hypertriglyceridaemia	Reaven *et al*[26], Frayne [27]
Suppression of GLUT4 activity (muscle and liver)	Insulin dysfunction	Leroith *et al*[33]
Suppression of insulin receptor activity (LIRKO) (liver)	Hyperinsulinemia, hepatic and peripheral insulin resistance, glucose intolerance, insulin dysfunction	Michael *et al*[37]
Nuclear receptor translocator (ARNT)	↓ Insulin secretion, alterations in gene expression	Gunton *et al*[47], Kewley *et al*[48]
Suppression of IRS-2	β-cell apoptosis, insulin resistance	Rhodes[53]

ARNT: Aryl hydrocarbon nuclear receptor translocator; LIRKO: Liver-specific insulin receptor knockout; IRS: Insulin receptor substrate.

Genetics in diabetes pathologies

Das and Elbein[57] (2006) presented some visible scenario suggesting the role of genetics in diabetes pathology (Figure 3). First, incidence of T2D varies among populations with different demographic histories[58]. Second, approximately a 4X higher risk of T2D was found in siblings of a diabetic over the normal population with a single diabetic parent, and 6.1 when both parents were affected[59]. Third, in twin studies this rate has been found ranging 0.29 to 1.00 in monozygotic twins, and 0.10-0.43 in dizygotic twins[60-63] with a consistent decline in both insulin sensitivity and insulin secretion in most T2D individuals[64].

T1D and T2D are in part, genetically controlled[65], a key element is located within major histocompatibility complex (MHC) on chromosome 6p21 that add to the ancestral clustering of T1D[66]. The data from United States, United Kingdom and Scandinavian countries along with recent data from T1D Genetics Consortium (http://www.t1dgc.org), 1435 multiplex families suggested a link of T1D "to the MHC (IDDM1), insulin (INS, IDDM2)" region containing many genes including "CTLA4 (2q31-q33 [IDDM12 and IDDM7]) and seven other chromosome regions"[67]. The genome-wide studies have identified multiple T2D risk genes including TCF7L2, KCNQ1 and KCNJ11[68]. Ali[68] (2013) has presented possible explanations for missing heritability including the role of rare variants, gene-environment interactions and epigenetics. The susceptibility variants within CAPN10 gene[69] has been identified because of an association between T2D and chromosome 2q37 in Mexican Americans[70]. Peroxisome proliferator-activated receptor-γ[71] is common variants but variants affecting IRS-1 pathway[72] and glucose homeostasis PTPN1[73] are not very common indicating that mixtures of sporadic and conjoint modification may enhance T2D risk in diverse communities. Applying a linkage analysis, Hanis *et al*[70] (1996) identified CAPN10 cysteine protease linked to T2D but as shown in a meta-analysis' variations in CAPN10 is likely[74] but not always linked to T2D[75].

The parents, siblings and children of T2D individuals have 3X greater chances to acquire diabetes than those who do not have a T2D family history[73]. The ancestral risk is greater in parents in the range of 35-60 years of age suggesting that environmental factors play a role in older population[76]. However, epigenetic factors can also yield congenital risk for subsequent generations. The genetic risk factor for T1D is very much intense in human leucocyte antigen region but this risk is not concerted in single region for T2D. It is because of possible interaction of many genes that are dispersed throughout the genome. A number of single-nucleotide polymorphisms in the transcription factor TCF7L2 and a member of Wnt signaling pathway has been linked to T2D in many ethnic groups[77]. TCF7L2 is known to function in beta cells, was identified through a linkage signal on chromosome 10q in a Mexican-American population[78]. Later, the region was identified in the population of other three countries including the United States[79]. TCF7L2 was also identified in a large-scale genome-wide association study that was performed in a French population[80]. Studies conducted in multiple ethnic groups indicated that the risk allele in intron 3 of the TCF7L2 gene increased the level of its protein in beta cells, impaired insulin secretion, and elevate hepatic glucose production[81]. Ali[68] (2013) lists PPARG, IRS-1 and IRS-2, potassium inwardly-rectifying channel, subfamily member 11 (KCNJ11), Wolfram syndrome 1 (wolframin-WFS1), HNF1 homeobox A, HNF1 homeobox B and HNF4A that are associated with T2D[68]. IRS-1 and IRS-2 the two-insulin receptor substrate play an important role in insulin signal transduction. Polymorphisms in both *irs-1* and *irs-2* results in reduce insulin sensitivity in some populations[82,83].

While genotyping 2000 T2D individuals, Wellcome Trust Case Control Consortium[84] has identified TCF7L2 as the most robust T2D signal but mutation in TCF7L2 shows no effect in beta cells[85]. In their meta-analysis, Fu *et al*[86] (2013) pooled 24 articles involving 88229 cases and 210239 controls and identified -30G>A polymorphism of glucokinase as a risk factor associated with increased T2D susceptibility, however, those associations vary in different ethnic populations.

Although genome studies, twin studies and linkage analysis have identified few T2D risk genes, their global impact on the perceived heritability of T2D remained low[87]. Phenotypes may depend on the nature of genetic variation within and across different ethnic group. We believe that T2D develop as a result of interaction between environmental factors and hereditary factors.

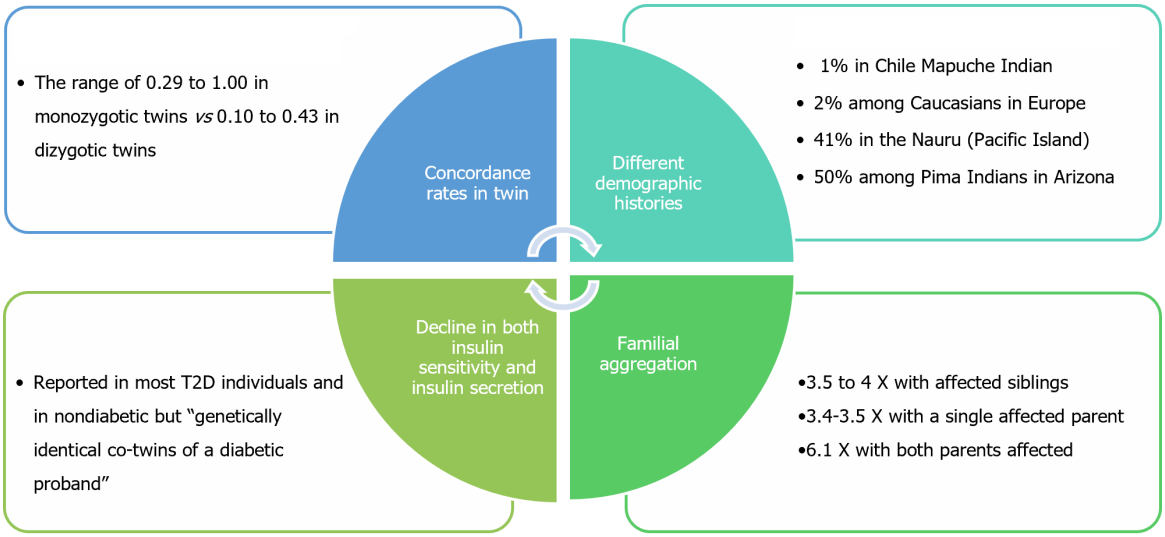

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Figure 3 Genetics-based evidences for diabetes. T2D: Type 2 Diabetes.

Diabetes and the environment

A series of epidemiological and clinical papers have shown serious effects of behavioral and environmental changes on the occurrence of diabetes. The changes in the environment ranges from endocrine disruption, sleep deprivation, physical inactivity, over eating and pollutants[88,89]. In addition, the sedentary lifestyles and the high-fat diets are interactive factors that are associated with high incidence of T2D (Figure 2). There are some excellent publications on these topics[88,90,91]. Numerous environmental factors including refined carbohydrates, stress, and exposure to chemical pollutants produce gradual weight gains increasing the risk of T2D, heart diseases and some cancers[92] but the relative contributions of these factors influencing T2D are not fully understood. Environment does play a critical role in diabetes development; it does not affect all individuals in a similar manner. Even living under the same environment some individuals are more vulnerable to diabetes risk because of some inherited factors suggesting that T2D occurs because of intense interactions between many genes and the environment[93]. Cells use several mechanisms in regulating gene expression in response to environmental cues not only remain in individual's lifespan but can also pass on to few generations[94]. Changes in maternal environment in early childhood have been implicated in long-lasting diseases[95]. This may also explain that some heritability of T2D can occur because of epigenetic changes that happen in intra-uterine which may be influenced by maternal environment. As our knowledge of the epigenetics changes and the detailed mechanisms of epigenetic become widely available, we may be able to understand clearly the effect of these changes on diabetes pathology. The molecular basis of genetic risk factors in T2D is not yet clear and it is certainly an area of intensive investigation.

Mitochondria in the pathophysiology of diabetes

The gene mutations in mitochondrial DNA also cause mitochondrial diabetes[96]. The role of mitochondria in the pathophysiology of diabetes is very imprecise involving both insulin sensitivity and secretion (Table 2). Our knowledge about the connection between mitochondrial dysfunction and defective insulin sensitivity and secretion is, however, sketchy[97,98]. According to Lu *et al*[97] (2010) both mitochondrial oxidative phosphorylation dysfunction and its morphology play an essential part in the pathology of insulin resistance-induced β-cell failure. As a result of oxidation, mitochondria create large amount of reactive oxygen species which are important in the pathophysiology of diabetes and its complications. Both clinical and rodent data demonstrate decreased oxidative phosphorylation in muscle mitochondria in insulin-resistant states. Kelley *et al*[99] (2002) investigated mitochondria obtained from *vastus lateralis* muscle by percutaneous biopsy during fasting from T2D, obese, and lean individuals to examine the effect of perturbation of mitochondrial function. They noted a reduction in both nicotinamide adenine dinucleotide oxidoreductase and citrate synthase activity in their mitochondria. They also found mitochondria of smaller size and numbers per unit volume compared with those in lean controls[100]. A reduced skeletal muscle oxidative phosphorylation was also noticed in insulin-resistant offspring of T2D individuals linked to elevated levels of fat droplets in muscle cells[101]. Petersen *et al*[101] (2003) investigated healthy, lean, elderly and young volunteers corresponded for lean body mass and fat mass and noted that elderly or aged individuals were insulin-resistant compared to young controls and the changes were linked to increased fat deposits in muscle and liver tissue and an approximately 40% reduction in mitochondrial oxidative and phosphorylation activity suggesting age-linked deterioration in mitochondrial function add to insulin resistance in the older population. Boushel *et al*[102] (2007) conducted individual based study where they investigated mitochondrial function in skeletal muscle obtained from 11 individuals with T2D and found reduced oxygen use in diabetic patients which could be linked to reduced mitochondrial content in muscles. The mitochondrial dysfunction and/or reduced mitochondria can cause insulin resistance. Dysfunctional mitochondria can result in reduced oxidation leading to increased fatty acyl-CoA, diacylglycerol and activates protein kinase C[103,104].

Table 2 Mitochondrial dysfunctions affecting diabetes

Defect	Consequence	Ref.
↑ Mitochondrial oxidative phosphorylation in pancreatic β-cells	↑ROS, β-cell failure	American Diabetes Association[96], Marroqui *et al*[98]
↓ Mitochondrial oxidative phosphorylation in skeletal muscle	↓ NADH oxidoreductase activity, ↓ citrate synthase activity, ↑ fat droplets in muscle cells, insulin resistance	Petersen *et al*[100], Petersen *et al*[101], Zhang *et al*[106]
↓ Size and number of mitochondria per unit	↑ Fatty acyl-CoA and diacylglycerol, ↑ protein kinase C activities, insulin resistance	Abdul-Ghani and DeFronzo[103], Lowell and Shulman[104]
↓ Expression of NRF-dependent genes	Insulin resistance	Lu *et al*[97], Patti *et al*[105]
UCP2 deficiency in β-cells	↑ Islet ATP levels, ↑ glucose-stimulated insulin secretion, obesity, β-cell failure	Zhang *et al*[106]

NADH: Nicotinamide adenine dinucleotide; NRF: Nuclear respiratory factor-1; ROS: Reactive oxygen species; UCP: Uncoupling protein 2.

Patti *et al*[105] (2003) have demonstrated that insulin resistance and T2D link with low level of various nuclear respiratory factor-1 (NRF-1)-dependent genes encoding key enzymes in mitochondrial function. The authors noted low levels of proliferator-activated receptor gamma coactivator (PGC)-1α and PGC-1β, coactivators of NRF-1 and PPARγ-dependent transcription involved in oxidative phosphorylation in both diabetic subjects and family history-positive nondiabetic subjects. Their conclusion was that the low PGC1 expression led to reduced NRF-dependent genes expression, thereby metabolic instabilities known for insulin resistance. Liver and skeletal muscle are involved in fatty acids oxidation but their failure to efficiently oxidize fatty acids leads to insulin resistance.

Mitochondria are known to play a key role in regulating insulin secretion. Beta cells detect glucose amid its metabolism and then subsequent increase in adenosine triphosphate (ATP) promotes insulin secretion. Zhang *et al*[106] (2001) found that uncoupling protein 2 (UCP2)-deficient mice had higher islet ATP levels and increased glucose-stimulated insulin secretion, suggesting that UCP2 negatively regulates insulin secretion. The UCP2 deficient ob/ob mice had restored first-phase insulin secretion, elevated serum insulin levels, and reduced levels of glycaemia suggesting UCP2 as a key component of beta cell glucose sensing, and as a vital link between obesity, beta cell failure, and T2D[106]. Bugger *et al*[107] (2008) suggested that mechanisms for mitochondrial dysfunction differ between insulin-deficient type 1 and insulin-resistant T2D hearts. Sivitz and Yorek[108] (2010) observed liver mitochondria of the STZ-diabetic rats and noted a significant tendency of reduced respiration. Karakelides *et al*[109] (2007) found that depriving diabetes patients from insulin did reduce muscle mitochondrial ATP production and expression of oxidative phosphorylation genes in T1D patients despite an increase in whole-body oxygen consumption. Although there are inconsistencies in the result outcome, most studies appear to imply that respiration and/or ATP production in muscle and heart mitochondria are lower when insulin level is low at least in isolated mitochondria. Friederich *et al*[110] (2008) in their decade old immune-histochemical studies on isolated mitochondria from kidneys showed an elevated proximal tubular UCP2 expression in STZ diabetic rats resulting in mitochondrial uncoupling and increased O_2 consumption. The successive low O_2 presence may add to diabetes-induced continuing kidney damage. However, other study exhibiting elevated mitochondrial membrane potential in mitochondria of STZ diabetic rat kidney[111].

Lipid metabolism dysfunction

Lipids play an important function in the pathogenesis of diabetes but the mechanistic links between lipids and diabetes is not very clear. Lipids metabolism involves a large number of enzymes catalyzed metabolic reactions engaging brain, adipose tissue, muscles, liver, and gut and its dysfunction results in fat build up that may also lead to diabetes. These organs are part of complex homeostatic system, communicating through hormones, neurons and metabolites. Just a small shift in the regulation of lipid metabolism can lead to a large change in energy homeostasis; it can result in diabetes, obesity, atherosclerosis, and accelerated aging. In its full-blown state T2D manifests two hallmarks in clinical patients, insulin resistance and β-cell failure. Fat buildup in insulin effector cells (liver cells, muscle cells, and adipocytes) can decrease their sensitivity to insulin and ultimately lead to insulin resistance. Conversely, fat buildup in non-adipose tissues may promote lipotoxicity and this toxicity can diminish or impair β-cell function to disrupt insulin supply by affecting insulin biosynthesis, processing, and secretion[112]. Abnormal fat buildup may also trigger inflammatory response, which in turn impairs both effector and source cells of insulin. High-fat diet negatively affect insulin resistance may result fatty acids overloads in mitochondria. Sparks *et al*[113] (2005) found that high-fat diets downregulated genes linked to oxidative phosphorylation and mitochondrial biogenesis, and those changes were interpreted as seen in diabetes. The adipose mitochondrial dysfunction causes increase in fatty acids levels which in turn can contribute to the insulin resistance. Wolfrum *et al*[114] (2004) noted that inactivating Foxa2 transcription factor in insulin-resistant mice led to lipid deposits in the liver, and promoted fat as well as glucose export. The adenoviral expression of Foxa2T156A, a nuclear, constitutively active Foxa2 in insulin resistant mice reduced hepatic triglyceride content, increased hepatic insulin sensitivity, reduced glucose production, and reduced plasma insulin. An *et al*[115] (2004) found that rats fed with high fat diets, the degradation of malonyl CoA in liver did encourage fat oxidation and decreased circulating free fatty acids, increased insulin sensitivity in both muscle and liver. Mice deficient in acetyl-CoA carboxylase 2 showed reduce malonyl-CoA, improve fatty acid oxidation but withstood diet-induced obesity and diabetes (Table 3)[116].

Table 3 Lipid metabolism dysfunctions affecting on diabetes

Defect	Consequence	Ref.
Fat buildup in insulin effector cells (liver cells, muscle cells, and adipocytes)	Insulin resistance, lipotoxicity, β-cell disruption	Muoio and Newgard [112]
Adipose mitochondrial dysfunction	↑ Fatty acids levels, insulin resistance	Sparks *et al*[113]
Inactivated Foxa2	Lipid deposits in the liver, insulin resistance	Wolfrum *et al*[114]
↓ Malonyl Co-A in liver	↑ Fat oxidation, ↓ circulating free fatty acids, ↑ insulin sensitivity in both muscle and liver	An *et al*[115]

Human gut microbiota

What about the presence of gut microbes and their possible mechanism in diabetes? The findings from recent microbiome studies have indicated significant association of gut microbiome with diabetes. While the clinical significance of gut microbes in diabetes can be measured the many variables related to these microbes remains to be fully understood. In a fascinating review, Li *et al*[6] (2020) have assessed auspicious studies which allow a better understanding of the probable mechanism of microbiota in diabetes epidemic. The human microbiome including both the oral and gut microbiota are linked with diabetes and therefore, in recent years the world scientific communities and medical professionals are beginning to focus attention on the relationship between human microbiome and diabetes. It is critical to understand that how microbes interact with the fundamental mechanisms of diabetes in humans and how much close is the relationship? The human gut is a complex network involving microbiome, host cells and nutrients[117]. Diet induced-obesity promotes insulin resistance by mechanisms involving self-regulation and dependent on gut microbiota. Saad *et al*[118] (2016) have deliberated that the lipopolysaccharide from gut bacteria can prompt a chronic inflammatory process, inducing insulin resistance *via* TLR4 activation. Han and Lin[119] suggest that gut microbiota can impact on body weight, bile-acid metabolism, proinflammatory activity and insulin resistance. A defect in short-chain fatty acids synthesis is a common feature across studies that suggest a relationship between gut microbiota with T1D[120]. Both T1D and T2D are linked with multifaceted immune system and gut microbiome interactions. Thus, gut microbiota disarrays can lead to T1D, which is allied to the interaction between gut microbiota and the innate immunity. Hänninen and colleague profiled intestinal microbiota investigated the incidence of T1D between two non-obese diabetic mouse groups with different gut microbiota. They found that a single symbiont, *Akkermansia muciniphila* with favorable metabolic and immune signaling may be able to minimize diabetes incidence when given as a probiotic[121]. In many studies *Akkermansia muciniphila* has been reported to reduce insulin resistance and also reduces damage of the intestinal wall[6]. The oral cavity and gut are the two uninterrupted regions linked *via* gastrointestinal tract serving as microbial environments, have a key function in microbiome-linked diseases. The oral and gut microbiome stay apart because of the presence of oral–gut obstacle. Yet, the transmission of the oral microbiota can take place to the intestinal mucosa in the event the oral–gut wall does not function properly. The oral and gut microbiomes have been found interdependently regulating human physiological functions and disease pathology[122]. The intestinal colonization of oral microbiota and fecal–oral transmission occurs regularly, which can affect the microbial ecosystem in both habitats, to modulate pathophysiology[123-125]. Research on gut microbes seems reasonably important because it could provide valuable insights for evaluating gut microbiome for the diagnosis and treatment of diabetes. In addition, it certainly ensures the future discovery of the microbiota-related underlying mechanisms of diabetes.

A key issue for diabetes research is to develop a eukaryotic preclinical model, such as *Caenorhabditis elegans* that enables researchers to understand mechanistic insight into the biology and genetics of diabetes.

Caenorhabditis elegans: A preclinical model

We are using a *Caenorhabditis elegans* (*C. elegans*) pre-clinical model to study Krüppel-like transcription factor (KLF) for their functional roles in obesity and diabetics. *C. elegans* encodes 3 members: *klf-1*[126], *klf-2*[127] and *klf-3* all contain three highly conserved C-terminal C_2H_2 zinc fingers. KLF extensively expressed throughout larval development and during adulthood with a predominant expression in intestine, a major endocrine system positioned close to sexual organs and engaged in nutrient sensing and energy metabolism[128-130]. Mutation or RNA interference in *klf-1, klf-2,* or *klf-3* leads to excess deposit of large fat droplets in the intestine of the mutant worm. Our detailed study on *klf-3* mutant (ok1975) suggest that mutation in *klf-3* also dysregulate insulin signaling. Most likely, the excessive fat buildup and defects in insulin signaling associated with mutation in *klf-3* result from damage that gradually takes place during development. We have also shown that KLF-3 is an important regulator of fatty acid biosynthesis, lipid absorption and secretion, mitochondrial proliferation, β-oxidation and physically interacts with genes essential in lipid metabolism[131-133]. These regulatory functions of KLF-3 provide an important lead aimed at studying the mechanism of human diabetes.

The worm KLFs share the highest identity with members of several mammalian KLFs, including KLF-2, 3, 4, 5 and 6 in terms of their C-terminal C_2H_2 zinc fingers. Some members of mammalian KLFs (KLF 2-7 and 15) have been recently identified as one of the major transcription factors controlling adipogenesis, lipogenesis, obesity and diabetes[134-137]. The insulin signaling pathway that controls aging and metabolism was built on experiments in *C. elegans* and the identification of genes underlying *daf* phenotypes[138]. Several KLFs have been implicated in lipogenesis *via* their residence and action in adipose tissue and non-adipose tissues (pancreas, liver or muscle): They regulate adipocyte differentiation [139-141] or promote lipogenesis[142,143] or tune glucose and lipid homeostasis[134,135]. However, no direct evidence is

shown that the KLF circuit intersects the insulin system. Small *et al*[144] (2011) have shown that the maternally expressed KLF14 which is associated with T2D and the cis-acting expression quantitative trait locus of high-density lipoprotein act as a master trans-regulator of adipose gene expression. Thus, *klf14* acts as a major regulator of events in fat tissue, with these alterations in the levels of *klf14* leading, through as yet unspecified mechanisms, to peripheral insulin resistance and T2D. Despite these advances a direct role for these KLFs in fat buildup and insulin resistance at an organism level remains to be established.

LIMITATION

Due to the heterogeneity of the studies cited, the duration of the study and the complexity of interactions of the molecules, genetic factors, environmental factors and gut microbes limited the ability to make direct comparisons between diabetes epidemic, and genetic, biological, environmental factors and the gut microbiota. However, we acknowledge the risk of developing diabetes or alleviating diabetes. We performed an arduous literature search, but we might have missed some studies published as an abstract. To sum up, bias is expected since articles published in languages other than English were not included in this review but we think this is the general limitations for many review articles published in English or vice versa.

CONCLUSION

Diabetes is a pressing health issue with a disturbing epidemic forecast, it could be attributed to diets, stress, absence of physical activities, insulin resistance, genetic and environmental factors. Diabetes involves the complex network of physiological dysfunction that can be attributed to insulin signaling, genetics, environment, obesity, and mitochondria. Although clinical severity of the disease can be measured the many variables' interactions in the incidence of diabetes remain to be fully understood.

The simple reason is that more or less severe clinical involvement of a specific factor has been difficult to identify. The emerging picture of genetics continues to support the general conclusion that there are a large number of risk susceptibility genes, each of them with relatively small effect. Yet, we lack understanding that how genes interact with each other and with the known environmental and other influencers that predispose to develop diabetes. There are intriguing findings regarding gut microbiome as the important regulator of diabetes and it is now known that oral and gut microbiomes interdependently regulate physiological functions and disease pathology. Although there are many models available to study the physiology, biology and genetics of diabetes, the difference between cellular, and animal models and human's biology restrain the applicability of these models in the mechanistic investigations and therapeutic intervention of diabetics. We are yet to be able to overcome the problems in the genetic manipulation to produce a reliable model to understand human diabetes. Although *C. elegans* enables us to understand the fundamental mechanistic insight into the physiology and genetics of diabetes it does not present a true picture of human diabetes. Our work in model system may not always translate to human disease problem. We still need to focus our basic research efforts toward methods that are more directly relevant to human physiology to understand the mechanism for diabetes treatment. In recent years. there are intriguing findings regarding gut microbiome as the important regulator of diabetes. Valid approaches are necessary for speeding medical advances but we should find a solution sooner given the burden of the metabolic disorder- What we need is a collaborative venture that may involve laboratories both in academia and industries for the scientific progress and its application for the diabetes control.

FOOTNOTES

Author contributions: Gaugler R and Hashmi S conceptualized the study design; Wang H, Akbari-Alavijeh S and Parhar RS performed the literature search and the analysis; Hashmi S wrote the manuscript and Wang H finalized the manuscript for submission; Parhar RS revised the manuscript.

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REVIEW

Role of glycolysis in diabetic atherosclerosis

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Abstract

Diabetes mellitus is a kind of typical metabolic disorder characterized by elevated blood sugar levels. Atherosclerosis (AS) is one of the most common complications of diabetes. Modern lifestyles and trends that promote overconsumption and unhealthy practices have contributed to an increase in the annual incidence of diabetic AS worldwide, which has created a heavy burden on society. Several studies have shown the significant effects of glycolysis-related changes on the occurrence and development of diabetic AS, which may serve as novel therapeutic targets for diabetic AS in the future. Glycolysis is an important metabolic pathway that generates energy in various cells of the blood vessel wall. In particular, it plays a vital role in the physiological and pathological activities of the three important cells, Endothelial cells, macrophages and vascular smooth muscle cells. There are lots of similar mechanisms underlying diabetic and common AS, the former is more complex. In this article, we describe the role and mechanism underlying glycolysis in diabetic AS, as well as the therapeutic targets, such as trained immunity, microRNAs, gut microbiota, and associated drugs, with the aim to provide some new perspectives and potentially feasible programs for the treatment of diabetic AS in the foreseeable future.

Key Words: Atherosclerotic plaque; Hyperglycemia; Trained immunity; microRNAs; Gut microbiota; Drugs

Core Tip: Diabetic atherosclerosis (AS) is becoming increasingly common today. Glycolysis, as a metabolic process that plays a significant role in its occurrence and development, has great potential to become an important therapeutic target in the future. We herein discuss the specific mechanisms of glycolysis in the development of diabetic AS and possible directions of therapeutic targets.

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INTRODUCTION

The global incidence and prevalence of diabetes are rapidly increasing. Notably, China, the most populous country in the world, bears the heaviest burden of diabetes[1]. A recent study revealed that in 2021, the global population of individuals living with diabetes was projected to reach 529 million, with an age-standardized prevalence of 6.1%. It is estimated that by 2050, 1.31 billion people will be diagnosed with diabetes worldwide[2]. Atherosclerosis (AS) is among the most common complications of diabetes, a well-established independent risk factor for AS[3]. AS is classified as a chronic inflammatory disease associated with complex etiopathogenesis. The disease originates from intimal lesions and is characterized by local lipid accumulation, fibrous tissue hyperplasia, and calcareous deposition with formation of plaques that reduce vessel elasticity and cause hardening of the vessel walls[4]. The disorder is referred to as AS owing to the yellowish appearance of lipids that accumulate in the arterial lining. AS may result in stroke, heart failure, coronary heart disease, and other serious cardiovascular complications[5].

AS develops earlier and progresses more rapidly in patients with diabetes than in the general population[6]. Compared with individuals without diabetes, those with diabetes show coronary plaques with typically larger necrotic cores and more pronounced inflammation, characterized by abundant macrophages[7]. The plaque load measured using the mean area and maximum wall thickness, is significantly higher in patients with diabetes than in those without diabetes, with a well-documented higher incidence of vascular calcification[8]. Diabetes-associated hyperglycemia (HG) disturbs vascular endothelial function, triggers inflammation, and promotes the formation of advanced glycosylation end-products (AGE) and a series of adverse effects[9,10]. Diabetes may also be associated with defective autophagy and destroys the internal homeostasis of smooth muscle cells (SMCs), leading to plaque expansion, core necrosis, and fibrous cap thinning, all of which favor plaque instability and increase the risk of plaque rupture[11]. Diabetic AS causes greater blood vessel damage, thereby emerging as the leading cause of disability and mortality in patients with diabetes globally[12]. Consequently, it gives rise to a substantial socioeconomic burden on society. Further research is warranted to gain deeper understanding of diabetic AS plaques, with the objective of exploring novel therapeutic approaches.

Endothelial cells (ECs), vascular SMCs (VSMCs), and macrophages play key roles in AS plaque formation, in which glycolysis is also an important contributor[13]. Abnormalities at any stage of the glycolytic pathway may promote AS. Numerous studies have investigated the mechanism underlying glycolysis in AS and plaque formation and described the effects of trained immunity, microRNAs, gut microbiota (GM), and other factors on glycolysis. Nevertheless, the comprehensive and precise mechanism of glycolysis in diabetic AS remains incompletely understood. The current findings provide novel concepts and potential strategies for targeted therapy of AS in the future. In this review, we summarize and discuss the role of glycolysis in the promotion, inhibition, and treatment of diabetic AS.

ROLE OF GLYCOLYSIS IN THE DEVELOPMENT OF DIABETIC AS

Glucose is the primary energy source for most body cells, serving as an essential substrate for various physiological and pathological activities. Glycolysis includes a series of biochemical reactions involved in the degradation of glucose by glycolytic enzymes, with the ultimate goal to produce pyruvate and adenosine triphosphate (ATP)[14]. Glycolysis is a common pathway in glucose metabolism that, under anaerobic conditions, culminates in the production of lactic acid, which subsequently enters the tricarboxylic acid cycle for oxidative phosphorylation when oxygen is available. However, these processes may differ under specific conditions. In the 1920s, the German scientist, Warburg, discovered significantly higher glycolytic activity in cancer cells than in normal cells[15]. Compared with the large amount of energy produced by mitochondrial oxidative phosphorylation, glycolysis generates limited amounts of energy. However, in contrast to normal cells, cancer cells rely on glycolysis for energy even under aerobic conditions, a phenomenon referred to as the Warburg effect[16]. Currently, a growing body of evidence suggests that aerobic glycolysis is not unique to tumor cells, and this phenomenon also significantly affects cells associated with AS[17,18].

ECs

The process of AS plaque formation commences with EC injury. Although ECs are in close proximity to oxygenated blood and receive abundant oxygen compared with other cells, they primarily rely on glycolysis for energy[19]. Under physiological conditions, glycolysis provides 85% of the ATP required by the entire EC unit[20]. ECs depend on glycolysis for energy production based on the following features: (1) The mitochondrial content in ECs is too low to provide sufficient ATP through oxidative phosphorylation[21]; and (2) glycolysis is the source of energy for survival and maintenance of the cell itself because the ATP production rate during glycolysis is much higher than that during oxidative phosphorylation[22]. HG is an important sign of diabetes[23]. Glucose is transported into ECs *via* the glucose transporter 1 (GLUT-1), a receptor whose activity is regulated by extracellular glucose concentration independent of insulin[24,25]. ECs in patients with diabetes are therefore more vulnerable. An intact vascular barrier composed of quiescent ECs is essential to maintain vascular homeostasis[26], which is a favorable factor against AS. However, in the

context of diabetes, HG can trigger overproduction of reactive oxygen species (ROS) in ECs, which disrupts the normal physiological state[27]. An increasing body of evidence shows that cardiovascular complications in diabetes mellitus occur secondary to an increase in nitrosative stress. Oxidative and nitrosative stress can lead to DNA injury, subsequently triggering the activation of the ribozyme, and poly polymerase 1 (PARP-1), and thus mediate the onset and progression of diabetic cardiovascular complications[28]. This ribozyme is a key enzyme involved in glycolysis in the nuclei of DNA-injured ECs[29]. PARP-1 not only slows glycolytic efficiency by facilitating NAD^+ consumption but also promotes adenosine diphosphate (ADP) ribosylation of proteins. However, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity decreases after ADP ribosylation. Therefore, GAPDH entry into the nucleus to form a complex with nuclear proteins (ADP ribosylation) inhibits glycolysis. Glycolytic intermediates are also transferred to other pathways (including the hexosamine and polyol pathways). These changes lead to endothelial dysfunction in individuals with diabetes and worsens AS[30-32]. Additionally, non-enzymatic glycosylation of proteins or lipids in patients with diabetes leads to the production of AGE, which bind to the receptor for AGE (RAGE) on ECs and produce inflammation and dysfunction of ECs[33-35]. Human umbilical vein ECs (HUVECs) treated with AGE reportedly showed a decrease in glycolysis, which leads to the conclusion that AGE inhibits the migration and proliferation of ECs[36]. Moreover, HG-induced ROS was shown to increase the expression of RAGE and its pro-inflammatory endogenous ligands[37]. Additionally, enhanced endothelial superoxide production in patients with diabetes results in increased AGE accumulation[38]. These processes collectively lead to a vicious cycle of endothelial dysfunction. In summary, the hyperglycemic environment itself in people with diabetes, as well as the accompanying oxidative stress, AGEs and other adverse factors interfere with glycolysis, leading to ECs dysfunction. These changes eventually disrupt vascular homeostasis, which leads to AS in people with diabetes. Therefore, a series of internal environmental changes caused by diabetes-related HG may play an important role in diabetic AS by influencing glycolysis, which deserves further study.

However, every situation has dual implications. Inhibit glycolysis disrupt the normal physiological state of ECs, thus destroying vascular homeostasis. Nonetheless, in patients with diabetic AS, glycolysis inhibition could potentially reduce angiogenesis within atherosclerotic plaques and stabilize them to a certain extent. Energy metabolism of ECs, which is intricately associated with their germination, migration, and proliferation, is an important prerequisite for angiogenesis [39]. In patients with diabetes, HG can significantly alter EC metabolism, resulting in higher risk of pathological neovascularization in these cells than that in healthy cells under normal conditions[40]. Plaque rupture is a primary contributor to acute cardiovascular events. Many studies have shown that plaque angiogenesis promotes AS progression, particularly plaque instability[41]. Restricted oxygen diffusion coupled with activation of inflammatory mediators leads to plaque hypoxia, which eventually accelerates neovascularization[42]. Newly formed vessels are fragile and highly vulnerable to bleeding or leakage, resulting in increased plaque instability and rupture[43]. Excessive or abnormal neovascularization in plaques significantly increases capillary permeability and tissue edema. This, in turns results in a likelihood of bleeding or rupture of diabetic AS plaques[44]. In glycolysis, 6-phosphofructokinase-2/fructose-2,6-bisphosphatase 3 (PFKFB3) is a key activator that provides active ATP and essential biosynthetic products for angiogenesis[45]. Based on these findings, previous studies have shown that the knockdown of PFKFB3-related genes in ECs can lead to defective angiogenesis, and the use of 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO, a PFKFB3 inhibitor) can reduce vascular germination *via* inhibiting EC proliferation and migration[46]. Notably, 3PO does not affect the glycolysis necessary for normal EC to maintain homeostasis but only reduces excess glycolysis required for EC germination[47]. Nonetheless, research has shown that 3PO can reduce T cell activation in vitro, which may adversely affect the body's immune suppressive function [48]. A recent study reported that partial inhibition of glycolysis prevented plaque angiogenesis without a particularly significant effect on the size, composition, and vulnerability of pre-existing plaques, although it reduced the frequency of plaque formation. The study also reported that 3PO-induced metabolic stress could stimulate autophagosome formation and promote autophagy in ECs[49]. Aging of ECs can lead to loss of function and transition to a pro-inflammatory state, which stimulates transformation of mononuclear macrophages into a pro-inflammatory phenotype[50]. The simultaneous increase in the expression of adhesion molecules in aging ECs accelerates macrophage migration and activation in plaques[51]. The aforementioned factors act synergistically to promote AS plaque progression. The previously described autophagic response can effectively inhibit EC senescence and apoptosis, thereby limiting plaque formation and development. Additionally, another study has shown that PFKFB-3 not only promotes glycolysis, but also directly participates in glycolytic-dependent DNA repair of diabetic ECs under oxidative stress damage, which may play a certain role in vascular protection of diabetes[52]. Therefore, the use of the glycolytic inhibitor 3PO may disrupt this protective effect, making the application of glycolytic inhibitors uncertain. In conclusion, although a substantial body of evidence suggests that targeting glycolysis inhibition can effectively improve plaque stability in patients with diabetic AS and prevent plaque rupture and bleeding by limiting EC metabolism and preventing plaque neovascularization, the safety and efficacy of this approach require further elucidation and warrant further research (Figure 1).

Macrophages

Macrophage polarization is a typical phenomenon associated with AS[53]. M1 and M2 constitute the common macrophage phenotypes. M1 macrophages show a pro-inflammatory phenotype and play a major role in unstable plaques[54], they are more commonly observed in the shoulder area of unstable and vulnerable-to-rupture plaques[55]. M2 macrophages show an anti-inflammatory phenotype and are more commonly expressed in stable plaques[56]. In contrast, M2 cells play a key role in the occurrence and progression of AS and maintain the stability of AS plaques. Notably, 15-lipoxygenase expressed by M2 macrophages is closely associated with the formation of foam cells and actively promotes AS plaque formation and progression. Simultaneously, M2 macrophages secrete various anti-inflammatory factors, such as transforming growth factor-β, which protects against AS[57]. Usually, the ratio of M1 to M2 cells plays an important role in AS plaque progression[58]. Diabetes-induced HG can enhance glucose metabolism and inflammatory response in macrophages[59]. ROS produced by macrophages under oxidative stress conditions can injure

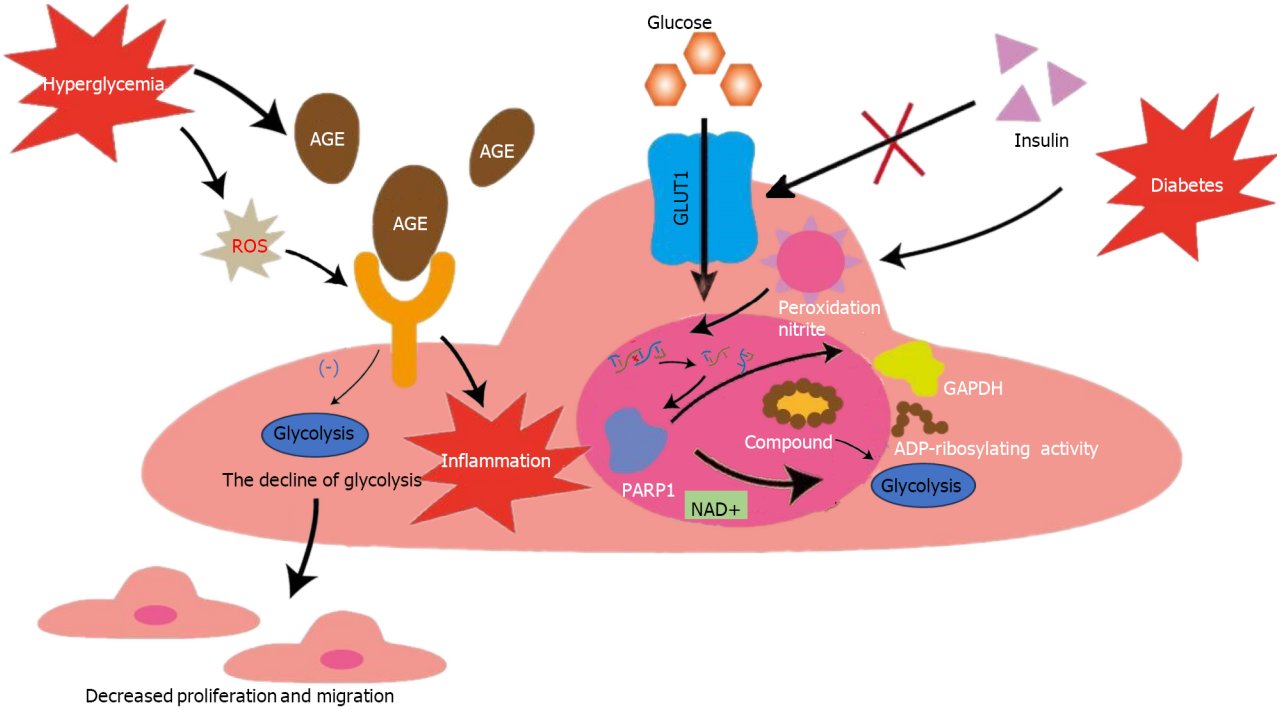

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Figure 1 Effects of glycolysis on endothelial cells in hyperglycemic environment. The activity of glucose transporter 1 is regulated by extracellular glucose concentration, independent of insulin, making endothelial cells in patients with diabetes more vulnerable. Nitrosation stress caused by diabetes can damage DNA and activate poly polymerase 1 (PARP1). PARP1 can not only promote the consumption of NAD+, but also reduce the activity of GAPDH after adenosine diphosphate ribosylation. Both pathways inhibit glycolysis and lead to dysfunction of ECs. Diabetes can promote the accumulation of advanced glycosylation end-products (AGEs), and diabetes-induced reactive oxygen species can increase the expression of receptor for AGE and pro-inflammatory endogenous ligands. The above process leads to the down-regulation of ECs glycolysis and the intensification of inflammation, causing decreased migration and proliferation of ECs. GLUT1: Glucose transporter 1; EC: Endothelial cell; AGE: Advanced glycosylation end-products; ROS: Reactive oxygen species; PARP-1: Poly polymerase 1; ADP: Adenosine diphosphate; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase.

mitochondrial DNA, leading to mitochondrial dysfunction and inhibiting oxidative phosphorylation. Simultaneously, ROS induces sustained expression of hypoxia-inducible factor 1α (HIF-1α), consequently promoting glycolysis[60]. The combination of the aforementioned factors eventually stimulates M1 and suppresses M2 activation[61], which favors plaque instability. Moreover, local intraplaque hypoxia can trigger a similar response *via* the HIF-1α pathway[62]. These changes in macrophage energy metabolism interfere with stable lipid metabolism and significantly increase the intracellular lipid content[63], which promotes transformation of macrophages into foam cells that participate in AS plaque formation. The production of large amounts of AGE is a typical feature of patients with diabetes. HIF-1α is up-regulated in AGE-bovine serum albumin (BAS)-induced M1 polarization, and HIF-1α knockdown reduces AGE-BAS-induced M1 polarization *via* regulation of pyruvate dehydrogenase kinase 4[64]. This study further highlighted the association between glucose energy metabolism in macrophages and diabetes-related inflammation. A recent study comparing macrophages in diabetic and non-diabetic mice found that glucose uptake and glycolysis were not increased but rather decreased in the former group[65]. Although it is premature to conclude whether these results were coincidental or influenced by some interfering factors, this finding challenges the notion that diabetes-induced HG directly promotes glucose metabolism in macrophages. Recently, other researchers have suggested that HG is not the only, or even the most important, factor in diabetes-related cardiovascular disease[66]. Diabetes is an extremely complex background, so the conditions to prove this point are very demanding. However, we still believe that this finding is worthy of further verification, which has important significance for us to understand the specific mechanism of glycolysis in diabetic AS and explore related treatment methods. Nevertheless, changes in glycolysis significantly affect macrophage energy metabolism and polarization in diabetic AS and therefore plays a crucial role in the development of diabetic AS and plaque stabilization (Figure 2).

Vascular SMCs

Proliferation and subintimal migration of VSMCs is a key event in AS formation[67]. VSMCs, which are viewed as plaque stabilizers, proliferate and migrate to plaque fibrous caps and produce collagen and extracellular matrix, which contribute to plaque stability[68,69]. Enhanced glycolysis in VSMCs is important for platelet-derived growth factor-induced VSMC proliferation and migration, which is an important contributor to AS[70,71]. In the context of diabetes, VSMC proliferation secondary to oxidative injury is a primary process that accelerates AS progression[72]. Intracellular transportation of low-density lipoprotein (LDL), followed by subintimal oxidation, results in the formation of oxidized LDL (ox-LDL)[73]. Ox-LDL significantly influences VSMC proliferation and migration and, through this effect,

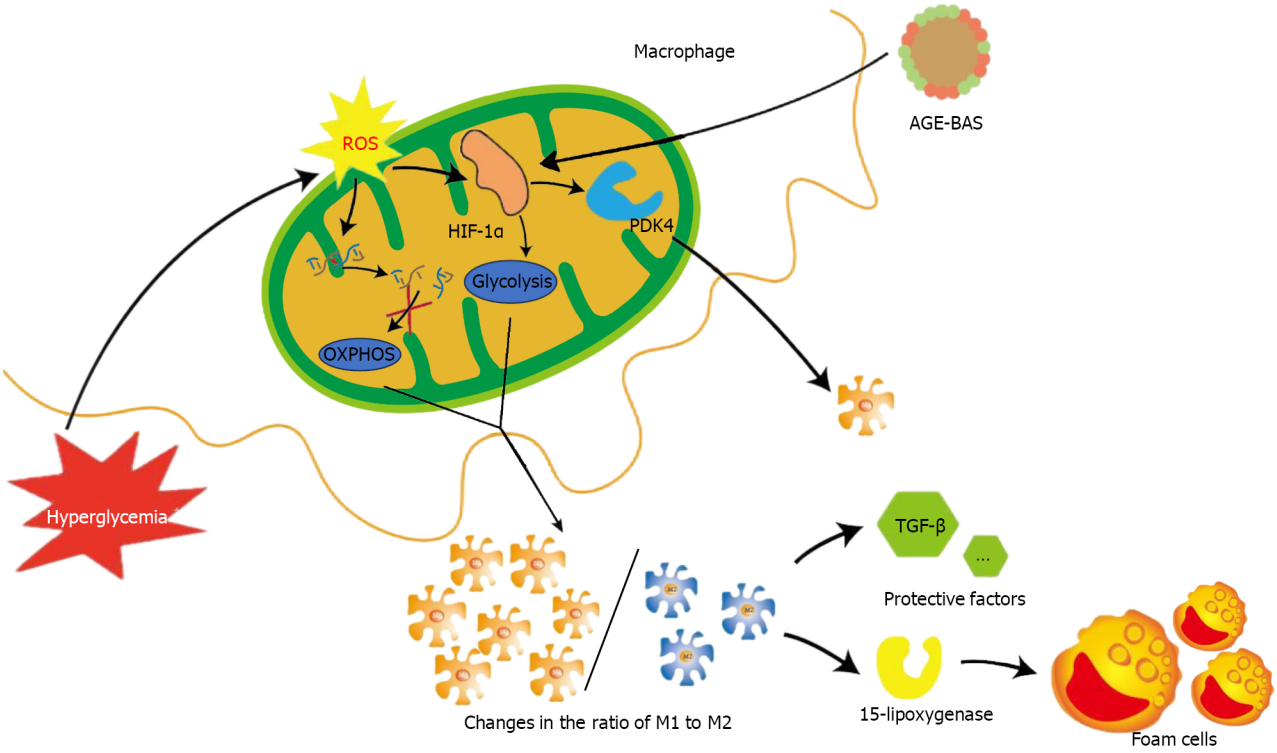

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Figure 2 Effects of glycolysis on macrophages in hyperglycemic environment. Reactive oxygen species (ROS) induced by hyperglycemia can damage mitochondrial DNA and inhibit oxidative phosphorylation. Simultaneously, ROS can induce the expression of hypoxia-inducible factor 1α and promote glycolysis. Under the above two conditions, the ratio of M1 and M2 changes. M2 has the ability to secrete 15-lipoxygenase to promote foam cell formation and atherosclerotic protective factors such as transforming growth factor-beta, which plays an important role in maintaining plaque stability. The increase of M1 and the decrease of M2 ultimately aggravate the instability of diabetic atherosclerotic plaques. OXPHOS: Oxidative phosphorylation; AGE: Advanced glycosylation end-products; BAS: Bovine serum albumin; TGF-β: Transforming growth factor-beta; HIF-1α: Hypoxia-inducible factor 1α.

contributes to plaque vulnerability and AS progression[74,75]. Pyruvate kinase subtype M2 (PKM2) is a key rate-limiting enzyme involved in glycolysis. Ox-LDL up-regulates PKM2-dependent glycolysis to trigger VSMC proliferation and migration and eventually promotes AS[76]. Additionally, AS vascular remodeling is accompanied by a shift in the VSMC phenotype from a contractile phenotype under normal physiological conditions to a synthetic proliferative phenotype under pathological conditions[77]. Furthermore, inflammatory stimulation in a diabetic environment with high glucose levels may also promote such phenotypic transformation of VSMCs[78]. A significant percentage of enzymes involved in glycolysis are crotonylated and ubiquitinated. Some researchers have suggested that the crosstalk between crotonylation and ubiquitination in glycolysis may be a potential mechanism underlying the phenotypic remodeling of VSMCs[79]. The results of a study on SMC-specific PKM2-deficient mouse model support the hypothesis that SMC-derived PKM2 promotes injury-induced neointimal hyperplasia *via* enhanced phenotypic conversion, proliferation, and migration from a genetic perspective[80]. However, the specific role of glycolysis-induced metabolic mechanisms in phenotypic switching of VSMCs remains unclear and requires further investigation. Nonetheless, glycolysis significantly affects VSMC participation in diabetic AS development (Figure 3).

TRAINED IMMUNITY, GLYCOLYSIS, AND AS

Earlier researchers held the belief that only adaptive immunity can establish immune memory. However, following extensive experimental studies have contradicted this perspective[81]. Innate immune cells produce immune memory following antigenic stimulation and tend to respond more strongly to reinfection in a nonspecific manner, a phenomenon termed as trained immunity[82]. Although the long-term activation of trained immune system strengthens the body's ability to fight infection, it also negatively affects chronic inflammation[83].

AS is a typical chronic low-grade vascular inflammatory disease; therefore, trained immunity has a major role in this disorder. β-glucan–induced trained immunity is a typical model[84]. In vitro studies using monocytes trained with dextran have shown that AKt-mTOR-HIF-1α signaling pathway is the metabolic basis underlying trained immunity[85]. Another study has also shown that the transition from oxidative phosphorylation to a significant increase in aerobic glycolysis was the driving force for the development of trained immunophenotype[86]. These changes in cellular metabolism observed during the induction of trained immunity constitute metabolic reprogramming, which can induce epigenetic remodeling and chromatin structure changes (such as methylation or an increase in mRNA of the key enzymes involved in glycolysis)[81]. Ultimately, these changes increase transcription of inflammatory genes, triggering the

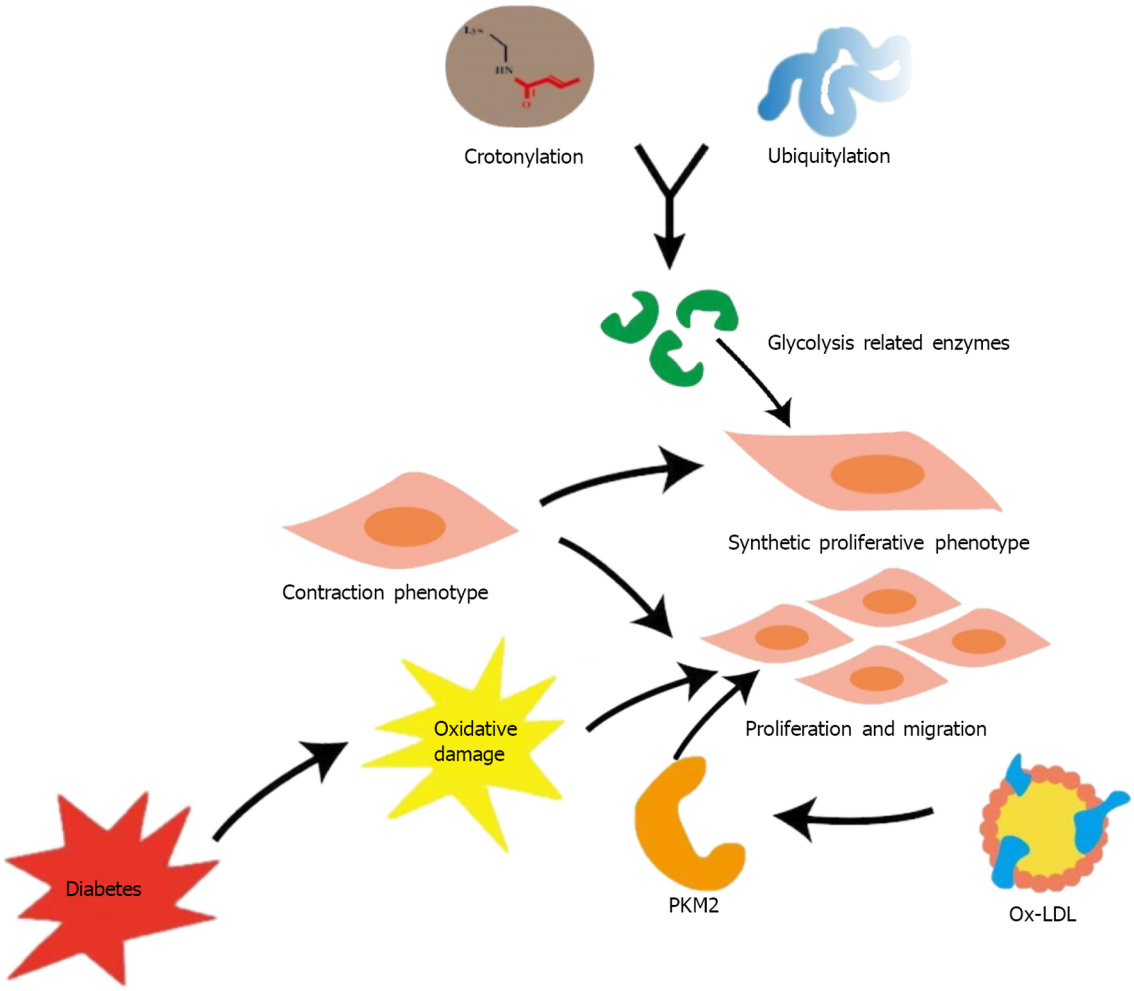

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Figure 3 Effects of glycolysis on vascular smooth muscle cells in hyperglycemic environment. The crosstalk between crotonylation and ubiquitination in glycolysis related enzymes may be a potential mechanism underlying the phenotypic remodeling of vascular smooth muscle cells (VSMCs). Ox-low-density lipoprotein promotes proliferation and migration of VSMC by up-regulating PKM2-related glycolysis. Oxidative damage in the context of diabetes plays an important role in these processes, causing the development of diabetic atherosclerosis. PKM: Pyruvate kinase subtype; LDL: Low-density lipoprotein.

immune response (these genes encode not only cytokines and chemokines associated with AS but also proteins associated with foam cells and plaque vulnerability)[87]. Another study observed that shear stress at AS sites throughout the vasculature shows similar effects of glycolytic up-regulation of histone modifications and signaling pathways[88], which reiterates the tight association between trained immunity and AS. Moreover, the HG environment in patients with diabetes induces long-term epigenetic regulation of inflammatory genes[89]. Corresponding research suggests that hypoglycemic therapy for patients with diabetes is likely to be affected by these findings, potentially reducing its efficacy and subsequently, increasing the risk of AS[90]. Glycolysis provides the energy for trained immunity, serving as its dynamic foundation. Thus, changes in glycolysis profoundly influence the role of trained immunity on diabetic AS.

Glycolysis forms the metabolic basis of both ECs and trained immunity, thereby implying a plausible correlation between the two. Atherogenic factors induce trained immunity in ECs *via* oxidative phosphorylation, glycolytic metabolic transformation, epigenetic modification of pro-inflammatory genes, and activation of the Akt-mTOR-HIF-1a signaling pathway[91]. Ox-LDL, a lipid that promotes AS, drives the production of innate immune cells and trained immune phenotypes in ECs[92]. Reportedly, training monocytes with this substance can also induce trained immunity, accompanied by a significant increase in glycolysis[93]. Additionally, trained immune phenotype is reversed after treatment with mammalian target of rapamycin (mTOR) inhibitors, glycolytic inhibitor 3, or the HIF-1a inhibitor following Ox-LDL exposure[85]. Therefore, it is conceivable to speculate that the reversal of trained immunity using glycolysis inhibitors or genes involved in glycolysis knockout may be a potential therapeutic option for AS.

To summarize, the relationship between trained immunity and glycolysis provides a new perspective on the treatment of diabetic AS. However, most current studies on trained immunity have been performed *in vitro* or in animal experimental models. Available and clinical data are insufficient to establish definitive conclusions[84]. Therefore, the clinical efficacy of these methods remains a potential research topic requiring further investigation.

MICRORNA, GLYCOLYSIS, AND AS

MicroRNAs (miRNAs) are a class of non-coding single-stranded RNA encoded by endogenous genes, approximately 22 nucleotides in length[94]. Their role as regulators of gene expression has long been of interest to researchers. An increasing number of recent studies have highlighted the role of miRNAs in AS and its progression. The NF-KB/miRNA-425-5P/MCT4 signaling axis can down-regulate the expression of monocarboxylate transporters (MCT4) within HUVECs derived from patients with diabetes, as well as HUVECs subjected to high glucose levels and interleukin (IL)-1β. This process leads to impaired lactate transport, thereby inducing EC dysfunction and even apoptosis[95]. The study discussed the mechanism underlying endothelial vascular injury in diabetes mellitus from a new perspective of glycolysis and lactate transport disorders. Therefore, inhibition of miRNA-425-5P expression and improvement in ECs may be a potential strategy for diabetic AS treatment. Another study on HUVECs showed that miR-143 inhibited glycolysis by directly targeting hexokinase 2 (HK2), leading to endothelial dysfunction and an increased risk of AS[96]. Therefore, down-regulation of the miR-143 Level to restore HK2 expression and restoration of the balance of glycolysis in EC are necessary for the prevention and treatment of AS plaques. miR-638 can inhibit proliferation, migration, and glycolysis of VSMCs by targeting lactate dehydrogenase A (LDHA)[97]. It is plausible to speculate that miR-638 can effectively inhibit the development and progression of AS plaques by targeting LDHA and inhibiting glycolysis in VSMCs. M1-type macrophages use aerobic glycolysis to rapidly generate energy[98]. miR-33 regulates the inflammatory phenotypic polarization program of macrophages *via* alteration of the balance between cellular fatty acid oxidation and glycolysis, which affects AS plaque progression. Anti-miR-33 was also found to exert a protective effect against AS[99], suggesting the potential value of therapeutically silencing miR-33 in the context of AS. Through the regulation of gene expression, such as down-regulating the amount of certain glycolytic enzymes or inhibiting their activity, miRNA significantly affects glycolysis, playing a non-negligible role in the occurrence and development of diabetic AS. Thus, targeting miRNA to regulate glycolysis, may potentially be an important therapeutic approach for treating diabetic AS.

GM AND AS

GM refers to the diverse microorganisms, including bacteria and fungi that colonize the gastrointestinal tract of humans and other animals including insects. Microbiota participate in the synthesis of various bioactive substances, which play key roles in human health and diseases[100,101]. GM-derived metabolites transmit signals for effective communication between the host and microbiota and are indispensable mediators in several important reactions[102]. Several metabolic diseases including diabetes are attributable to a dysfunctional gut microbiome[103]. Bacterial DNA is shared between the gut and AS plaques[104]. With regard to the microbial composition of unstable and stable plaques, the feces of patients with unstable plaques show a decrease in the Roseburiam species[105]. AS plaque and its stability may be closely associated with the human GM. Additionally, transplantation of GM affects the host's susceptibility to AS[106]. In conclusion, various phenomena suggest that GM and its metabolites are intricately and closely associated with diabetic AS.

Trimethylamine-N-oxide (TMAO) is mainly derived from the metabolism of methylamine-rich nutrients by the GM. TMA, produced and processed in the liver in the presence of flavin monooxygenase, results in the generation of TMAO [107]. Experimental and clinical studies have reported the role of TMAO in the etiology of diabetes[108], and TMAO has also gained increasing attention as a contributor to AS. High blood TMAO concentrations can promote cholesterol transport in macrophages for the formation of foam cells, eventually causing AS[109]. The amount of Bacteroides in the human intestine was positively correlated with plasma TMA concentrations[110].

Metagenomic analysis of the GM has revealed that the percentage of Bacteroidetes was significantly higher in patients with symptomatic AS than in controls[111]. Notably, plaques in patients with high levels of TMAO tend to show thinner fibrous caps and a greater number of microvessels[112]. The association between elevated TMAO plasma levels and unstable AS plaques is readily evident. This notion has been supported by an animal study[113], and further research underscores that high TMAO plasma levels can increase pro-inflammatory gene expression, consequently leading to a marked increase in inflammatory cytokines levels, adhesion molecules, and chemokines[114]. In summary, TMAO produces adverse effects in AS. The NLP3 is a multiprotein complex formed by pattern recognition receptor activation [115]. Studies performed using carotid ECs in mice with partially ligated carotid arteries have reported TMAO-induced NLP3 inflammasome activation, which increased IL-1B levels, caspase-1 activity, and cell permeability, subsequently leading to EC injury in AS[116]. Among these, caspase-1 activation was shown to play a vital role in mitochondrial injury and proteolytic cleavage of glycolytic enzymes[117]. Some studies have also shown that glycolytic changes are closely associated with NLRP3 activation[118]. Therefore, we hypothesize that intervening in glycolysis may, to some extent, counteract the adverse effects of TMAO in diabetic AS.

Butyrate, a short-chain fatty acid (SCFA), is another product of the GM[119] that plays a key role in the regulation of cellular energy metabolism, particularly glycolysis. For example, butyrate can cross-link with T cell receptors to switch cells from mitochondrial respiration to glycolysis during T cell activation[120]; butyrate can inhibit glucose transport and glycolysis by reducing GLUT1 and cytoplasmic glucose-6-phosphate dehydrogenase abundance regulated by GPR109A-AKT signaling in colorectal cancer cells[121]. Patients with diabetes have lower levels of butyrate-producing bacteria than those without diabetes[122]. Some researchers argue that the effects of butyrate-producing bacteria on AS are attributed to the metabolic effect of butyrate in the intestines. They showed that gut-associated butyrate-producing bacteria interact with dietary plant polysaccharides and affect gene expression of distal intestinal cells with a switch from glycolytic metabolism toward fatty acid utilization, which consequently reduces systemic inflammation and improves AS[123]. In

addition, studies have shown that the use of live B. vulgatus and B. dorei can also help suppress the pro-inflammatory immune response to prevent coronary AS. However, the specific mechanism and whether glycolysis is involved have not been clarified, which also deserves further study[124]. As a result, the concept of supplementing anti-atherosclerotic bacteria for patients with diabetes hold promise as a topic worthy of study. This approach may contribute to the treatment of diabetic AS through glycolysis regulation.

Many studies have reported good efficacy of berberine (BBR), an isoquinoline alkaloid extracted from herbs, including Coptis coptidis, in the treatment of metabolic and cardiovascular diseases[125,126]. BBR can simultaneously regulate insulin signaling, inhibit A-glucosidase, induce glycolysis, and inhibit gluconeogenesis; therefore, it plays a significant role in reducing blood glucose levels in diabetes[127,128]. Following the upsurge in GM research, the effect of BBR on GM has attracted widespread attention. BBR can cause changes in more than 20 genera in DB/DB mice (C57BLKS/JNju, an animal model of type 2 diabetes). Notably, significant alterations were observed in the expression of seven operational taxonomic units, including increased prevalence of a series of SCFA-producing bacteria[129]. For example, Butyricimonas promotes glycolysis of branched-chain amino acids to produce SCFA as a source of energy[130]. Effects of BBR on AS are also closely associated with GM activity. A comparison between BBR-treated and untreated mice fed the same high-fat diet showed significant differences in the abundance of Firmicutes and Verrucobacteria; the BBR-treated mice showed reduced expression of inflammatory factors and a lower incidence of AS[131]. Other studies also support the role of BBR in inhibition or destruction of some harmful intestinal bacteria and in increasing the numbers of bacteria that reduce TMAO concentration and AS plaque size[132]. In conclusion, BBR not only has a significant effect on the treatment of diabetes through inducing glycolysis but also the capacity for the prevention and treatment of AS by affecting the GM.

Hence, it is reasonable to conclude that glycolysis metabolism-related therapies, such as regulating GM through probiotic supplements or fecal transplantation[133], have a huge potential for future treatments of diabetes AS.

DRUGS, GLYCOLYSIS, AND AS

Drugs constitute an important component of the therapeutic arsenal against diabetic AS. Many researchers have emphasized the rapid development of drugs from the perspective of glycolysis. Ethyl pyruvate is a stable pyruvate derivative[134], that has been shown to provide energy for the differentiation of regulatory T cells (Tregs) and enhance their proliferation *via* the up-regulation of glycolysis, which increases the number and function of Tregs and improves the clinical symptoms of type 1 diabetes in mice[135]. Furthermore, that aspalathin and its associated compounds can specifically inhibit sirtuin 6 at a certain concentration, improve insulin-mediated activation of AKT, enhance glycolysis, and inhibit gluconeogenesis through the activation of non-repressor protein 5 and peroxisome proliferator-activated receptor-γ coactivator. Maintaining glucose homeostasis is important in patients with type 2 diabetes mellitus[136]. Diabetes is the root cause of a more severe and complex symptoms of diabetic AS; therefore, improving diabetes is fundamental to the treatment of diabetic AS.

Rapamycin, a classic glycolysis inhibitor, has pharmacological effects that can inhibit the mTOR pathway and suppress cell glycolysis in addition to its anti-inflammatory and antiproliferative actions; it can also effectively inhibit AS progression[137]. Polylactic acid glycolic acid copolymers coated with rapamycin can target AS plaques in mice and may locally deliver glycolysis inhibitors. This method has been shown to be safe *in vitro*[138]. Therefore, it can be concluded that nanoparticles coated with glycolytic inhibitors on macrophage membrane coating may be useful for precise treatment through targeted inhibition of AS. Several studies have shown that glutamine antagonists down-regulate mTORC1 activity and attenuate the up-regulation of glycolysis in response to growth factor stimulation and effectively control vascular restenosis caused by excessive VSCM proliferation[139,140]. Therefore, glutamine antagonists may be useful for the treatment of AS and AS-induced vascular occlusive disease. Recent studies have demonstrated a positive correlation between PFKFB3 expression and unstable plaque phenotypes in human coronary and carotid arteries. Mice in which the glycolysis inhibitor, PFK158, repressed PFKFB3 showed improved AS plaque stability and fibrous cap thickening[141]. AS plaque progression is closely associated with the influx of specific immune cells[142]; therefore, inhibiting PFKFB3 also reduces the glycolysis flux of immune cells, effectively inhibits their metabolism and further minimizes AS progression[141]. Therefore, PFK158 may be important for AS plaque stabilization and reducing the risk of AS development.

In conclusion, targeting both diabetes and AS can effectively reduce the risk of acute cardiovascular events secondary to diabetic AS. Furthermore, this approach can also counteract the role of a major risk factor for diabetic AS in the long term, which can facilitate better treatment of diabetic AS (Figure 4).

CONCLUSION

With the global incidence of diabetes increasing year by year, diabetic AS is a growing threat to society. The mechanisms of diabetic AS are highly intricate, and this paper aims to stimulate interest in the emerging field hat delves into the roles of glycolysis in the occurrence and development of diabetic AS. Glycolysis is the metabolic basis of main cells involved in the development of diabetic AS, including ECs, macrophages, and VSMCs. Glycolysis plays an important role in diabetic AS by influencing the functional status of ECs, polarization of macrophages, and proliferation, migration and phenotypic transformation of VSMCs. Therefore, glycolysis should be considered as a potential target for treating diabetic AS. However, it must be acknowledged that, in comparison with the study of glycolysis in cancer treatment, the study concerning the role of glycolysis in diabetic AS does not go that far. Nonetheless, as the significant metabolic mechanism

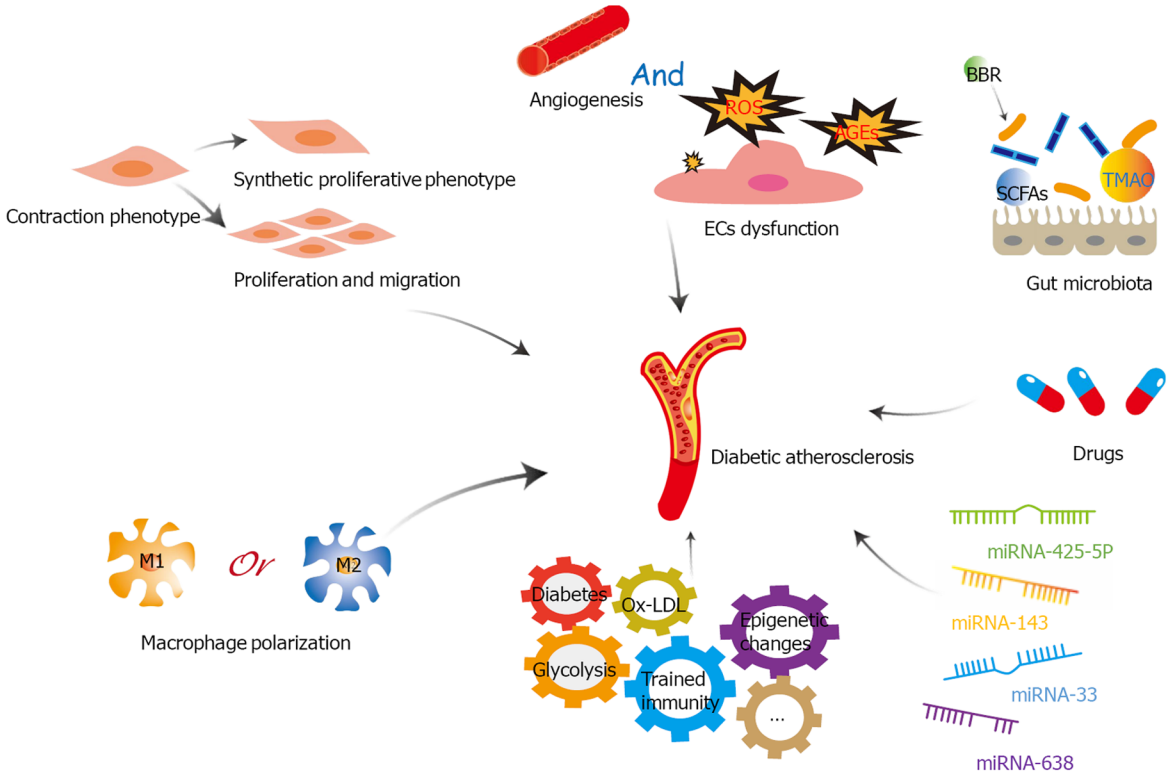

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Figure 4 A variety of factors play important roles in diabetic atherosclerosis through glycolysis, including endothelial cells dysfunction, proliferation, migration and phenotypic transformation of vascular smooth muscle cells, macrophage polarization, trained immunity, microRNAs, gut microbiota, and drugs. EC: Endothelial cell; LDL: Low-density lipoprotein; ROS: Reactive oxygen species; TMAO: Trimethylamine-N-oxide; BBR: Berberine; miRNA: microRNA; SCFAs: short-chain fatty acids.

shared by cancer and AS cells, the role of glycolysis in cancer cells also has a considerable reference significance AS cells. As mentioned above, butyrate produced by intestinal flora can inhibit glycolysis in colon cancer cells, providing an important foundation for research on the role of butyrate-producing bacteria in AS. Therefore, in-depth exploration of GM, trained immunity, miRNA, and drugs, which play important roles in the regulation of tumor glycolysis, is also expected to significantly improve our research on diabetic AS glycolysis. HG is the main reason for the abnormal function of vascular ECs and the polarization of macrophages due to the change of energy metabolism, causing AS. However, many scholars argue that HG is not a single factor that affects glycolysis in diabetic AS. We believe that diabetes products such as AGEs and the inflammatory environment caused by diabetes may be involved in this effect. However, the specific influencing mechanism requires further research. In addition, most studies on the role of glycolysis in diabetic AS remain in animal or cellular models at present. Thus, there is a need to bridge the gap between results of research and their clinical applications. Nevertheless, we firmly believe that the that regulation of glycolysis is a potentially promising therapeutic strategy for diabetic AS in the future.

FOOTNOTES

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MINIREVIEWS

Accessibility and utilization of healthcare services among diabetic patients: Is diabetes a poor man's ailment?

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Abstract

Diabetes is a non-communicable ailment that has adverse effects on the individual's overall well-being and productivity in society. The main objective of this study was to examine the empirical literature concerning the association between diabetes and poverty and the accessibility and utilization of medical care services among diabetic patients. The diabetes literature was explored using a literature review approach. This review revealed that diabetes is an ailment that affects all individuals irrespective of socioeconomic status; however, its prevalence is high in low-income countries. Hence, despite the higher prevalence of diabetes in developing countries compared with developed countries, diabetes is not a poor man's ailment because it affects individuals of all incomes. While the number of diabetic patients that access and utilize diabetes medical care services has increased over the years, some personal and institutional factors still limit patients' access to the use of diabetes care. Also, there is a lacuna in the diabetes literature concerning the extent of utilization of available healthcare services by diabetic patients.

Key Words: Accessibility; Diabetes; Healthcare services; Patients; Poverty

Core Tip: Diabetic patients require more medical care services than patients without diabetes as a result of their high chances of comorbidities, poor glycemic control, and frequent hospitalization. Despite the promising upsurge in the number of diabetic patients seeking medical care services due to awareness, some personal and institutional factors continue to limit patients' chances of access to diabetes care. Furthermore, there is a lacuna in the diabetes literature concerning the extent of utilization of medical services available by individuals with diabetes.

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INTRODUCTION

Diabetes is a major emerging public health non-communicable disease that poses problems across nations[1,2]. Diabetes has been described as a non-communicable disease that occurs when the pancreas stops producing sufficient insulin or when the insulin produced is not effectively used in the body. The symptoms of diabetes include but are not limited to feeling very thirsty, frequent urination, blurred vision, tiredness, and weight loss. Individuals who are obese, physically inactive, and hypertensive have a high chance of getting diabetes[3-5].

The number of persons with diabetes increased from 108 million in 1980 to 422 million in 2014[6]. Diabetes prevalence in 2021 was 536.6 million people, and it is estimated to increase to 783.2 million in 2045[7]. Diabetes accounted for 1.5 million deaths in 2019, and 48% of all these deaths occurred before the age of 70 years[6]. Diabetes contributed to 460000 kidney disease deaths and increased blood glucose and contributed to 20% of cardiovascular deaths[8].

Even though diabetes is a global non-communicable disease, there is variability in adverse effects and mortality rates between nations. There is a 3% increase in age-standardized mortality rates from diabetes in high-income countries, while in low-income countries, the mortality rate increased to 13%[6]. This striking gap in the mortality rate between high-income countries and low-income countries may depict the devastating effects of poverty in terms of managing diabetic conditions. Low-income earners are characterized by inadequate housing, irregular medical care coverage, and food insecurity, making it extremely hard for the poor individual to manage their ailments[9]. This may equally imply that the low-income population would have a higher rate of diabetic complications since poverty can be impactful on the uncontrollable diabetes rate and complications.

Furthermore, accessibility and utilization of health care services have become the major factors that contribute to worsening health crises for individuals with diabetes. Access to state-of-art facilities in urban and rural areas has lagged due to the growing number of individuals with diabetes that require medical care services[10]. There is also a report concerning diabetic patients' inability to have access to syringes and glucose meters in some hospitals[11]. Accessibility to health care services such as insurance coverage has been found to play a significant role concerning preventive measures for diabetes crises. On the contrary, lack of insurance coverage has been linked to a lower use of preventive services[12]. This means that insurance coverage is essential for diabetic patients due to the high medical care required for the management of chronic symptoms.

Diabetic patients require more use of medical care services than patients without diabetes as a result of their high chances of comorbidities, poor glycemic control, and frequent hospitalization[13]. Furthermore, healthcare facilities have been reported to be overstretched especially in low-income countries due to an upsurge in the number of individuals with diabetes[14]. This could imply that there is an insufficient medical care supply that hinders accessibility and utilization of health care services by individuals with diabetes. Hence, there is a need to examine the current diabetes literature to establish the nexus between diabetes and poverty as well as establish the accessibility and utilization of diabetes healthcare services among people with diabetes. In this article, we examined the accessibility and utilization of health care services among diabetic patients to establish whether a disparity in access and use of health care services by diabetic patients exists. Using the review approach, we further aimed at providing descriptive evidence of the nexus between poverty and diabetes.

METHODS

We conducted a preliminary search to review studies on the nexus between poverty and diabetes and the accessibility and utilization of healthcare services by diabetic patients in several databases. The Preferred Reporting Items for Systematic and Meta-Analysis guidelines for Scoping Review were followed in this study[15]. This review was registered with the Open Science Framework on April 19, 2023. The JBI framework was used to conduct this study[16].

Research questions

The questions that guided this study were: (1) What is the nexus between diabetes and poverty?; (2) What is the rate of accessibility of health care services by diabetic patients?; and (3) What is the rate of utilization of health care services by diabetic patients?

Literature search

A literature search was carried out in numerous electronic databases such as PubMed, Embase, *Reference Citation Analysis*, Elsevier Scopus, Medline, the Cochrane Library, and the Web of Science. The search terms and keywords were developed by the research team and an experienced digital librarian. Some of the keywords used included: "the association between poverty and diabetes," "the nexus between socioeconomic status and diabetes," "accessibility of healthcare services by diabetic patients," and "utilization of healthcare by diabetic patients." We used the date limit of 2000 to 2023 to search some databases that do not have controlled vocabulary terms or thesaurus. We also explored the reference list of the selected studies. When the full text was unavailable, we emailed the authors to gain access to the full article.

Eligibility of studies

This study included all qualitative and quantitative studies carried out between 2000 and 2023. Based on the review questions formulated to guide the study, studies that dealt with intervention programs and epidemiology outcomes for diabetic patients were excluded. Only articles covering diabetes and poverty, accessibility of healthcare services for diabetic patients, and utilization of healthcare services were included in the program. Peer-reviewed articles and a book of abstracts were included to facilitate uniform reports of the published literature. Non-peer-reviewed articles were not considered, such as anecdotal reports, opinion papers, or supplementary commentary. This enabled the researchers to conduct a broad assessment of the published literature to identify lacunas in existing research. We further limited our search to studies reported exclusively in English. Furthermore, studies that included participants aged 18 and above were selected.

Data collection

All the identified studies from the earlier search were subjected to title and abstract screening by one of the project reviewers, while a full review of potentially relevant articles was conducted by two reviewers. All the selected texts were reassessed against the key inclusion criteria, and Microsoft Excel was used to extract the relevant data. Whenever differences between the two reviewers were observed, they reached a consensus through discussion. At the end of the critical data review, data were extracted from all selected studies. These data included the authors' names, the year of publication, the objective of the study, the design of the study, and the results.

RESULTS

The search produced 59 records of articles in peer-reviewed journals. After these articles were screened by the researchers using the stipulated inclusion criteria, 36 articles were excluded. Based on the predetermined inclusion criteria, 23 articles were included. Empiricism was characteristic of all the studies selected for this study. According to the research questions that guided this study, the findings were summarized.

Nexus between diabetes and poverty

Diabetes is a non-communicable disease that affects both high-income and low-income earners. But over the years, most people erroneously perceived diabetes as an ailment that was associated with poverty. Available empirical studies in the diabetes literature have shown that there is a lack of consensus on whether diabetes is exclusive to low-income earners (Table 1)[9,17,19-25]. Structural poverty has been described as the major driver of health disparities and a source of diabetes[17]. In addition, the literature has revealed that an increase in the poverty rate leads to an increase in the incidence of diabetes[9] and that poverty is highly associated with diabetes. Hence, it is more prevalent in low-income populations[18].

Contrary to the above findings, empirical evidence has also shown that the incidence of diabetes was lower among low-income earners compared with higher-income earners, *i.e.* the incidence of diabetes is high among higher socioeconomic groups compared to lower socioeconomic groups[19,20]. Therefore, it may be safe to argue that diabetes is not a an ailment for low-income earners only. However, poverty contributes to the severity of diabetes since it either enhances patients' consumption of food that induces diabetes or limits the patient's access to the required medical care.

Rate of accessibility of health care services by diabetic patients

Accessibility of medical care is substantial for the management of diabetic patients irrespective of the individual's financial capability[10]. The inability to access medical care for diabetic patients has been linked to either institutional factors or individual problems. This scoping review produced seven empirical studies that investigated diabetic patients' access to medical care services as well as the limitations of the patient's access to medical care (Table 2)[10,11,26-30]. One of the studies showed that the number of participants that sought medical care increased 305% from 2006 to 2015[26]. Another study suggested that routine access to hemoglobin A1c testing can promote diabetes control as well as offer critical data to inform the population of the current level of diabetes complications[10].

Table 1 Empirical evidence concerning association between diabetes and poverty

Publication year	Objective(s)	Design	Data collection	Results	Ref.
2013	The study examined the association between neighborhood-level poverty and hospital admission rates for T2DM in Rhode Island	Longitudinal study	Rhode Island's hospital discharge data	The study found that poverty increased from 3% to 40%, and the associated diabetes admission rates increased from less than 2% to 30% per 1000 residents	[9]
2011	The study examined ''upstream'' influences (the social determinants of health) that contribute to ''downstream'' health disparities, focusing on variations in T2DM risk	Exploratory study	Mixed data collection of focus group and survey	The results showed that the most significant barriers to health and the source of T2DM disparities in the target population were structural. In other words, they were derived from the conditions within which individuals live, work, and play	[17]
2002	The study investigated the profile of diabetes and its complications	Comparative study	Medical diagnosis	The results revealed that the prevalence of diabetes and impaired glucose tolerance was substantially lower among the low-income group than in the high-income group	[19]
2012	The study assessed the relationship between SES and T2DM in India	Cross-sectional survey	Self-reporting diabetes status	The study revealed that individuals with the highest SES seem to be at extreme risk for T2DM	[20]
2012	The study sought to determine whether inequality of income was connected with diabetes prevalence and inequality of care under a national health insurance program in Asia	Cross-sectional survey	National Health Insurance Scheme	The study revealed that the prevalence of diabetes was higher in low-income earners compared to middle-income counterparts	[21]
2014	The study examined the role of neighborhood poverty and racial composition in predicting race differences in diabetes incidence	Cross-sectional survey	The National Health and Nutrition Examination Survey, medical examination and interview	The study found that poverty was positively associated with diabetes for both Black and White people. Residing in a poor neighborhood amplified the odds of having diabetes for Black and White people	[22]
2019	It evaluated socioeconomic disparities in undiagnosed, diagnosed, and total diabetes as well as lifestyle variables as contributing factors to diabetes disparities in South Africa	Cross-sectional study	South African National Health and Nutrition Examination Survey	As measured by self-reported clinical data, diabetes was more prevalent among higher socioeconomic groups in South Africa	[23]
2023	This study compared rural-urban differentials in prevalence and lifestyle factors associated with pre-diabetes and diabetes in the elderly in southwest China	Cross-sectional health interview and examination survey	Anthropometric measurements as well as blood pressure and fasting blood glucose measurements	The study revealed that the incidence of pre-diabetes and diabetes was higher among urban older adults compared to their rural contemporaries in southwest China	[24]
2023	The study examined the trends in income-related inequalities in diabetes prevalence and identified the contribution of determining factors	Estimation of income-related inequalities in diagnosed diabetes	National Health Interview Survey	The study revealed that diabetes was more prevalent in low-income populations	

SES: Socioeconomic status; T2DM: Type 2 diabetes mellitus.

Three other studies identified factors that hindered diabetic patients from accessing medical care services; these factors included inadequate medical facilities, high-cost medical services, insufficient preservative facilities, structural barriers, quantification of need, equitable distribution of insulin, unavailability of syringes and testing equipment, and over-crowded clinics[10,11,27]. Two other studies emphasized that diabetes control was associated with insurance coverage and some health care visits, while the accessibility of diabetes care, availability of diabetes services, quality of diabetes care, disease management tactics, basic facilities of the health system, and health education resources played substantial roles in providing diabetes care services to patients[28,29].

Utilization of health care services by diabetic patients

Empirical studies that investigated the utilization of health care by diabetic patients have been published (Table 3). One study revealed that the majority of individuals with diabetes utilized the service of general practitioners, emergency room services, and specialist services[14]. The choice of these healthcare services was affected by the knowledge possessed by diabetic patients, which affected their utilization of these services[31]. Older adults with diabetes have been found to utilize emergency services and some outpatient visit services more than younger individuals[32]. A study conducted by Shalev *et al*[33] revealed that gender influences the utilization of health care services as females use more health care

Table 2 Accessibility of healthcare services among diabetic patients

Publication year	Objective(s)	Design	Data collection	Results	Ref.
2018	The study examined diabetic patients' access to hemoglobin A1c testing in rural Africa	Review	-	The study proposed that routine access to hemoglobin A1c testing would allow for close monitoring of diabetes control as well as provide critical data informing the population level of diabetes complications. The study equally revealed that the major limitation for rural patients' access to health care included high-cost medical services and a lack of preservative facilities	[10]
2005	The study assessed the barriers to care for patients with insulin-requiring diabetes	Rapid assessment protocol	Interviews, discussions, and site visits	The study revealed that several factors limited patients' access to diabetes care, which included inadequate supply, the problem of quantification of need, equitable distribution of insulin, and unavailability of syringes and testing equipment	[11]
2019	This study analyzed the diabetes-related information routine in Kwazulu Natal	Descriptive survey	Data from the District Health information system of South Africa	The study revealed that the number of diabetic patients seeking medical care increased 305% between 2006 to 2015, while the number of defaulters has decreased since 2012	[26]
2015	The study investigated females' experience with diabetes care in Soweto, a township of Johannesburg	Qualitative study	Interview	The study revealed that females identified structural barriers such as overcrowded clinics and poor access to medicines as hindering treatment adherence	[27]
2012	This study examined the association between access to health care and diabetes control	Correlational research	National Health and Nutrition Examination Survey, current health insurance coverage	The study revealed that lack of access to health care was linked with severe diabetic ailments. Diabetes control was associated with insurance coverage and some healthcare visits	[28]
2022	The study examined diabetes care factors and assessed their relative importance	Cross-sectional study	Survey questionnaire	The study revealed that accessibility of diabetes care, availability of diabetes services, quality of diabetes care, diabetes management strategies, a health system's basic amenities, and health education resources played a significant role in providing diabetes care services	[29]
2019	The study aimed to comprehend the factors that affected the utilization of DRSS and follow-up to inform health promotion strategies and improve the uptake of these services	Qualitative study	Focus group discussion	The study found that several factors affected patient uptake of diabetic retinopathy screening services, which included a lack of knowledge of both conditions and the need for screening, economic reasons, institutional factors, long waiting times at eye clinics, and fear of discomfort among others	[30]

DRSS: Diabetic Retinopathy Severity Scale.

services and have a high morbidity rate compared to males. Shalev *et al*[33] and Aro *et al*[34] affirmed that patients that are affected by diabetes utilized medical care more compared with their counterparts. Two studies identified factors that limited diabetic patients' utilization of health care services, which included a lack of finance and transportation that hindered the utilization of health care among diabetic patients[35-37].

DISCUSSION

This review investigated the association between diabetes and poverty. Comprehending the empirical evidence in the diabetes literature linking diabetes and poverty is crucial to guide future researchers as well as intervention programs and policies needed to manage the adverse effects of diabetes on patients. This discussion is organized based on the research questions that guided the study.

Diabetes is an emerging health problem both in low-income and middle-income countries. Despite the higher prevalence of diabetes in developing countries than in developed countries, diabetes affects both high-income and low-income earners[38]. Empirical evidence has revealed that there is more diabetes in high-income earners compared with low-income earners[19,20]. This could be attributed to environmental dispositions concerning what the high-income earners are bound to consume as well as the lack of knowledge and awareness of the major cause of various kinds of diabetes. The root contributing factor to the incidence of diabetes among high-income earners is an individual's physical inactivity.

However, other empirical studies in the diabetes literature associated diabetes with poverty because it requires long-term medical care and services that are capital intensive mostly in developing countries, and individuals with diabetes have chances of developing other ailments such as kidney problems and cardiovascular disease[39]. This means that individual poverty is a contributing factor that increases the prevalence of diabetes while some of the causative factors are

Table 3 Utilization of healthcare services among diabetic patients

Publication year	Objective(s)	Design	Data collection	Results	Ref.
2020	The purpose of this study was to investigate the service needs and healthcare utilization among people with T2DM	Cross-sectional study	Self-report questionnaire	The study revealed that diabetic patients utilized outpatient visits, special visits, general practitioner visits, emergency room, and hospitalization	[14]
2021	The study investigated the impact of diabetes comorbidities on the health care use and cost of a cohort of elderly patients with diabetes and high care needs based on real-world data	Descriptive survey	National Health Datasets	The results showed that high-need elderly patients accessed emergency care and several outpatient visits	[32]
2005	This study described differences in healthcare utilization and indicators of patients with diabetes based on gender	Survey	Computerized medical record	The study revealed that females with diabetes use more healthcare services and have a higher morbidity rate than their male counterparts	[33]
2022	This study compared the utilization of primary healthcare services by elderly patients with and without T2DM	Survey study	Electronic patient records, health-related quality of life, self-rated health	Patients with diabetes utilized primary healthcare more than those without diabetes	[34]
2022	This study evaluated whether social determinants were associated with an increased risk of proliferative diabetic retinopathy	Survey study	National Institutes of Health *All of Us* Research Program data repository	This study revealed that patients affirmed that financial concerns and lack of access to transportation were the major reasons for delaying or avoiding access to health care	[35]
2022	The study examined the costs sustained by patients with IDDM who received hospital inpatient/observation/emergency department care (Higher care) for diabetes-related events with those who did not receive such care to identify a target group for treatment in a subsequent study	Institutional review	Documented institutional data	It was found in the study that 8.4% of IDDM patients received higher care yet incurred 20% in medical costs and nearly 40% in diabetic-related spending	[36]
2017	A study was conducted in Bangladesh to determine diabetes-related knowledge and factors affecting healthcare services utilization among patients with T2DM	Analytical study	Interviewer and semi-structured questionnaires	Among patients with T2DM, the study found that patients had average knowledge of diabetes management, which might affect the use of healthcare services	[37]

IDDM: Insulin-dependent diabetes mellitus; T2DM: Type 2 diabetes mellitus.

unhealthy diet and physical inactivity. Furthermore, residing in poor neighborhoods has been found to increase the odds of having diabetes irrespective of race[22]. This implies that poor neighborhoods could predispose residents to unhealthy diets that contribute to a high chance of developing diabetes. Furthermore, empirical evidence has established that an increase in poverty leads to a corresponding increase in diabetes rate[9]. Poverty may compel individuals to consume unhealthy foods that can predispose them to diabetic conditions. However, just like other non-communicable diseases, diabetes can affect individuals irrespective of race and socioeconomic status, and its incidence is rising worldwide as a result of lifestyle factors like lack of physical inactivity and unhealthy diets.

Increased accessibility to health care is extremely important for diabetic patients because diabetes requires long-term management. Diabetic patients need unlimited access to medical care services to avert complications or crises and maintain a good quality of life. This requires frequent access and availability of a team of medical experts and pharmacists as well as the service of a diabetic care team[40]. The diabetes literature has shown that between 2006 to 2015, the number of diabetic patients that were seeking medical care increased 305%[26]. This indicates that patients with diabetes are willing and eager to access the medical care services provided by the government and non-governmental organizations.

Despite the promising upsurge in the number of diabetic patients seeking medical care services due to awareness, some personal and institutional factors often limit the patient's chances of access to diabetes care. Some studies have identified several factors that limit diabetic patients' access to medical care services. Piyasena *et al*[30] identified a lack of knowledge of the diabetic condition and the need for screening, financial burden, institutional factors, long waiting times at eye clinics, and fear of discomfort as the factors that hindered patient uptake of diabetes retinopathy screening services. Other studies emphasized the high cost of medical services, lack of preventative facilities, the problem of quantification of needs, limited distribution of insulin, overcrowded clinics, and lack of testing instruments for earlier detection of diabetes [10,11,27].

The majority of these identified factors that hinder patient accessibility to diabetes care services are human factors that can be resolved by government and non-governmental organizations by prioritizing the management of diabetes. To enhance the accessibility of health care services by diabetic patients, policies and intervention programs should be formulated and geared towards eliminating these existing factors that hinder diabetic patient access to health care services. As noted by Itumalla *et al*[29], government and non-governmental organizations should focus on improving the quality of diabetes care services, basic amenities of health services, and health awareness program services to facilitate the provision of efficient medical care services to diabetic patients[23].

The utilization of healthcare services can help to manage and sustain diabetic patients' healthcare-related problems as well as curtail the complications of diabetes. The utilization of health care services portrays how diabetic patients value the effectiveness of the current diabetes medical care services. This current study found in the diabetes literature that few studies have been carried out concerning the utilization of diabetic medical care services across the globe despite the upsurge in the incidence of diabetes.

Some empirical studies have identified some aspects of medical care services utilized by diabetic patients. Diabetic patients have been found to utilize outpatient visits, special visits, general practitioner visits, emergency room, and hospitalization[14,34]. This means that diabetic patients value the kinds of medical care services provided by these specialists; however, studies did not disclose the extent of utilization of these services by diabetic patients. More studies need to be conducted concerning how patients follow the recommended guidelines of taking their drugs, value routine check-up services, and abstain from consumption of edibles that escalate diabetes crises.

A study revealed that 8.4% of diabetic patients received higher care but incurred 20% of medical expenses and nearly 40% of diabetes-related expenses[36]. This finding implies that 91.6% of diabetic patients utilize low-care or no-care diabetes medical care. This finding revealed that diabetes medical care services are expensive for middle-income and low-income earners who are within the 91.6% of individuals with diabetes that could utilize low or no professional medical care services. Thus, more empirical studies are needed concerning the utilization of medical care services among individuals with diabetes.

CONCLUSION

Diabetes affects all individuals regardless of social class. Therefore, diabetes is not a disease particular to low-income earners. In the diabetes literature, the prevalence of diabetes among high-income earners has been associated with physical inactivity, while the prevalence of diabetes among low-income earners has been attributed to consumption of unhealthy diets as well as insufficient funds to manage the adverse effects of diabetes ailments. Access to medical care services is crucial to the management of diabetes. The available literature has shown that the number of patients seeking access to medical care services has increased over the years; however, several factors have been identified in the literature that hinder patient accessibility to the available medical care services. When medical care services are not accessible by the patients, the primary objectives of providing such services are marred. Hence, the after-effect is that the health condition of diabetic patients will deteriorate, especially in patients who are low-income earners in developing countries.

Utilization of medical care services is the major objective of all medical services; this review has documented that diabetic patients utilize some of these medical care services even though the percentage of individuals that utilize these services is very low. Diabetes medical care services are insufficient in developing countries where there are many individuals with diabetes. More scoping studies need to be conducted concerning different categories of patients with diabetes and their health, behavioral, and environmental implications. Future studies should widen the scope of their review concerning all ages and include publications in different languages to capture more empirical findings.

FOOTNOTES

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MINIREVIEWS

Gut microbiome supplementation as therapy for metabolic syndrome

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Abstract

The gut microbiome is defined as an ecological community of commensal symbiotic and pathogenic microorganisms that exist in our body. Gut microbiome dysbiosis is a condition of dysregulated and disrupted intestinal bacterial homeostasis, and recent evidence has shown that dysbiosis is related to chronic inflammation, insulin resistance, cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), and obesity. It is well known that obesity, T2DM and CVD are caused or worsened by multiple factors like genetic predisposition, environmental factors, unhealthy high calorie diets, and sedentary lifestyle. However, recent evidence from human and mouse models suggest that the gut microbiome is also an active player in the modulation of metabolic syndrome, a set of risk factors including obesity, hyperglycemia, and dyslipidemia that increase the risk for CVD, T2DM, and other diseases. Current research aims to identify treatments to increase the number of beneficial microbiota in the gut microbiome in order to modulate metabolic syndrome by reducing chronic inflammation and insulin resistance. There is increasing interest in supplements, classified as prebiotics, probiotics, synbiotics, or postbiotics, and their effect on the gut microbiome and metabolic syndrome. In this review article, we have summarized current research on these supplements that are available to improve the abundance of beneficial gut microbiota and to reduce the harmful ones in patients with metabolic

syndrome.

Key Words: Gut dysbiosis; Metabolic syndrome; Diabetes mellitus; Prebiotics; Probiotics; Postbiotics

Core Tip: Gut microbiome dysbiosis is related to chronic inflammation, insulin resistance, metabolic syndrome, cardiovascular diseases (CVD), and obesity. It is well known that obesity, type 2 diabetes mellitus and CVD are caused or worsened by multiple factors like genetic predisposition, environmental factors, unhealthy high calorie diets, and sedentary lifestyle. However, recent evidence from human and mouse models suggest that the gut microbiome is also an active player in modulation of these metabolic diseases. Hence it is important to review the role of microbiome supplementation that has been shown to improve the gut microbiome in patients with metabolic syndrome.

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INTRODUCTION

The gut microbiome is defined as an ecological community of commensal symbiotic and pathogenic microorganisms that exist in the body[1,2]. Gut microbiome dysbiosis is defined as dysregulated and disrupted intestinal bacterial homeostasis [2,3]. Recent evidence has shown that dysbiosis is related to chronic inflammation, insulin resistance, type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), and obesity[2]. It is known that obesity, T2DM and CVD are caused or worsened by multiple factors like genetic predisposition, environmental factors, unhealthy high calorie diet, and sedentary lifestyle[4-6]. However, recent evidence from human and mouse models suggests that the gut microbiome is also an active player in the modulation of these diseases[7]. Host and gut microbiome dysbiosis can influence local or systemic immunity and inflammation by regulating intestinal barrier permeability or by triggering the innate immune system as seen in obesity and T2DM[7]. *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* are among the protective bacteria that play a significant role in maintaining this intestinal barrier[7]. Hyperglycemia in T2DM can disrupt this intestinal barrier, which causes gram negative bacterial products like lipopolysaccharides (LPS) to enter the systemic circulation, leading to endotoxemia, and further local and systemic inflammation[3,7].

Metabolism is the process used by the body to create energy from the food we eat, and metabolic diseases, such as type 2 diabetes and obesity, occur due to metabolic dysregulation. Metabolic syndrome refers to a set of risk factors including hyperglycemia, dyslipidemia, and obesity that increases the risk for CVD, T2DM, non-alcoholic fatty liver, and other diseases[8]. Animal studies have shown a causal link between the gut microbiome profile and metabolic syndrome[8]. A study in mice fed a 30-d high fat diet showed significant increase of bacteria of the phylum *Firmicutes* and *Proteobacteria* with reduction of *Bacteroidetes* and *Verrucomicrobia*[9]. Another study with high-glucose or high-fructose fed mice showed the gut microbiome of these mice to be significantly altered with an increase in *Proteobacteria* and decrease in *Bacteroidetes* [10].

The gut microbiota consume the host's diet and produces certain metabolites which act on the host receptors and exert their endocrine effects, leading to hormone secretion, inflammation, and insulin resistance[11]. Studies have shown that these microbiota are sensitive to the host's diet composition and the microbiome diversity changes with animal vs. plant-based diets[1]. The gut microbiome produces certain beneficial metabolites like short chain fatty acids (SCFA)[2], such as butyrate which promotes colonic health and is protective against T2DM and CVD[1,3,7,11]; propionate which promotes the release of glucagon like peptide-1 and peptide YY, which improves insulin sensitivity and weight[2]. Secondary bile acids are converted from primary bile acids by the gut microbes, which activate takeda G protein coupled receptor 5, increasing cyclic adenosine monophosphate production, improving insulin sensitivity, interacting with the farnesoid X receptor, pregnane X receptor and vitamin D receptor to regulate lipid metabolism and glucose metabolism, subsequently slowing the progression of CVD and T2DM[7,11]. Other favorable metabolites are esculin, anthocyanin, urolithin A, and enterolactone[3].

Research has also revealed some unfavorable metabolites produced by the gut microbiome, of which trimethylamine is the most prominent. Trimethylamine is oxidized to trimethylamine N-oxide which works by increasing low-density lipoprotein uptake in cells, reducing cholesterol excretion, and promoting recruitment of activated leukocytes and platelet aggregation, and thus, trimethylamine promotes atherosclerosis, thrombosis, CVD and diabetes[3,12]. In patients with chronic kidney disease (CKD), studies have shown that high indoxyl sulfate levels predict major adverse cardiac events, high P-cresyl sulfate levels correlate with CVD and all-cause mortality, and phenylacetylglutamine is associated with overall mortality and CVD[13,14]. Since all of the above mentioned metabolites are uremic toxins, CKD can increase the buildup and worsen the effects of these metabolites resulting in CVD progression[3].

Current research is directed towards finding treatment options for improving the number of beneficial gut microbes and to reduce the harmful ones with the use of probiotics and prebiotics[7]. Efforts are also underway to identify novel gut microbiome-host interactions, their associations and mechanisms leading to T2DM, CVD and to design new therapies to modulate these disease processes[11]. The purpose of this article is to summarize the use of microbiome supplementation to improve the abundance of the beneficial gut microbes and to reduce the harmful ones in patients with diabetes mellitus and metabolic syndrome.

PREBIOTIC, PROBIOTIC, SYNBIOTIC AND POSTBIOTIC SUPPLEMENTATION

Microbiome supplementation has been found to alter the composition of the gut microbiome and possibly have effects on human health and diseases[15]. There are four types of supplements that are studied. In 2016, the International Scientific Association for Probiotics and Prebiotics (ISAPP) defined prebiotics as a substrate utilized selectively by microorganisms in the host and conferring a benefit to the host's health[16]. The widely accepted scientific definition of probiotics as defined by an expert panel convened by the ISAPP in 2013 is "Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"[17]. In 2019, the ISAPP convened and defined synbiotics as, "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host"; thus, synbiotics are a combination of prebiotics and probiotics[18]. Lastly, in 2019, ISAPP defined postbiotics to be inanimate microorganisms with or without their components that confer a health benefit to the host[19]. This section will review the current data for each of these supplements and directions for future research. Table 1 summarizes the definitions and examples of the each of these supplements and we have summarized the similarities and differences between each supplements' influence on metabolic syndrome in Table 2 and presented the same in a figure format in Figure 1.

Prebiotic

Prebiotics are consumable substances selectively utilized by microorganisms in the host and confer a benefit to the host [16]. Prebiotic effects have been studied in several metabolic diseases with animal studies, but few studies have been done on humans. Inulin, lactulose, fructooligosaccharides (FOS), and galactooligosaccharides (GOS) are the most widely known prebiotics[20]. Other prebiotics include human milk oligosaccharides, polydextrose, pectic oligosaccharides, arabinoxylans, and xylooligosaccharides[21]. Prebiotics confer a wide range of health benefits, including immune modulation through increased production of interleukins and immunoglobulins with reduction of pro-inflammatory interleukins and production of SCFAs, such as butyrate and acetate[21]. SCFAs indicate bacterial fermentation in the gastrointestinal tract and improve the health of the gut through mucus production, protecting against inflammation, and promoting the intestinal barrier integrity[21]. Production of SCFAs also results in a reduction on intestinal pH, inhibiting the growth of pathogenic bacteria[21].

Bacteria that promote gut health, such as *Bifidobacterium* and *Lactobacillus*, proliferate upon consumption of prebiotics [11]. Inulin oligofructose supplementation in mice fed a high fat diet showed a reduction in the *Firmicutes* to *Bacteroidetes* ratio[22], and reduction in the *Firmicutes* to *Bacteroidetes* ratio has been the hallmark of obesity[23,24]. A study done with a group of 10 elderly women over 19 days of inulin supplementation showed an increase in *Bifidobacteria* and decrease in *Enterococci* and *Enterobacteriaceae*[21], which is associated with a decreased risk of inflammatory bowel disease[25]. FOS supplementation in a rat model improved the gut microbiome by increasing *Bifidobacterium*[26]. Additional, fermentation of FOS generates SCFAs, decreasing the luminal pH and increasing the bioavailability of minerals in the gut[21]. GOS supplementation for prolonged periods in mice fed with a western diet led to increased abundance in *Akkermansia mucinophila* and *Prevotella*[27]. In another study, the activity of GOS was analyzed in sequencing fecal samples from humans after GOS administration, and the data showed an increased in *Facecalibacterium prausnitzii* and *Bifidobacteria* with a decrease in *Bacteroides*[21]. *Facecalibacterium prausnitzii* produces the SCFA butyrate and is associated with reduced inflammation[28]. *Bifidobacteria* promotes gut health, decreases expression of inflammatory cytokines, and improves insulin sensitivity[29]. Decrease in *Bacteroides* is beneficial to humans, as it is a pathogen common in anaerobic infections with significant antibiotic resistance[30].

Additional studies found that treatment with prebiotics improved glucose homeostasis and increased leptin sensitivity [31]. It also decreased inflammation by improving gut barrier integrity, thus decreasing the number of endotoxins able to leak from the gut lumen into the bloodstream[32]. They have also been shown to have a regulatory effect on metabolic disorders, especially those associated with obesity such as dyslipidemia, hypertension, diabetes, and liver steatosis[33]. Thus, several *in vivo* and *in vitro* studies have shown that prebiotics have beneficial impact on diabetes and obesity. Many prebiotics cause an increase in the growth of *Lactobacillus* and *Bifidobacterium*, but it is not fully understood how prebiotics cause these changes in the gut microbiome[21]. It is well-known that prebiotics are fermented by gut microbiota, leading the production of SCFAs, lowering the pH of the colon[21]. Figure 2 summarizes the beneficial effects of prebiotics leading to improved glucose homeostasis and reduced inflammation. Further research is necessary to elucidate the impact of prebiotics on the gut microbiome and the molecular signaling mechanisms of SCFAs.

Synbiotic

Synbiotics are combinations of prebiotics and probiotics, consisting of a combination of live microorganisms and substances that are selectively utilized by the host microbiota to confer a benefit to the host[18]. The benefits of synbiotics are thought to come from the initial selection of beneficial commensal microbiome species and aiding these species in subsequent food processing and fermentation[34]. These include reduced oxidative stress on intestinal cells and overall

Table 1 Definition and examples of prebiotics, probiotics, synbiotics, and postbiotics

Category	Definition	Examples
Prebiotic	Non-digestible substances utilized by microbiota and confer a benefit to the host	Inulin
		Lactulose
		Fructooligosaccharides
		Galactooligosaccharides
Probiotic	Live microorganisms that provide a benefit to the host	*Bifidobacterium*
		Lactobacillus
Synbiotic	Prebiotics and probiotics taken together	
Postbiotic	Inanimate strains with or without their byproducts that provide a benefit to the host	Heat killed *Akkermansia Mucinophila*
		Heat inactivated *Lactobacillus paracasei*
		Heat-inactivated *Bifidobacterium bifidum*
		Byproduct of the above inanimate strains: Butyrate and Proprionate

Table 2 The influence of prebiotics, probiotics, and postbiotics on metabolic syndrome

Category		Influence	
Prebiotic	Inulin	Decrease *Firmicutes* to *Bacteroidetes* ratio[22]	Improvement in Obesity
	Fructooligosaccharides	Increase *Bifidobacterium*[26]	Promotes gut health
			Decrease expression of inflammatory cytokines
			Improved Insulin sensitivity
	Galactooligosaccharides	Increase *Akkermansia mucinophila*. Increase in *Prevotella*[27]	Intestinal barrier protection
			Improved Insulin sensitivity
			Decrease inflammation
Probiotic	Bifidobacterium	Increasing *Akkermansia mucinophila*[56]	Intestinal barrier protection
			Improved Insulin sensitivity
			Decrease inflammation
	Lactobacillus	Decreasing *Firmicutes* to *Bacteroidetes* ratio[57]	Improvement in Obesity
Postbiotic	Heat-killed *Akkermansia mucinophila*		Improves metabolic state in Obesity
	Heat-inactivated *Lactobacillus paracasei*		Reduces the risk of pharyngitis, laryngitis, and diarrhea
	Heat-inactivated *Bifidobacterium bifidum*		Reduces symptoms of irritable bowel syndrome
	Butyrate (SCFA produced by the inactive microbe)	Increasing *Lachnospiraceae*[46]	Protection against diabetes and cardio-vascular diseases
		Increasing *Proteobacteria*[46]	Increased gut mucus production
		Decreasing *Clostridiaceae*[46]	Increased gut barrier integrity

SCFAs: Short Chain Fatty Acids.

decreased inflammation, thus maintaining the gut barrier[35]. Studies show that supplementation with synbiotics or probiotics may lead to beneficial reduction in fasting blood glucose (FBG), although the impact on FBG was more pronounced when multispecies probiotics were used instead of single species probiotics[36]. Current synbiotics include the most well-studied probiotics, including *Bifidobacterium* and *Lactobacillus*, which ferment indigestible sugars, such as FOS[34]. Thus, synbiotic administration of probiotics with FOS aims to increase the abundance of FOS fermentation products in the gut, such as lactic acid[34].

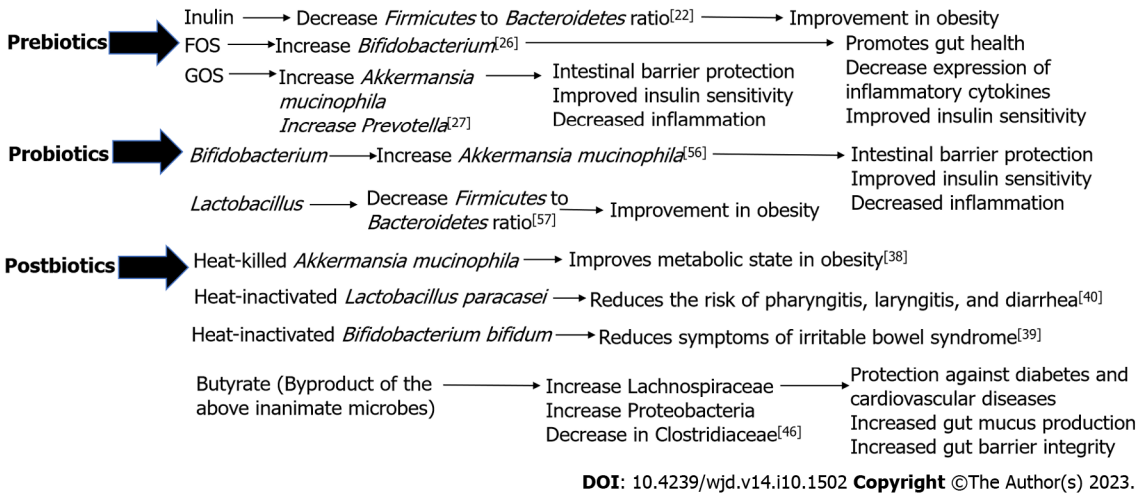

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Figure 1 The overall beneficial effects of gut microbiome supplementation on metabolic syndrome. FOS: Fructooligosaccharides; GOS: Galactooligosaccharides; SCFAs: Short Chain Fatty Acids.

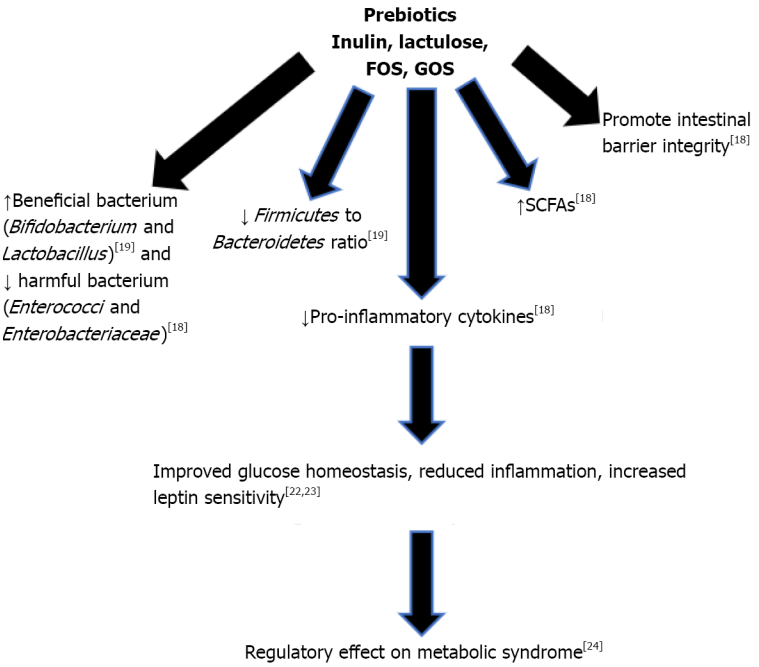

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Figure 2 The beneficial effects of prebiotics on metabolic syndrome. FOS: Fructooligosaccharides; GOS: Galactooligosaccharides; SCFAs: Short Chain Fatty Acids.

Many species rely on products from other species for survival, for example some species require lactic acid for substrate production and thus rely on lactic acid-producing species. This suggests that synbiotics will need to become more complex and involve multiple strains rather than just one, in addition to the prebiotics required for survival[34]. The effects of these supplements may also be altered by the individual's characteristics[37]. Person-to-person variation in gene expression was shown in one study to be the main determinant for differences in transcriptomes created post-supplementation[37]. This may be a species-specific phenomenon or even location specific, i.e., in the duodenum but not in the jejunum; thus, further trials are required.

Postbiotic

Postbiotics consist of inanimate microorganisms with or without their components and metabolites that confer a health benefit to the host[38]. Contrasting with probiotics, which consist of live microorganisms, postbiotics consist of microorganisms that are no longer alive, such as heat-killed *Akkermansia mucinophila*[38]. There are several challenges to the survival of probiotics during production and storage of food, such as reactions with chemical compounds, acidity, and storage temperature[38]. It has long been known that non-viable microbes in addition to their components and

metabolites can have significant impact on health[38]. In one clinical trial, heat-inactivated *Bifidobacterium bifidum* was found significantly alleviate the symptoms of irritable bowel syndrome[39]. In a similar study, *Akkermansia muciniphila* was found to improve the metabolic state of obese and overweight participants in both its living and inactive forms[38]. In another systematic review, postbiotics were studied for the prevention and treatment of infectious diseases in children under five years of age, revealing treatment with heat-killed *Lactobacillus acidophilus* reduced the duration of diarrhea and heat-inactivated *Lactobacillus paracasei* reduced the risk of pharyngitis, laryngitis, and diarrhea[40].

Postbiotics are promising for the development of food supplements with longer stability in comparison to prebiotic supplements[38]. Additionally, postbiotics have the potential to broaden the spectrum of microbes used for supplementation, as microbes that could not be administered live due to safety concerns can be administered in the inanimate form. The mechanism of action of postbiotics is due to both the components of the inactivated microbes and the metabolites produced by the microbes, such as SCFAs[38].

An inverse relationship between decline in anti-inflammatory microbiome species and abnormal SCFA production has been demonstrated[41]. SCFAs, such as butyrate and propionate, are among the metabolites produced from inactive microbes. Gut microbiome produced SCFA have been shown to have strong effects on metabolic and cardiovascular health through a variety of tissue-specific mechanisms including appetite regulation, glucose homeostasis and metabolism, proper gut barrier and colonocyte maintenance and function, and immunomodulation[41]. For example, butyrate is integral in colonocytes for energy production and expanding the regulatory T cell population in the immune system, while propionate is suggested to have a role in gluconeogenesis[42]. However, increase in acetate production has been shown to activate glucose-stimulated insulin secretion, increase ghrelin secretion and hyperphagia, leading to obesity and related diseases[43]. This suggests that to develop a treatment protocol, the specific proportion of postbiotics in a patient will need to be examined to allow for appropriate adjustment. Increased production of acetate has been found in obesity and decreased production of butyrate and propionate is seen in T2DM[44,45]. In mice studies, butyrate was shown to be associated with increased production of *Lachnospiraceae* and *Proteobacteria* and decreased production of *Clostridiaceae*[46].

However, the mechanism directly responsible remains elusive, and some results from animal models conflict with results from human trials. Many metabolic diseases are associated with a chronic state of low-grade inflammation. The maintenance of the gut barrier is also critical for reducing the amount of pro-inflammatory bacterial byproducts that can cross into the bloodstream, thus potentially decreasing the level of inflammation in the body. Specifically, a high fat diet reduces expression of tight junction genes, thus leading to a leaky barrier[47]. This allows inflammatory bacterial byproducts, such as LPS, to circulate in the body leading to an inflammatory response[48]. Hyperglycemia can also increase this leakiness and cause hyperpermeability, leading to a similar inflammatory phenomenon[49]. However, these findings are mainly in animal studies and further studies in humans are required. Additionally, there is a need for studies on the impact of inanimate microbes on the host without associated metabolites to determine the extent that health benefits are conferred. There is also need for additional research on the mechanisms that are driving the benefits of postbiotics. Figure 3 summarizes the beneficial effects of postbiotics, leading to improved glucose homeostasis and reduced inflammation.

Probiotic

Probiotics are live microorganisms that confer a benefit to the host when administered[17]. *Bifidobacterium* and *Lactobacillus* are the two most widely known probiotics. Various studies in animals have shown their benefits in improving gut microbiome composition[50,51]. Probiotic administration has been shown to be potential therapeutic target for metabolic syndrome prevention and treatment[52]. There is a fine balance between the host's immune system and gut microbiome, and imbalance can lead to systemic inflammation through passage of bacteria and bacterial fragments, such as LPS, through the gut barrier and into systemic circulation[52]. Chronic systemic inflammation can lead to the development of insulin resistance and obesity[52].

Additionally, many diseases have been found to have microbial dysbiosis either from an overgrowth of pathogenic species or a loss of microbiome diversity[53]. However, it should be noted that there is not a clear definition of a healthy gut microbiome composition, so the term "dysbiosis" is inherently vague[45]. This change in microbial composition is found to be associated with increased inflammation, specifically in obese patients since low-grade inflammation is a common finding in many metabolic disorders[45]. This suggests that microbiome composition affects the inflammatory state of people. An increase of pro-inflammatory bacterial species has also been found in patients with T2DM, especially with a decrease of anti-inflammatory species[41].

The microbiome present in obese individuals has been found to be different from that of lean individuals though specific differences are difficult to qualify[54]. In a study with obese and lean adolescents, it was found that a lower amount of *Bacteroidetes* and higher proportion of *Firmicutes* was associated with obesity[55]. The microbiome of obese individuals has been shown in animal models to extract more energy from the diet, and this phenomenon still occurs when the microbiome from obese mice is transplanted into lean mice[54]. *Bifidobacterium* supplementation in diet-induced obese and insulin resistant mice showed an increase in *Akkermansia mucinophila*[56]. In another study, *Lactobacillus* supplementation in high-fat diet induced hypertensive mice showed a reduction in the ratio of *Firmicutes* to *Bacteroidetes*[57].

Probiotics have been found to have an influence on the expression of inflammation-related genes and proteins[58]. Many animal studies have shown interactions between the gut microbiome and the immune system[45]. These studies reduced the gene expression of immune system components with known or theorized links to metabolic dysfunction. Researchers then studied the effects or interactions of these mutation with the gut microbiome. Knock out of toll-like receptor 5 (TLR5) in mice was found to cause the hallmark features of metabolic syndrome in correlation with changes to the gut microbiome and findings of colitis[59]. Upon transfer of the microbiome from the knock-out mice to wild-type germ-free mice, metabolic dysfunction was also transferred, leading to hyperlipidemia, hypertension, and insulin

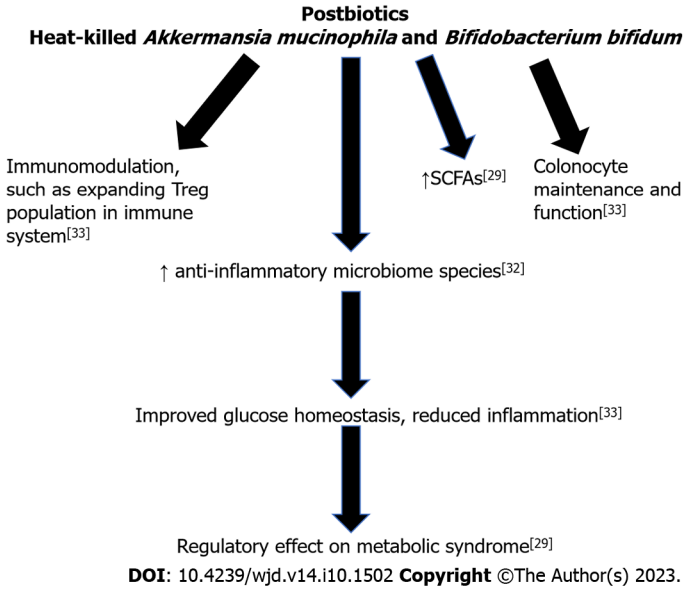

Figure 3 The beneficial effects of postbiotics on metabolic syndrome. Treg: Regulatory T cell; SCFAs: Short Chain Fatty Acids.

resistance. Food restriction was able to prevent obesity but had no effect on insulin resistance, suggesting that the TLR5 and subsequent microbiome changes have a metabolic effect. Additionally, deletion of myeloid differentiation factor 88 and a high fat diet induced hyperglycemia, leading to metabolic syndrome in knock-out mice along with an increase in bacterial translocation across the intestinal barrier[29]. The mice were then given *Bifidobacterium animalis* subsp. lactis 420 (B420) as a probiotic. The result was a general normalization of gut microbiome composition, a decrease in the expression of major inflammatory cytokines, and a complete normalization of insulin sensitivity and levels, although glucose metabolism was only moderately affected[29]. However, data on specific benefits conflict from study to study. Improvements in glucose metabolism is more significant in patients with T2DM, and some studies report little effect on cholesterol and lipid levels[45]. Supplementation of *Akkermansia muciniphila* has been found in rodents and humans to improve insulin sensitivity and decrease inflammation[60]. The findings are less prominent in humans but indicate the supplement's clinical potential. Another study with 40 participants with insulin resistance were placed in a double-blind trial and given either *Akkermansia muciniphila* or a placebo, and the study showed reduction in inflammatory markers and improved insulin sensitivity in the *Akkermansia muciniphila* group[61].

Only a small number of studies have been conducted to analyze the effect of probiotic administration on weight and glycemic control in humans. In one study, 87 subjects with higher body mass index (BMI) (24.2-30.7 kg/m^2) were randomly assigned to a group received fermented milk containing *Lactobacillus* (LG2055) or fermented milk without *Lactobacillus* for 12 wk. It was found that the group receiving the milk containing LG2055 experienced a significant reduction in abdominal visceral and subcutaneous fat and BMI[62]. Another study showed probiotic yogurt consumption reduced FBG and HgbA1c in patients with type 2 diabetes[63]. A double-blind trial with 21 participants showed administration of *Lactobacillus reuteri* improved insulin and incretin secretion[64]. Thus, the results from clinical experiments are encouraging, but larger trials are needed to confirm the effect of probiotics on improving insulin sensitivity and weight loss[65]. Figure 4 summarizes the beneficial effects of probiotics, leading to improved glucose homeostasis and reduced inflammation.

Future directions

Future research is needed to confirm the clinical efficacy of microbiome supplementation. Several times, studies have reached opposing or ambiguous conclusions, even though the research was of high methodological quality[58]. This may be due to several factors including data collection methods, different analysis parameters and metrics, and varied methods of interpretation[58]. Some studies used self-reporting surveys to measure patient quality of life and psychosocial effects. Others looked at lab values that may not necessarily have significance clinically, such as inflammatory markers or glucose metabolism protein levels in generally healthy individuals. Some studies had animal models while others involved human subjects and may have been observational or randomized with placebo controls. There is also the question of funding and conflicts of interest, as some studies are funded or linked to probiotic companies. While that does not necessarily bias the project, independent research should be a focus in the future.

Additionally, research on the effects of specific strains is lacking and may even vary from stain to strain, thus weakening the argument for the use of specific strains in a project[58]. One study found that both mice and humans had colonization resistance to probiotics based on the current composition of their gut microbiome, and that in humans this resistance varies from person to person because microbiome composition is individualized based on person-specific needs, geographic region, and diet among other factors[66]. In fact, many of the live probiotic strains were found to still be viable in stool samples after passage through the GI tract[66], and it remains unclear if the colonization that does occur persists after supplementation ceases. This contradicts *in vitro* studies in which probiotics were able to adhere to human

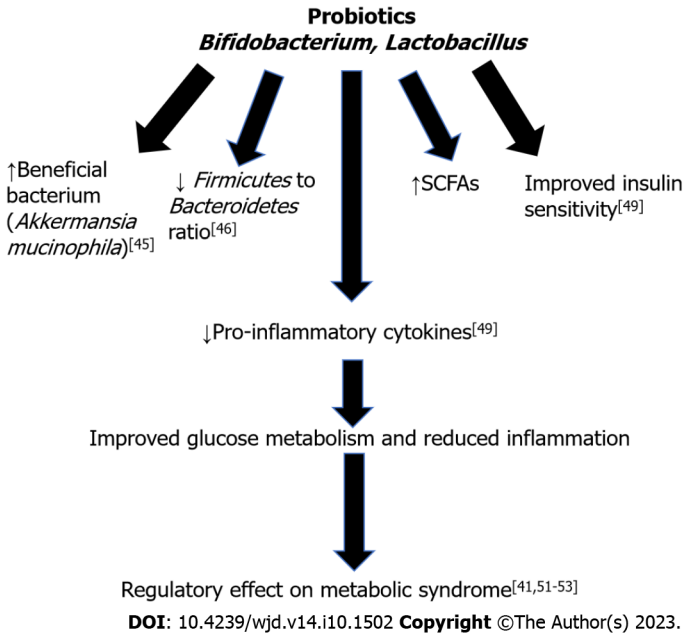

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Figure 4 The beneficial effects of probiotics on metabolic syndrome. SCFAs: Short Chain Fatty Acids.

GI mucosal cells[67], indicating that lab-based work may be a poor predictor of efficacy in human subjects[58]. *In vitro* studies in general may be poor models for this topic of research since it does not include *in vivo* signaling and factors that may play an important role in colonization and efficacy[58]. This could also contribute to conflicting results and would require further *in vivo* studies.

Additional studies have also looked at whether the effects of probiotics change depending on a person's specific microbiome composition and have found that it does make a difference. Song *et al*[68] classified fifty obese but otherwise healthy subjects based on the ratio of two bacterial species, *Prevotella* and *Bacteroidetes*, two of the major enterotypes[68]. The administration of probiotics improved obesity-related markers, but the efficacy was greater in the *Prevotella*-dominant enterotype. This, along with colonization resistance, could explain why previous studies have found such varied results and accounting for these differences could help reconcile conflicting data[66]. This highlights the need for a patient-centered protocol rather than general supplementation.

Postbiotics is the newest area of research and thus will require the most work in future studies. There is the potential to alter bacteria to produce new biological compounds. In one study using a mouse model of alcoholic liver disease, *Lactobacillus reuteri* was engineered to produce interleukin-22 (IL-22), an anti-inflammatory cytokine, after it was determined that chronic alcohol use reduces intestinal production of IL-22[69]. IL-22 has been found in previous studies to protect against atherosclerosis and CVD[70] as well as protect against beta cell stress and normalize hyperglycemia and insulin levels [71]. The increased levels of IL-22 allowed for increased expression of the regenerating islet-derived genes (REG3-gamma gene), which creates a protein that prevents bacterial translocation across the gut barrier. This reduced ethanol-induced steatohepatitis, a direct hepato-protective effect made possible by genetically altered probiotic supplementation. Through this, we have found that it is possible to manipulate commensal bacteria to fit the roles needed in the patient and can treat an enormous variety of metabolic diseases.

Meta analyses may help resolve some of the ambiguity but are not impervious to biases[58]. They may include studies that involve different strains of bacteria and thus are difficult to compare. They may also include outlier studies that skew the data and conclusions or be diluted by papers without significant findings. Therefore, efforts should be placed in developing randomized, large-scale, and high-quality experiments and clinical trials to assess the use of prebiotics, probiotics, and postbiotics to modify the gut microbiome and affect various metabolic syndromes.

CONCLUSION

The relationship between human health and the microbiome has piqued researchers' curiosity in the last decade. Our knowledge of the gut microbiome's composition and functions has considerably improved over the past several years due to rapid advancements in metagenomic sequencing techniques. As a result, it is evident that almost no area of host physiology is fully immune to the effects of gut microbes and their products. Indeed, the gut microbiota's influence extends beyond the gastrointestinal tract's traditional digestion function to include altering the physiology of other organ systems such as the liver, adipose tissue, lung, and brain. With better insight into the interactions between the host and microbiota, human gut microbiome supplementation has emerged as a promising novel therapeutic target. Current research is directed towards finding treatment options for improving the number of beneficial gut microbiota and to reduce the harmful ones with the use of prebiotics, probiotics, synbiotics, and postbiotics. Efforts are also underway to

identify novel gut microbiota-host interactions, their mechanisms, and associations with T2DM, CVD and to design new therapies to modulate these disease processes.

FOOTNOTES

Author contributions: Antony MA and Kant R designed the outline, performed the writing, prepared the figure, and edited the paper; Edem D, Raj R, Verma V, Nain P, Chowdhury A, and Joglekar M performed the writing, and prepared the table and figure; Antony MA and Kant R provided the input in writing the paper, performed the writing and edited the paper.

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ORIGINAL ARTICLE

Retrospective Study

Effects of vitamin D supplementation on glucose and lipid metabolism in patients with type 2 diabetes mellitus and risk factors for insulin resistance

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Abstract

BACKGROUND

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease featured by insulin resistance (IR) and decreased insulin secretion. Currently, vitamin D deficiency is found in most patients with T2DM, but the relationship between vitamin D and IR in T2DM patients requires further investigation.

AIM

To explore the risk factors of IR and the effects of vitamin D supplementation on glucose and lipid metabolism in patients with T2DM.

METHODS

Clinical data of 162 T2DM patients treated in First Affiliated Hospital of Harbin Medical University between January 2019 and February 2022 were retrospectively analyzed. Based on the diagnostic criteria of IR, the patients were divided into a resistance group (n = 100) and a non-resistance group (n = 62). Subsequently, patients in the resistance group were subdivided to a conventional group (n = 44) or a joint group (n = 56) according to the treatment regimens. Logistic regression was carried out to analyze the risk factors of IR in T2DM patients. The changes in glucose and lipid metabolism indexes in T2DM patients with vitamin D deficiency were evaluated after the treatment.

RESULTS

Notable differences were observed in age and body mass index (BMI) between the resistance group and the non-resistance group (both P < 0.05). The resistance

group exhibited a lower 25-hydroxyvitamin D_3 (25(OH)D_3) level, as well as notably higher levels of 2-h postprandial blood glucose (2hPG), fasting blood glucose (FBG), and glycosylated hemoglobin (HbA1c) than the non-resistance group (all $P < 0.0001$). Additionally, the resistance group demonstrated a higher triglyceride (TG) level but a lower high-density lipoprotein-cholesterol (HDL-C) level than the non-resistance group (all $P < 0.0001$). The BMI, TG, HDL-C, 25(OH)D_3, 2hPG, and HbA1c were found to be risk factors of IR. Moreover, the post-treatment changes in levels of 25(OH)D_3, 2hPG, FBG and HbA1c, as well as TG, total cholesterol, and HDL-C in the joint group were more significant than those in the conventional group (all $P < 0.05$).

CONCLUSION

Patients with IR exhibit significant abnormalities in glucose and lipid metabolism parameters compared to the non-insulin resistant group. Logistic regression analysis revealed that 25(OH)D_3 is an independent risk factor influencing IR. Supplementation of vitamin D has been shown to improve glucose and lipid metabolism in patients with IR and T2DM.

Key Words: Vitamin D; Type 2 diabetes mellitus; Glucose and lipid metabolism; Insulin resistance; Risk factors

Core Tip: A retrospective analysis was conducted on 162 type 2 diabetes mellitus (T2DM) patients to analyze the risk factor for insulin resistance (IR) and to investigate the effects of vitamin D supplementation on glucose and lipid metabolism in patients with T2DM and IR. It was found that 25-hydroxyvitamin D_3 and body mass index were risk factors for IR in T2DM patients, and vitamin D supplementation improved the glucose and lipid metabolism in patients with IR. The treatment regimen with vitamin D supplementation led to more significant decreases in 2-h postprandial blood glucose, fasting blood glucose, glycosylated hemoglobin, triglyceride, and total cholesterol levels and more increase in high-density lipoprotein-cholesterol than the conventional regimen. It is suggested that vitamin D supplementation may be an effective intervention for T2DM patients with vitamin D deficiency and IR.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease affecting hundreds of millions of patients worldwide[1]. According to the data from the World Health Organization, there are approximate 425 million DM patients globally, and it is estimated that this number will increase to 700 million by 2045[2]. Over the past few years, with the improvement of living standards and changes in lifestyle, the number of DM patients in China has increased dramatically[3]. According to an estimation, there are approximate 114 million DM patients in China, accounting for 1/4 of the global number of patients [4]. As a public health problem, DM places a heavy burden on the economic and medical systems[5]. Without timely and effective treatment, patients with DM are prone to various complications, such as cardiovascular diseases, nephropathy, retinopathy, and neuropathy, which seriously compromise the quality of life and lifespan of the patients[6,7].

Insulin, a hormone produced by the pancreas, plays a crucial role in facilitating the absorption of blood glucose by cells for energy production. Insulin resistance (IR) refers to a condition in which the body becomes less responsive to insulin [8], leading to an increase in blood glucose level. In response to hyperglycemia, the pancreas tries to compensates by secreting higher amounts of insulin[9]. However, over time, the pancreas may not be able to produce sufficient insulin to meet the demand, resulting in DM[10]. Patients with type 2 diabetes mellitus (T2DM) often develop IR first, followed by a gradual decline in insulin secretion, which eventually triggers the inability to effectively regulate blood glucose levels[11].

Vitamin D is a fat-soluble hormone that plays a crucial role in the metabolism of calcium and phosphorus, and it is also implicated in many physiological processes, including immune regulation, inflammation and insulin synthesis and secretion[12]. In recent years, vitamin D supplementation has attracted much attention in promoting blood glucose control, suppressing inflammation, enhancing insulin secretion and improving muscle function in T2DM patients[13]. Reportedly, about 50% of T2DM patients have vitamin D deficiency, and approximately 1/3 to 2/3 of them are accompanied with decreased bone density, which increases the risk of falls, fractures and death in elderly patients[14].

This study aimed to analyze the risk factors for IR in T2DM patients and the effects of vitamin D supplementation on glucose and lipid metabolism in the patients.

MATERIALS AND METHODS

Subjects

Clinical data of 332 T2DM patients treated in First Affiliated Hospital of Harbin Medical University between January 2019 and February 2022 were retrospectively analyzed. This study was performed with approval from the Medical Ethics Committee of First Affiliated Hospital of Harbin Medical University.

Inclusion and exclusion criteria

Patients were eligible if they met the diagnostic criteria in Guidelines for Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020)[15] and held complete clinical data.

Patients were excluded if they had diabetes other than T2DM, recently suffered from acute infection or acute complications of DM, or had a history of mental illness.

Criteria of IR

The homeostasis model assessment of IR (HOMA-IR) was adopted for the evaluation of the IR degree. According to the Consensus of Chinese Diabetes Experts, IR is indicated by HOMA-IR ≥ 2.69.

Criteria of vitamin D deficiency

According to the criteria of vitamin D deficiency in the Consensus of Clinical Application of Vitamin D and Its Analogs [16], vitamin D deficiency is indicated by serum 25-hydroxyvitamin D (25(OH)D_3) less than 50 nmol/L.

Grouping of patients

A total of 332 patients were screened based on the inclusion and exclusion criteria, and 162 patients who met the criteria were finally included. Based on the criteria of IR, the patients were divided into a resistance group (n = 100) and non-resistance group (n = 62). Subsequently, patients in the resistance group were subdivided into a conventional group (conventional treatment for DM, n = 44) or a joint group (conventional treatment for DM plus vitamin D supplementation, n = 56) according to the treatment regimens. The patient screening flow chart is shown in Figure 1.

Therapeutic regimens

Patients in both groups received routine treatment and nursing interventions, and healthcare records were established for each patient during hospitalization. All patients were given metformin [Merck & Co. Inc, State Food and Drug Administration (SFDA) approval number: H20023370] and insulin pump (biosynthetic human insulin, Novo Nordisk, SFDA approval number: S20153001). Metformin was administered with a small initial dosage (0.50 g, twice daily, or 0.85 g, once daily, taken with meals), and the dosage was gradually increased based on the patient's conditions. Insulin is administered subcutaneously using an insulin pump at a dose of 0.15 IU/kg of body weight. The patients were required to take the medication as prescribed, and provided with relevant healthcare and exercise instruction manuals for disease knowledge education. After discharge, the patients were followed up every month and provided with personalized diet and exercise advice according to the changes in blood glucose level. Each patient received continuous intervention for 3 months, during which they were reminded to regularly monitor their blood glucose levels, maintain a reasonable diet, and engage in regular exercise.

Patients in the joint group received additional vitamin D supplementation by giving oral calcium carbonate D_3 tablets (Wyeth Company, SFDA approval number: H10950029), once a day, one tablets each time, for three consecutive months.

Clinical data collection

The laboratory indicators and baseline data of patients were collected from the hospital electronic medical records. The laboratory indicators included 25(OH)D_3, 2-h postprandial blood glucose (2hPG), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), triglyceride (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and HOMA-IR, Using a Hitachi 7600 fully automatic biochemical analyzer for testing. The baseline data included sex, age, course of disease, body mass index (BMI), smoking history and alcoholism history.

Outcome measures

Primary outcome measure was the risk factors for IR, which was analyzed by Logistic regression analysis in the included patients.

Secondary outcome measures were changes in glucose metabolism indexes (25(OH)D_3, 2hPG, FBG, and HbA1c) and lipid metabolism indexes (TG, TC, HDL-C, and LDL-C) in T2DM patients with IR after treatment.

Statistical analysis

SPSS 26.0 software was used for statistical analysis. The measurement data conforming to a normal distribution were expressed by mean ± SD, and the inter-group comparisons were conducted using t test. Counting data were described by cases (%), and their inter-group comparisons were conducted using chi-square test. Logistic regression analysis was used for analyzing the risk factors for IR in T2DM patients. GraphPad Prism 9.0 software was adopted for data visualization. P < 0.05 was considered a significant difference.

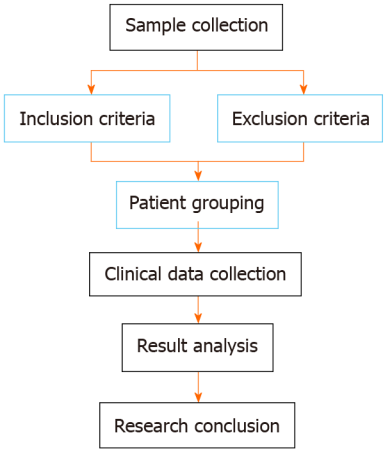

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Figure 1 Flowchart.

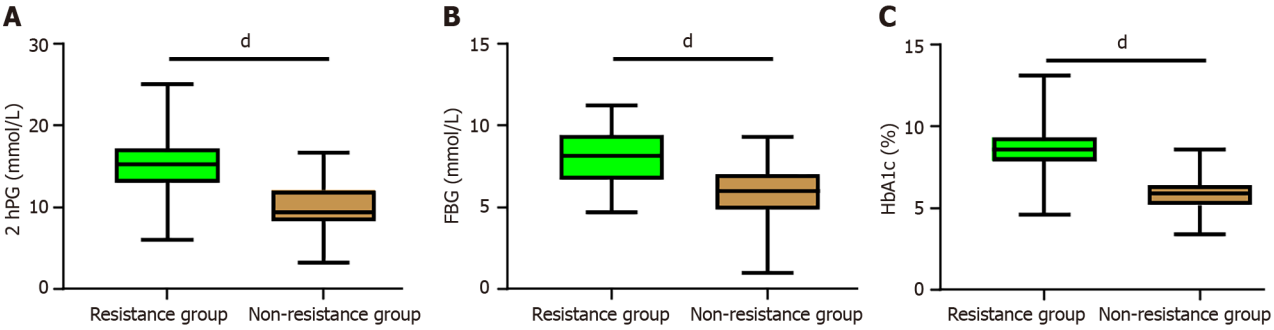

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Figure 2 Comparison of glucose metabolism indexes between patients with or without insulin resistance. A: Comparison of 2 h postprandial blood glucose; B: Comparison of fasting blood glucose; C: Comparison of glycosylated hemoglobin. 2hPG: 2 h postprandial blood glucose; FBG: Fasting blood glucose; HbA1c: Glycosylated hemoglobin. $^{d}P < 0.0001$.

RESULTS

Comparison of baseline data

The baseline data were compared between the resistance group and the non-resistance group. The results showed that there were no statistically significant differences in gender, disease duration, smoking history, and alcohol consumption between the Resistance group and the Non-resistance group (all $P > 0.05$, Table 1). However, the proportion of patients aged > 60 years and with BMI > 25 kg/m^2 was higher in the Resistance group compared to the Non-resistance group. Additionally, the Resistance group had lower levels of 25 (OH) D_3 compared to the Non-resistance group (all $P < 0.05$, Table 1).

Comparison of glucose metabolism indexes between the resistance group and the non-resistance group

Comparison of glucose metabolism indexes between the Resistance group and Non-resistance group. The results showed that Patients in the Resistance group had higher levels of 2hPG, FBG, and HbA1c compared to the non-resistance group (all $P < 0.0001$, Figure 2).

Comparison of lipid metabolism indexes between the resistance group and the non-resistance group

When comparing the lipid metabolism indexes between the Resistance group and the Non-resistance group, no significant differences were found in the levels of LDL-C and TC (all $P > 0.05$). However, the Resistance group exhibited significantly higher levels of TG compared to the Non-resistance group, while the Resistance group had lower levels of HDL-C than the Non-resistance group (all $P < 0.0001$, Figure 3).

Analysis of risk factors for IR

A logistic regression analysis was performed using the collected and assigned significant variables (Table 2). The results revealed that BMI (OR:16.802, 95%CI: 2.557-110.43), HDL-C (OR:0.069, 95%CI: 0.009-0.540), 25(OH)D_3 (OR:26.109, 95%CI: 4.285-159.098), 2hPG(OR:31.804, 95%CI: 5.567-181.709) and HbA1c (OR:90.379, 95%CI: 13.622-599.650) (all $P < 0.05$,

Table 1 Clinical data

Factors		Resistance group (*n* = 100)	Non-resistance group (*n* = 62)	*P* value
Age				0.041[a]
	> 60 yr old	60	27	
	≤ 60 yr old	40	35	
Sex				0.240
	Male	61	32	
	Female	39	30	
BMI				< 0.0001[d]
	> 25 kg/m^2	44	10	
	≤ 25 kg/m^2	56	52	
Course of disease				0.458
	> 5 yr	38	20	
	≤ 5 yr	62	42	
Smoking history				0.240
	Yes	61	32	
	No	39	30	
Alcoholism history				0.988
	Yes	8	5	
	No	92	57	
25(OH)D_3		35.92 ± 7.12	44.78 ± 4.52	< 0.001[c]

[a]$P < 0.05$.
[c]$P < 0.001$.
[d]$P < 0.0001$.
BMI: Body mass index; 25(OH)D_3: 25-hydroxyvitamin D_3.

Table 2 Assignment

Factors	Assignment
Age	> 60 = 1, ≤ 60 = 0
BMI	> 25 kg/m^2 = 1, ≤ 25 kg/m^2 = 0
25(OH)D_3	Data belonging to continuous variables were analyzed with their raw data
2hPG	Data belonging to continuous variables were analyzed with their raw data
FBG	Data belonging to continuous variables were analyzed with their raw data
HbA1c	Data belonging to continuous variables were analyzed with their raw data
TG	Data belonging to continuous variables were analyzed with their raw data
HDL-C	Data belonging to continuous variables were analyzed with their raw data
Insulin resistance	Yes = 1, No = 0

BMI: Body mass index; 25(OH)D_3: 25-hydroxyvitamin D_3; 2hPG: 2-h postprandial blood glucose); FBG: Fasting blood glucose; HbA1c: Glycosylated hemoglobin; TG: Triglyceride; HDL-C: High-density lipoprotein-cholesterol.

Table 3 Analysis of risk factors

Factors	β	Standard error	χ^2	*P* value	OR value	95%CI	
						Lower limit	Upper limit
Age	0.257	0.770	0.111	0.739	1.293	0.286	5.851
BMI	2.822	0.961	8.626	0.003[b]	16.802	2.557	110.430
TG	1.148	0.853	1.808	0.179	3.151	0.591	16.783
HDL-C	-2.68	1.053	6.476	0.011[a]	0.069	0.009	0.540
25(OH)D_3	3.262	0.922	12.517	< 0.001[c]	26.109	4.285	159.098
2hPG	3.460	0.889	15.137	< 0.001[c]	31.804	5.567	181.709
FBG	0.751	0.756	0.985	0.321	2.119	0.481	9.329
HbA1c	4.504	0.965	21.762	< 0.001[c]	90.379	13.622	599.650

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.

BMI: Body mass index; 25(OH)D_3: 25-hydroxyvitamin D_3; 2hPG: 2-h postprandial blood glucose; FBG: Fasting blood glucose; HbA1c: Glycosylated hemoglobin; TG: Triglyceride; HDL-C: High-density lipoprotein-cholesterol.

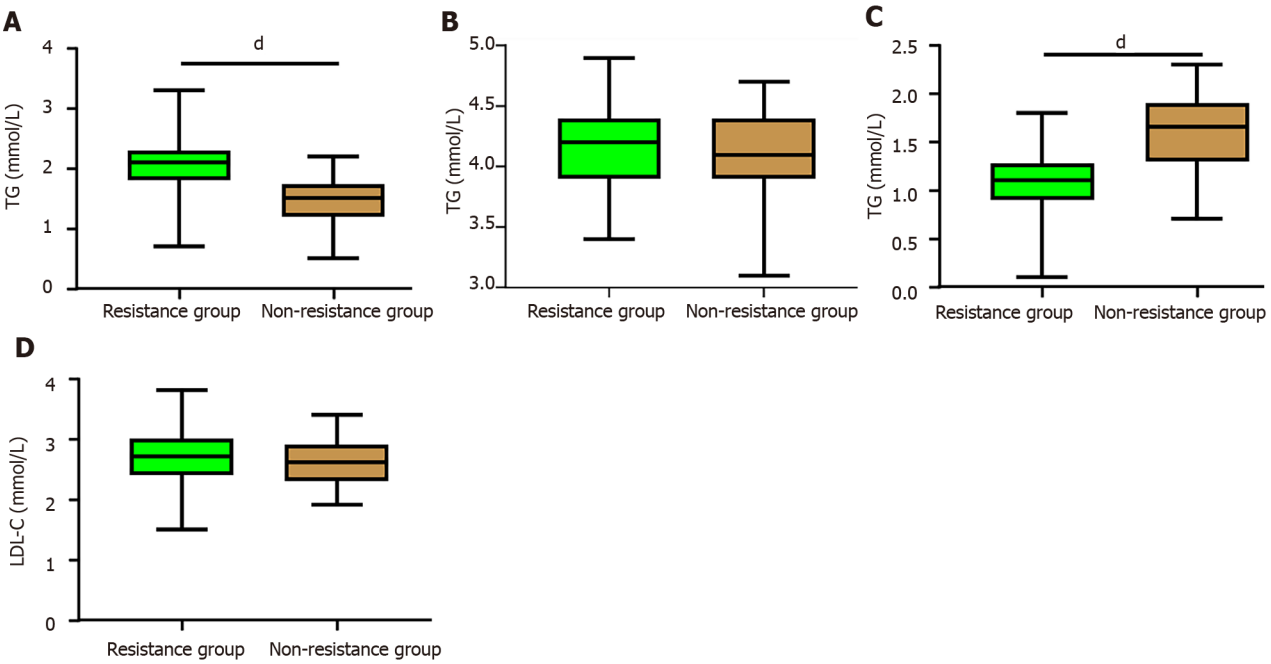

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Figure 3 Comparison of lipid metabolism indexes between patients with or without insulin resistance. A: Comparison of triglyceride; B: Comparison of total cholesterol; C: Comparison of high-density lipoprotein-cholesterol; D: Comparison of low-density lipoprotein-cholesterol. TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol. [d]$P < 0.0001$.

Table 3).

Effects of vitamin D supplementation on glucose metabolism in T2DM patients with IR

In order to determine the effects of vitamin D supplementation on glucose metabolism in patients with T2DM and IR, we analyzed the changes of glucose metabolism indicators before and after the treatment. It was found that the levels of 2hPG, FBG, and HbA1c in both the conventional group and the joint group decreased notably after treatment (all $P < 0.01$, Figure 4), but the joint group demonstrated more significant decreases in all the three indices than the conventional group (all $P < 0.05$, Figure 4).

Effect of vitamin D supplementation on lipid metabolism indexes in T2DM patients with IR

In order to determine the effect of vitamin D supplementation on lipid metabolism in T2DM patients with IR, we

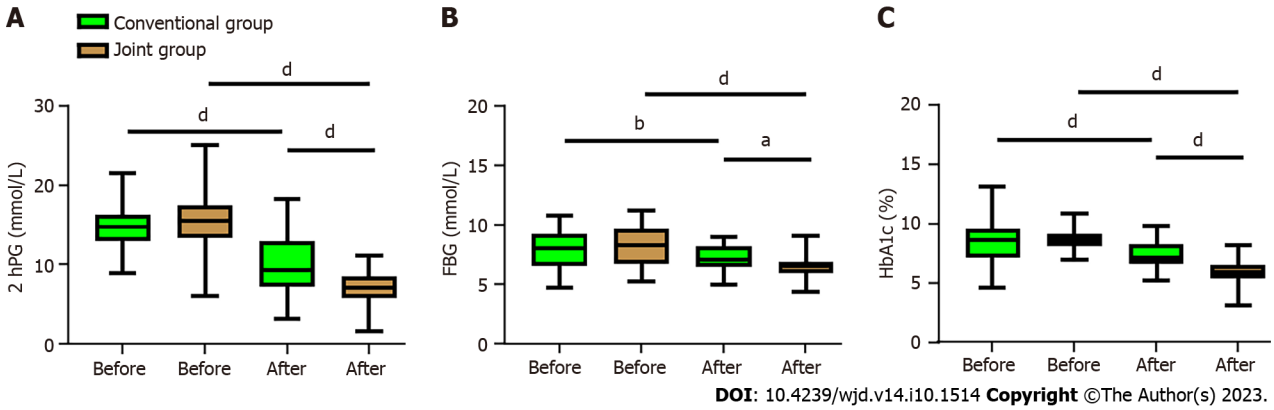

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Figure 4 Changes of glucose metabolism indexes in type 2 diabetes mellitus patients with insulin resistance before and after the treatment. A: Comparison of 2-h postprandial blood glucose between the joint group and the conventional group; B: Comparison of fasting blood glucose between the joint group and the conventional group; C: Comparison of glycosylated hemoglobin between the joint group and the conventional group. 2hPG: 2-h postprandial blood glucose; FBG: Fasting blood glucose; HbA1c: Glycosylated hemoglobin. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{d}P < 0.0001$.

analyzed the changes in lipid metabolism before and after treatment. It was found that both groups exhibited decreased TG and TC, as well as increased HDL-C after treatment (all $P < 0.05$, Figure 5). Furthermore, the joint group presented notably lower TG and TC levels but a considerably higher HDL-C level than the conventional group (all $P < 0.05$, Figure 5). However, no significant different was observed in the LDL-C level between the two groups and between before and after treatment.

DISCUSSION

IR plays a crucial role in the development of T2DM[17-19]. Primarily, IR is manifested with a decrease of insulin sensitivity in the body, which leads to the secretion of a large amount of insulin by the pancreas to maintain the stability of blood glucose, thus triggering hyperinsulinemia[20]. IR affects the efficiency of glucose intake in DM patients and further triggers metabolic disorders of glucose, fat and protein, which underlie the common pathogenesis of hypertension, dyslipidemia, coronary heart diseases and obesity[21-23]. Therefore, effectively improving IR is crucial for the treatment of T2DM and contributes to the prevention and treatment of related diseases.

This study evaluated the risk factors for IR in T2DM patients and found that BMI, TG, HDL-C, 25(OH)D_3, 2hPG, and HbA1c were the independent risk factors for IR. Previous studies also reported TG, HDL-C, 2hPG and HbA1c as risk factors for IR in T2DM patients[24,25]. We also investigated the effects of vitamin D supplementation on glucose and lipid metabolism in the patients with T2DM and IR. Vitamin D is a fat-soluble vitamin that is transformed into the active form 1,25$(OH)_2D_3$ through the action of the liver and kidney[26]. According to prior research[27], vitamin D is essential to stimulate insulin secretion and maintain normal glucose tolerance under physiological conditions. Vitamin D deficiency can lead to a decrease in β cell insulin secretion, exacerbating IR and increasing the risk of DM[28]. By binding to the receptor, vitamin D regulates the expression of immune- and apoptosis- related genes in pancreatic tissues, protecting islet β cells and weakening apoptosis[29]. In addition, vitamin D can affect insulin secretion and release by regulating intracellular calcium levels, and further improves insulin sensitivity by regulating insulin receptor expression and glucose transport sensitivity[30]. In this study, BMI was found to be an independent risk factor for IR in T2DM patients [31]. A previous study[32] also reported that the increase of BMI was associated with the increased risk of IR, especially for those of overweight and obesity. A high BMI is often indicative of excessive body fat, especially visceral fat. Adipocytes can secrete pro-inflammatory factors and hormones that may interfere with insulin signal transduction, thus leading to IR.

Recent studies[33,34] have revealed that approximately 50% of T2DM patients have vitamin D deficiency, and the level of vitamin D impacts insulin secretion, sensitivity and resistance. In this study, after vitamin D supplementation, the joint group showed more notable decreases in 2hPG, FBG, HbA1c and a more notable increase in 25(OH)D_3 than the conventional group. In addition, the joint group presented lower TG and TC levels but a higher HDL-C level than the conventional group. These results indicate that vitamin D supplementation can improve the glucose and lipid metabolism in T2DM patients with IR. We believe this is mainly because vitamin D can improve IR and insulin sensitivity, posing a positive effect on glucose metabolism. By increasing the expression of insulin receptor and promoting glucose transport, vitamin D is helpful to reduce blood glucose level and alleviate the glucose metabolic disorder in T2DM patients. In addition, vitamin D also has a regulatory effect on lipid metabolism. It can lower the level of inflammatory factors released by adipocytes, thus improving IR. Moreover, vitamin D can regulate the adipohormone secreted by adipocytes, promote the oxidation of fatty acids, and help to lower the blood lipid level[35,36].

However, the study still has some limitations. Firstly, the long-term prognosis of patients was followed up in this study, so whether vitamin D supplementation has a long-term efficacy still needs to be further studied. Secondly, this is a single-center study with limited participants, which may lead to bias in the results. We hope to carry out further clinical

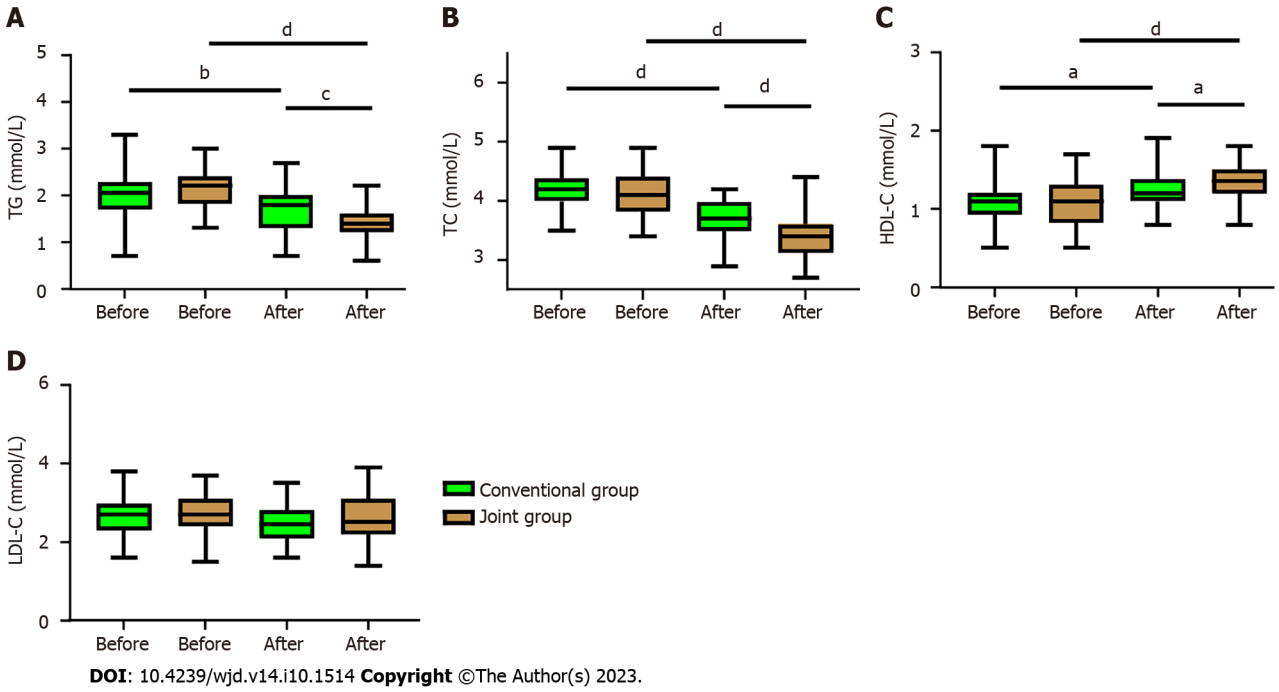

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Figure 5 Comparison of lipid metabolism index in type 2 diabetes mellitus patients with insulin resistance before and after the treatment.
A: Comparison of triglyceride between the joint group and the conventional group; B: Comparison of total cholesterol between the joint group and the conventional group; C: Comparison of high-density lipoprotein-cholesterol between the joint group and the conventional group; D: Comparison of low-density lipoprotein-cholesterol between the joint group and the conventional group. TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$, $^{d}P < 0.0001$.

experiments in future to verify and improve the research conclusions.

CONCLUSION

Patients with IR exhibit significant abnormalities in glucose and lipid metabolism parameters compared to the non-insulin resistant group. Logistic regression analysis revealed that 25(OH)D_3 is an independent risk factor influencing IR. Supplementation of vitamin D has been shown to improve glucose and lipid metabolism in patients with IR and T2DM.

ARTICLE HIGHLIGHTS

Research background

This study was founded on the understanding of the crucial role of insulin resistance (IR) in the development of type 2 diabetes mellitus (T2DM). A lack of insulin sensitivity in the body leads to increased insulin secretion by the pancreas, triggering hyperinsulinemia, and affecting the efficiency of glucose intake, ultimately leading to metabolic disorders.

Research motivation

Given that these metabolic disorders underlie several other conditions such as hypertension, dyslipidemia, coronary heart diseases, and obesity, finding effective ways to improve IR is a critical part of treating T2DM and preventing related diseases. The motivation was to evaluate risk factors for IR and study the effects of vitamin D supplementation on glucose and lipid metabolism in patients with T2DM and IR.

Research objectives

To identify independent risk factors for IR in T2DM patients and investigate the effects of vitamin D supplementation on their glucose and lipid metabolism.

Research methods

The study carried out a comprehensive evaluation of risk factors for IR in T2DM patients, including parameters like BMI, TG, HDL-C, 25(OH)D_3, 2hPG, and HbA1c. Furthermore, it explored the impact of vitamin D supplementation on glucose and lipid metabolism in T2DM patients with IR.

Research results

The study found that BMI, TG, HDL-C, 25(OH)D_3, 2hPG, and HbA1c were independent risk factors for IR. After vitamin D supplementation, the test group showed notable decreases in 2hPG, FBG, HbA1c and a notable increase in 25-hydroxyvitamin D (25(OH)D_3), as well as lower TG and TC levels but higher HDL-C level than the control group.

Research conclusions

Patients with IR exhibit significant abnormalities in glucose and lipid metabolism parameters compared to the non-insulin-resistant group. The study concluded that 25(OH)D_3 is an independent risk factor influencing IR and supplementation of vitamin D has been shown to improve glucose and lipid metabolism in patients with IR and T2DM.

Research perspectives

While promising, the study has some limitations including the need for long-term patient prognosis and the possibility of bias due to it being a single-center study with limited participants. Further clinical experiments are needed to verify and improve the research conclusions, especially to assess the long-term efficacy of vitamin D supplementation.

FOOTNOTES

Author contributions: Zhan XR conceived and designed the study; Sun LJ, Lu JX, Li XY, and Zheng TS collected the data; Sun LJ and Zhan XR analyzed the findings; Sun LJ and Lu JX wrote the manuscript; and all authors revised and approved the final version.

Institutional review board statement: This study was reviewed and approved by the Ethical Committees of the First Affiliated Hospital of Harbin Medical University.

Informed consent statement: All patient data obtained, recorded, and managed only used for this study, and all patient information are strictly confidential, without any harm to the patient, so the informed consent was waived by the Ethics Committee of First Affiliated Hospital of Harbin Medical University.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Effect of individualized nutrition interventions on clinical outcomes of pregnant women with gestational diabetes mellitus

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Abstract

BACKGROUND

Gestational diabetes mellitus (GDM) can lead to excessive pregnancy weight gain (PWG), abnormal glucolipid metabolism, and delayed lactation. Therefore, it is necessary to provide appropriate and effective interventions for pregnant women with GDM.

AIM

To clarify the effects of individualized nutrition interventions on PWG, glucolipid metabolism, and lactation in pregnant women with GDM.

METHODS

The study population consisted of 410 pregnant women with GDM who received treatment at the Northern Jiangsu People's Hospital of Jiangsu Provinceand Yangzhou Maternal and Child Health Hospital between December 2020 and December 2022, including 200 who received routine in-terventions [control (Con) group] and 210 who received individualized nutrition interventions [research (Res) group]. Data on PWG, glucolipid metabolism [total cholesterol, (TC); triglycerides (TGs); fasting blood glucose (FPG); glycosylated hemoglobin (HbA1c)], lactation time, perinatal complications (cesarean section, premature rupture of

membranes, postpartum hemorrhage, and pregnancy-induced hypertension), and neonatal adverse events (premature infants, fetal macrosomia, hypo-glycemia, and respiratory distress syndrome) were collected for comparative analysis.

RESULTS

The data revealed markedly lower PWG in the Res group *vs* the Con group, as well as markedly reduced TG, TC, FPG and HbA1c levels after the intervention that were lower than those in the Con group. In addition, obviously earlier lactation and statistically lower incidences of perinatal complications and neonatal adverse events were observed in the Res group.

CONCLUSION

Individualized nutrition interventions can reduce PWG in pregnant women with GDM, improve their glucolipid metabolism, and promote early lactation, which deserves clinical promotion.

Key Words: Individualized nutrition interventions; Gestational diabetes mellitus; Pregnancy weight gain; Glycolipid metabolism; Lactation time

Core Tip: Gestational diabetes mellitus (GDM) will increase the risk of perinatal complications and neonatal adverse events. This study mainly analyzed the clinical application of individualized nutrition interventions in pregnant women with GDM from the perspective of pregnancy weight gain, glycolipid metabolism, lactation time, perinatal complications, and neonatal adverse events, aiming to provide an optimal choice for the pregnancy management of pregnant women with GDM.

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INTRODUCTION

Gestational diabetes mellitus (GDM), a condition of abnormal glucose tolerance that occurs during pregnancy, is related to glucose homeostasis imbalance due to pancreatic β cell dysfunction[1,2]. Evidence has linked GDM to perinatal complications in pregnant women and adverse events in newborns, as well as an increased risk of developing type 2 diabetes, obesity and cardiovascular diseases in both mothers and infants[3]. According to relevant epidemiological data, the incidence of GDM is as high as 42%, and the pregnancy and delivery expenses of mothers with GDM are nearly 7000 RMB higher than those of mothers without GDM[4,5]. In addition, women with GDM often suffer from excessive pregnancy weight gain (PWG), abnormal glucolipid metabolism, and delayed lactation[6-8]. Therefore, providing appropriate and effective intervention measures for pregnant women with GDM has great clinical implications for improving maternal and infant outcomes.

Lifestyle interventions have been indicated to control blood glucose (BG) in 70%-85% of mothers with GDM[9]. The clinical application value of individualized nutrition interventions as a lifestyle intervention in pregnant women with GDM needs further exploration. The intervention program introduced in this study included nutrition guidance during pregnancy, exercise guidance, BG monitoring, lactation massage and guidance, *etc.*, with the patient-centered intervention plan specified depending on the patient's physical condition, aiming to achieve the best outcome and service experience for both the mother and child[10,11]. Nutrition programs tailored to pregnant women's individual conditions have also shown substantial benefits for maternal and neonatal clinical outcomes[12]. In addition, exercise during pregnancy reduces not only maternal PWG but also the risk of GDM, according to a randomized controlled trial[13]. As reported by Rasmussen *et al*[14], exercise during pregnancy can help pregnant women with GDM better control their BG levels and help the body to regulate glucose and insulin levels. Another report by Park *et al*[15] suggests that giving pregnant women with GDM lactation massage and guidance can promote maternal and infant health and prevent related complications by improving breastfeeding methods.

This study conducted an in-depth analysis of the clinical application of individualized nutrition interventions in pregnant women with GDM from the perspectives of PWG, glycolipid metabolism, lactation, perinatal complications, neonatal adverse events, *etc.*, aiming to provide a new choice for the management of mothers with GDM.

MATERIALS AND METHODS

Patient information

The study participants were 410 pregnant women with GDM selected between December 2020 and December 2022. Among these women, 200 were included in the control (Con) group and received routine interventions, and 210 were included in the research (Res) group and received individualized nutrition interventions. The two groups of pregnant women were clinically comparable, with no significant difference in general data ($P > 0.05$).

Eligibility and exclusion criteria

All the included patients met the diagnostic criteria for GDM, with singleton pregnancy and no history of diabetes before pregnancy.

Pregnant women with diabetes confirmed before pregnancy, overt diabetes diagnosed during gestation, the use of insulin therapy during pregnancy, pregnancy-induced hypertension, heart disease, threatened abortion or other high-risk pregnancies were excluded, as well as those with serious heart, lung, kidney, endocrine system and other medical conditions.

Methods

The Con group received routine interventions, including routine nutrition guidance, reduced fat consumption, increased fiber intake, and appropriate vitamin supplementation. In addition, the pregnant women were advised to eat multiple small meals and control their body mass and BG levels and were encouraged to exercise properly.

The Res group received the following individualized nutrition intervention measures: (1) Nutrition guidance during pregnancy: After gaining a comprehensive understanding of the mother's daily diet and specific condition, a professional dietitian developed an individualized nutrition plan according to her body mass index (BMI) and energy demands, with the calories needed reasonably distributed. Meals per day were divided into breakfast, an extra meal, lunch, an extra meal, dinner, and an extra meal, and the proportion of calories in each meal was strictly controlled at 15%-30%, 5%, 30%, 10%, 25%-30%, and 10%-15%, respectively, with all extra meals arranged 2.5 h to 3 h after the main meal; (2) Exercise guidance during pregnancy: After understanding the weight gain of the patients, the medical staff communicated with the patients and their families to encourage the pregnant women to continue to exercise (walking, yoga, aerobics, *etc.*), set reasonable exercise times and amounts, and be aware of the importance of exercise management during pregnancy. Exercise was generally carried out 30 min after meals and was not done on an empty stomach; (3) BG monitoring: The 2-h postprandial BG level of pregnant women should be controlled at 6.7 mmol/L and the fasting BG (FPG) level should be at 5.1 mmol/L. Insulin was used if the BG level still did reach the standard after two weeks of the individualized nutrition intervention; and (4) Lactation massage and guidance: Patients were given basic massage of the breast, lobule of the breast, acinus, and mammary ducts, as well as targeted massage to alleviate the corresponding symptoms of galactostasis, breast induration, short flat depression of the nipple and so on. At the same time, mothers were given guidance on breastfeeding to strengthen their confidence in breastfeeding and help them master the correct breastfeeding methods, breastfeeding skills, and preservation methods.

Outcome measures

The PWG of both cohorts was recorded, and glucolipid metabolism indices such as total cholesterol (TC), triglyceride (TG), FPG, and glycosylated hemoglobin (HbA1c) levels were determined before and after the intervention. The lactation initiation time of all patients was recorded. Maternal perinatal complications (*e.g.*, cesarean section, premature rupture of membranes, postpartum hemorrhage and pregnancy-induced hypertension) and the occurrence of neonatal adverse reactions (*e.g.*, premature birth, macrosomia, hypoglycemia and respiratory distress syndrome) were observed and recorded in both cohorts, and the corresponding incidence was calculated for evaluation.

Statistics and methods

In this study, the number of cases/percentage (n/%) is used to represent the counting data, and the χ^2 test was used for between-group comparisons. For measurement data described in the form of ($x \pm s$), between-group and intragroup (before and after the intervention) comparisons were performed using the t test and the paired t test, respectively. Data were statistically analyzed by SPSS 19.0 software, and statistical significance was considered at the $P < 0.05$ Level.

RESULTS

Baseline data of pregnant women with GDM in the two groups

The age, gestational age, prepregnancy BMI, primiparity (yes/no), and educational level of the two cohorts were analyzed, and no significant difference was identified in the above baseline data between the groups ($P > 0.05$), indicating clinical comparability (Table 1).

Influence of individualized nutrition interventions on PWG in pregnant women with GDM

By analyzing PWG in the two groups, it was found that the PWG was significantly lower in the Res group than in the Con group ($P < 0.05$) (Figure 1).

Table 1 Baseline data of the two groups of pregnant women with gestational diabetes mellitus

Factors	Control group (*n* = 200)	Research group (*n* = 210)	χ^2/t value	*P* value
Age (yr)	29.66 ± 4.94	29.44 ± 6.07	0.401	0.688
Gestational age (wk)	38.90 ± 5.16	39.16 ± 5.32	0.502	0.616
Pre-pregnancy BMI (kg/m^2)	20.10 ± 2.27	20.36 ± 2.38	1.131	0.259
Primiparity (yes/no)			0.995	0.318
Yes	119 (59.50)	135 (64.29)		
No	81 (40.50)	75 (35.71)		
Educational level			0.432	0.511
Junior college or below	104 (52.00)	116 (55.24)		
Bachelor degree or above	96 (48.00)	94 (44.76)		

BMI: Body mass index.

Table 2 Perinatal complications in the two groups of pregnant women with gestational diabetes mellitus

Factors	Control group (*n* = 200)	Research group (*n* = 210)	χ^2	*P* value
Cesarean section	14 (7.00)	7 (3.33)	-	-
Premature rupture of membranes	7 (3.50)	4 (1.90)	-	-
Postpartum hemorrhage	10 (5.00)	0 (0.00)	-	-
Pregnancy induced hypertension	20 (10.00)	6 (2.86)	-	-
Total	51 (25.50)	17 (8.10)	22.430	< 0.001

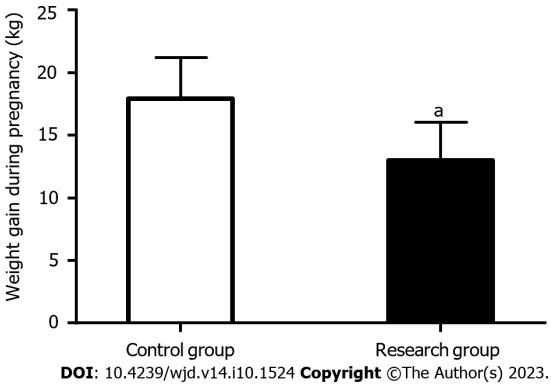

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Figure 1 The influence of individualized nutrition interventions on pregnancy weight gain in pregnant women with gestational diabetes mellitus. $^aP < 0.01$ *vs.* control group.

Influence of individualized nutrition interventions on glucolipid metabolism in pregnant women with GDM

We also analyzed the glucolipid metabolism levels of both groups of pregnant women with GDM. No evident intergroup differences were identified in preintervention TG, TC, FPG, and HbA1c ($P > 0.05$) levels; these indices of both groups were significantly reduced after the intervention ($P < 0.05$), with even lower values in the Res group ($P < 0.05$) (Figure 2).

Impact of individualized nutrition interventions on lactation in mothers with GDM

Statistical analysis of the lactation initiation time showed markedly earlier lactation in the Res group than in the Con group, with statistical significance ($P < 0.05$) (Figure 3).

Influence of individualized nutrition interventions on perinatal complications in mothers with GDM

Through the comparative analysis of perinatal complications (cesarean section, premature rupture of membranes, postpartum hemorrhage and pregnancy-induced hypertension) in mothers with GDM, we found an overall incidence of 8.10% in the Res group and 25.50% in the Con group, with statistical significance ($P < 0.05$) (Table 2).

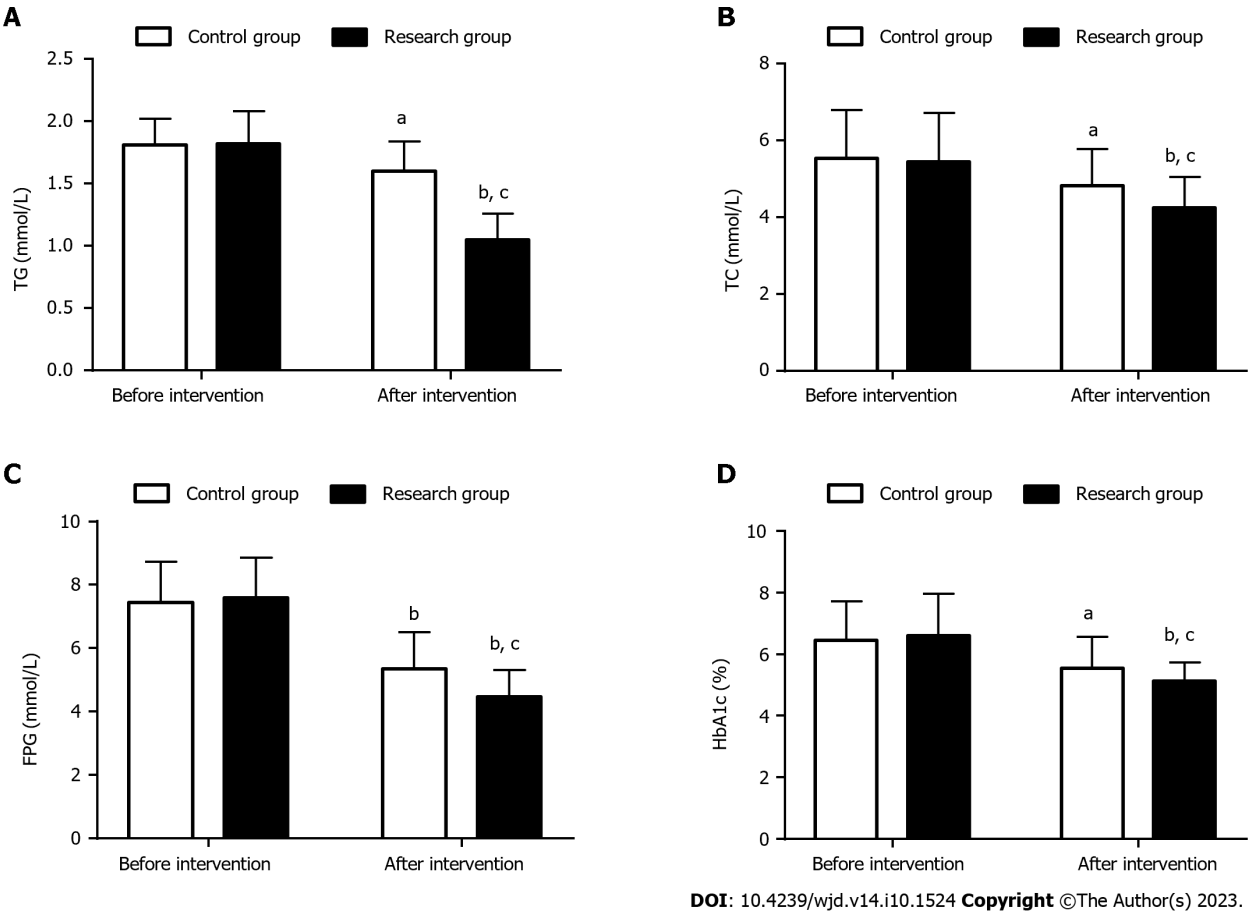

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Figure 2 Influence of individualized nutrition interventions on glucolipid metabolism in pregnant women with gestational diabetes mellitus. A: Pre- and postintervention total cholesterol levels in both groups of pregnant women with gestational diabetes mellitus (GDM); B: Pre- and postintervention triglyceride levels in both groups of pregnant women with GDM; C: Pre- and postintervention fasting blood glucose levels in both groups of pregnant women with GDM; D: Pre- and postintervention glycosylated hemoglobin levels in both groups of pregnant women with GDM. $^{a}P < 0.05$ *vs.* before treatment; $^{b}P < 0.01$ *vs.* before treatment; $^{c}P < 0.05$ *vs.* control group. FPG: Fasting blood glucose; HbA1c: Glycosylated hemoglobin; TC: Total cholesterol; TG: Triglyceride.

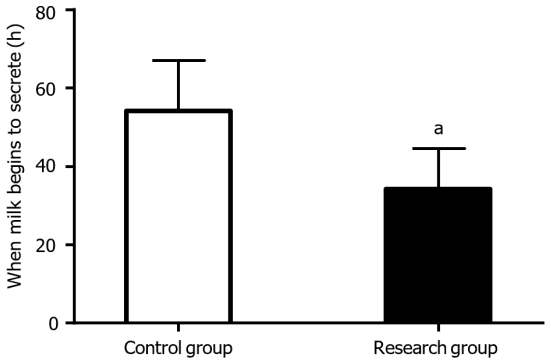

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Figure 3 Impact of individualized nutrition interventions on lactation time in pregnant women with gestational diabetes mellitus. $^{a}P < 0.01$ *vs* control group.

Effect of individualized nutrition interventions on adverse events in the neonates of mothers with GDM

According to statistics, the incidence of adverse events in neonates born to mothers with GDM in the Res group was 9.05%, which was markedly lower than that of 28.50% in the Con group ($P < 0.05$) (Table 3).

Table 3 Adverse events in neonates born to mothers with gestational diabetes mellitus in the two groups

Factors	Control group (*n* = 200)	Research group (*n* = 210)	χ^2	*P* value
Premature infant	18 (9.00)	12 (5.71)	-	-
Macrosomia	15 (7.50)	3 (1.43)	-	-
Hypoglycemia	11 (5.50)	0 (0.00)	-	-
Respiratory distress syndrome	13 (6.50)	4 (1.90)	-	-
Total	57 (28.50)	19 (9.05)	25.670	< 0.001

DISCUSSION

GDM, as a maternal metabolic disorder, not only complicates the pregnancy process but also has long-term negative effects on the newborn[16]. It is known that developing fetuses rely primarily on glucose from the placenta for energy. The abnormal increase in glucose levels due to GDM can promote fetal insulin secretion, resulting in hypertrophy of tissues such as the myocardium, fat, and liver (manifested as macrosomia), which may adversely influence maternal and infant outcomes[17]. To minimize the negative impact of GDM on maternal and infant outcomes, an in-depth analysis of reasonable, effective, and reliable intervention methods for the treatment of GDM was the focus of this study.

Under individualized nutrition interventions, individualized intervention programs were formulated based on the pregnant women's daily diets, specific illnesses, BMI, energy demands, weight gain, BG levels, and breasts, which provided support for mothers in all aspects of pregnancy while taking into account the control and maintenance of the BG level and body mass[18,19]. This intervention model has also been shown to be effective in reducing frailty and enhancing physical performance in older adults and in improving the long-term prognosis of colorectal cancer patients [20,21]. In this study, we compared the effects of individualized nutrition interventions *vs* routine interventions. The PWG was statistically lower in the Res group than in the Con group, indicating a more significant suppression of PWG and a better ability to control weight within the healthy range in pregnant women with GDM by individualized nutritional interventions. Ferrara *et al*[22] reported that individualized nutrition interventions could reduce excessive PWG in pregnant women by improving their health behaviors and modulating insulin resistance markers, similar to our findings. The statistically lower postinterventional TG, TC, FPG, and HbA1c levels in the Res group suggested that individualized nutrition interventions had a more significant effect on regulating and improving glucolipid metabolism in mothers with GDM. In the research of Fard *et al*[23], individualized nutrition interventions significantly reduced TG, TC, and high-density lipoprotein cholesterol levels in pregnant women while effectively modulating the body's blood lipids. There is also evidence indicating the potent inhibition action of individualized nutrition interventions against FPG, HbA1c and other BG indices and its effective control of BG in pregnant women with GDM 42 d after delivery[24], which supports our findings. An earlier onset of lactation was also observed in the Res group, suggesting that individualized nutrition interventions have a positive effect on lactation in pregnant women with GDM. In terms of maternal and infant outcomes, the Res group had a lower incidence of maternal complications (*e.g.*, cesarean section, premature rupture of membranes, postpartum hemorrhage and pregnancy-induced hypertension) and a markedly reduced incidence of neonatal adverse events (*e.g.*, premature birth, macrosomia, hypoglycemia and respiratory distress syndrome) than the Con group. This indicates the effectiveness of individualized nutrition interventions in improving maternal and infant outcomes compared with routine interventions and the ability to effectively prevent maternal complications and neonatal adverse events. In the study by Li *et al*[25], individualized nutrition interventions were effective in reducing the incidence of complications such as macrosomia and hyperbilirubinemia in older pregnant women, consistent with our research results.

Some limitations of this study need to be mentioned: (1) This study had a limited sample size; the sample size should be increased in future studies to better understand more information; (2) This was a single-center study; it would be beneficial if the scope of sample inclusion could be expanded to multiple centers, which would help eliminate potential information collection bias; and (3) The analysis of influencing factors for perinatal complications and neonatal adverse events could be supplemented to help further understand potential approaches to risk reduction in this area. In the future, research will be gradually improved based on the above recommendations.

CONCLUSION

Conclusively, individualized nutrition interventions are of higher clinical value than routine interventions in pregnant women with GDM, as they not only effectively control PWG, improve glucolipid metabolism, and promote lactation but also exert a significant preventive effect on maternal complications and neonatal adverse events, which is clinically beneficial.

ARTICLE HIGHLIGHTS

Research background

Gestational diabetes mellitus (GDM) is a kind of impaired glucose tolerance during pregnancy. Women with GDM often have problems such as excessive pregnancy weight gain (PWG), abnormal glucolipid metabolism, and delayed lactation.

Research motivation

Appropriate and effective intervention measures for pregnant women with GDM are of great value and clinical significance to improve maternal and infant outcomes.

Research objectives

This paper intends to determine the effects of individualized nutrition interventions on PWG, glucolipid metabolism, and lactation in pregnant women with GDM.

Research methods

The study population constituted 410 pregnant women with GDM who received treatment at the Northern Jiangsu People's Hospital of Jiangsu Province between December, 2018 and December, 2022, including 200 cases receiving routine interventions [control (Con) group] and 210 cases receiving individualized nutrition interventions [research (Res) group]. PWG, glucolipid metabolism [total cholesterol (TG); triglyceride (TC); fasting blood glucose (FPG); glycosylated hemoglobin (HbA1c)], lactation time, perinatal complications, and neonatal adverse events were collected for comparative analysis.

Research results

A markedly lower PWG and obviously reduced TG, TC, FPG and HbA1c were determined in the Res *vs* the Con after intervention. In addition, obviously earlier lactation and statistically lower incidences of perinatal complications and neonatal adverse events were determined in the Res.

Research conclusions

Individualized nutrition interventions can reduce PWG in pregnant women with GDM, improve their glucolipid metabolism, and promote early lactation, which deserves clinical promotion.

Research perspectives

This study verified the clinical advantages of individualized nutrition interventions for pregnant women with GDM from the perspectives of PWG, glycolipid metabolism, lactation, perinatal complications, and neonatal adverse events, which can provide a new option for the management of mothers with GDM.

FOOTNOTES

Author contributions: Luo JY and Chen LG contributed equally to this work; Luo JY and Chen LG designed the research study; Yan M, Mei YJ, Cui YQ and Jiang M contributed reagents and analytic tools; Luo JY, Chen LG and Jiang M analyzed the data; Luo JY and Chen LG wrote the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Medical Ethics Committee of Northern Jiangsu People's Hospital of Jiangsu Province (Approval No. 2023ky150).

Informed consent statement: This is a retrospective study, and since the analysis used anonymous clinical data approved by the Ethics Committee of Northern Jiangsu People's Hospital of Jiangsu Province, the need for informed consent from subjects or guardians was waived.

Conflict-of-interest statement: The authors declare no competing interests.

Data sharing statement: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Effects of insulin aspart and metformin on gestational diabetes mellitus and inflammatory markers

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Abstract

BACKGROUND

Gestational diabetes mellitus (GDM) refers to hyperglycemia caused by insulin resistance or insufficient insulin secretion during pregnancy. Patients with GDM have a high risk of pregnancy complications, which can adversely affect both maternal and fetal health. Therefore, early diagnosis, treatment and monitoring of GDM are essential. In recent years, a new treatment scheme represented by insulin aspart combined with metformin has received increasing attention.

AIM

To explore the effects of insulin aspart combined with metformin on patients with GDM and inflammatory markers.

METHODS

From April 2020 to September 2022, 124 patients with GDM in Sanya Women and Children's Hospital Managed by Shanghai Children's Medical Center were collected and analyzed retrospectively. The control group (CG) comprised 62 patients treated with insulin aspart alone, and 62 patients treated with insulin aspart and metformin formed the observation group (OG). Before and after treatment, improvement of blood-glucose-related indexes [fasting blood glucose (FBG), 2-h postprandial glucose (2h PG) and hemoglobin A1c (HbA1c)], serum related factor [serum homocysteine (Hcy)], serum inflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-6 and C-reactive protein (CRP)] were compared between the two groups. The clinical efficacy, adverse pregnancy outcomes and incidence of pregnancy complications were compared between the two groups.

RESULTS

After treatment, the levels of FBG, 2h PG, HbA1c, Hcy, TNF-α, IL-6 and CRP in

both groups were significantly decreased ($P < 0.05$), and the levels of FBG, 2h PG, HbA1c, Hcy, TNF-α, IL-6 and CRP in the OG were lower than in the CG ($P < 0.05$). The total clinical effectiveness in the OG was higher than that in the CG ($P < 0.05$). The total incidence of adverse pregnancy outcomes and complications in the OG was significantly lower than in the CG ($P < 0.05$).

CONCLUSION

Insulin aspart combined with metformin are effective for treatment of GDM, which can reduce blood-glucose-related indexes, Hcy and serum inflammatory cytokines, and risk of adverse pregnancy outcomes and complications.

Key Words: Insulin aspart; Metformin; Gestational diabetes mellitus; Efficacy; Homocysteine; Tumor necrosis factor-α; Interleukin-6; C-reactive protein

Core Tip: This study investigated the clinical effect of insulin aspart combined with metformin on gestational diabetes mellitus and serum homocysteine (Hcy), tumor necrosis factor-α, interleukin-6 and C-reactive protein, which represents a novel aspect in the field. The combination of drugs significantly improved the condition of patients, reduced adverse pregnancy outcomes and incidence of adverse reactions, decreased blood-glucose-related indicators, Hcy, and serum inflammatory cytokine levels, and exhibited a high level of safety. These findings provide an important basis for the clinical application and popularization of this combination therapy.

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INTRODUCTION

Gestational diabetes mellitus (GDM) refers to different degrees of abnormal glucose metabolism that develops or is first found during pregnancy[1,2]. In recent years, with the change of life style and the fertility policy, the disease has shown a significant increasing trend[3]. It is reported that the incidence of GDM is 1%-14% globally and 1%-5% in China[4,5]. Although most parturients can return to normal after delivery, the risk of type II diabetes greatly increases[6]. If the patient is not treated in time, the disease can lead to various adverse pregnancy outcomes, such as fetal distress, fetal macrosomia, premature delivery, and abortion, and even endanger the life of the mother and baby. Therefore, the harm of GDM to the mother and newborn cannot be underestimated[7]. At present, the patients with GDM are treated with drugs, nutritional therapy, exercise therapy and blood sugar monitoring to keep their blood sugar in the normal range, thus reducing the complications to parturients and newborns, decreasing the perinatal mortality and improving adverse pregnancy outcome[8].

Insulin aspart is an analog of rapid-acting human insulin, and its activity is close to that of natural insulin. After subcutaneous injection, it can quickly help the body to ingest and utilize glucose in the blood, thus effectively maintaining the blood sugar level[9]. Insulin aspart takes effect faster and acts for a shorter time than soluble human insulin, so it should be injected immediately before meals. Studies have shown that insulin aspart is effective for treatment of GDM and pregestational diabetes, with stable control of blood sugar level and high safety[10]. Metformin is a biguanide hypoglycemic agent that mainly reduces blood sugar by inhibiting gluconeogenesis and glycogen decomposition and reducing the output of liver glucose[11]. In addition, metformin can improve the intake and utilization of glucose by muscle and adipose tissues, and can also play multiple roles in reducing body weight, improving insulin sensitivity and reducing insulin resistance[12]. Metformin can control the blood sugar level of parturients and newborns in the treatment of GDM, and reduce the risk of blood sugar, with a high level of safety[13]. Metformin has been widely used in clinical treatment, and has become the first choice to control blood sugar in overweight and obese patients with type II diabetes. Therefore, insulin aspart and metformin are potential effective drugs for the treatment of GDM.

However, the efficacy of the combination of the two drugs for treatment of GDM has not been systematically evaluated. Therefore, this study was designed to use insulin aspart and metformin for treatment of GDM, and explore the effect of the drug combination on patients and serum-related factors, to provide a reliable basis for clinical research.

MATERIALS AND METHODS

Clinical data

From April 2020 to September 2022, 124 patients with GDM in Sanya Women and Children's Hospital Managed by Shanghai Children's Medical Center were collected and analyzed retrospectively. The control group (CG) comprised 62 patients treated with insulin aspart alone, and the other 62 patients treated with insulin aspart and metformin formed the observation group (OG). This study was approved by the Ethics Committee of Sanya Women and Children's Hospital Managed by Shanghai Children's Medical Center.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients met the diagnostic criteria for GDM; GDM was diagnosed if fasting blood glucose (FBG) during pregnancy was ≥ 5.1 mmol/L, blood glucose after taking glucose for 1 h was ≥ 10.0 mmol/L, or blood glucose after taking glucose for 2 h was ≥ 8.5mmol/L; (2) Blood sugar could not be controlled by diet or exercise, so drugs were needed for intervention; (3) Patients gave informed and signed consent for voluntary participation; and (4) Clinical data were complete.

Exclusion criteria: (1) Patients with multiple pregnancies; (2) Patients with diabetes before pregnancy or a family history of diabetes; (3) Comorbid hepatic and renal insufficiency; (4) Comorbid pregnancy complications; (5) Comorbid mental or cognitive dysfunction; and (6) Allergic to the drugs in this study.

Therapeutic schemes

In both groups, patients were given routine health education on GDM, diet control and exercise guidance. The CG was treated with subcutaneous injection of insulin aspartate before dinner at an initial dose of 0.2-0.3 IU/kg once daily. The dose of insulin aspart was adjusted according to the patient's blood glucose regulation, and the maximum dose was not more than 30 IU/d. The OG was treated with insulin aspart at the same dose as in the CG, and the initial dose of metformin was 500 mg twice daily. The dose of metformin was adjusted according to the patient's blood glucose, and the maximum dose was not more than 2000 mg. In both groups, the drug treatment lasted until delivery.

Blood analysis

In the morning, 10 mL of median cubital vein blood was withdrawn from all patients after fasting for 8 h, and stored in three tubes. At 2 h after a meal, 4 mL of median elbow vein blood was withdrawn to detect the concentration of 2-h postprandial glucose (2h PG). An automatic biochemical analyzer was used to detect the blood-glucose-related indexes before and after treatment, including FBG, 2h PG and glycosylated hemoglobin (HbA1c). ELISA was used to detect serum-related factors [serum homocysteine (Hcy)] and serum inflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-6, and C-reactive protein (CRP)] before and after treatment.

Outcome measures

Primary outcome measures: improvement of blood-glucose-related indexes before and after treatment was compared between the two groups, including FBG, 2h PG and HbA1c. Hcy levels were compared between the two groups before and after treatment. Serum inflammatory cytokines, including TNF-α, IL-6 and CRP, were compared between the two groups before and after treatment. The clinical therapeutic effect was compared between the two groups. The evaluation criteria for efficacy are shown in Table 1. Total effective rate = (markedly effective + effective) × 100%/total number of patients. Secondary outcome measures: Baseline data of the two groups were compared. Adverse pregnancy outcomes and pregnancy complications were compared between the two groups.

Statistical analysis

SPSS 20.0 (Chicago, IL, United States) was applied to analyze the collected data. GraphPad Prism 8 (La Jolla, CA, United States) was applied to visualize the data. The data were analyzed by *t* test. Classified variables were compared by c^2 test. The difference was statistically significant with $P < 0.05$.

RESULTS

Comparison of baseline data

There was no significant difference between the two groups in age, gestational age, height, maternal category, or education level ($P > 0.05$) (Table 2).

Changes in blood-glucose-related indexes before and after treatment

Compared with before treatment, FBG, 2h PG and HbA1c levels were significantly decreased in both groups after treatment ($P < 0.05$). In addition, the intergroup comparison showed that the levels of FBG, 2h PG and HbA1c in the two groups had no significant change before treatment ($P > 0.05$), but after treatment, the levels of FBG, 2h PG and HbA1c in the OG were significantly lower than in the CG ($P < 0.05$) (Figure 1).

Table 1 Efficacy evaluation criteria

Efficacy grade	Evaluative criteria
Markedly effective	After treatment, clinical symptoms disappeared and blood sugar decreased obviously
Effective	After treatment, clinical symptoms improved and blood sugar decreased
Ineffective	After treatment, clinical symptoms did not improve, and blood sugar did not decrease, or even worsened

Table 2 Comparison of baseline data

Factors	CG (n = 62)	OG (n = 62)	χ^2	P value
Age, yr				
≤ 30	38	41	0.314	0.575
> 30	24	21		
Gestational age, yr				
≤ 30	34	30	0.517	0.472
> 30	28	32		
Maternal category				
Primipara	38	36	0.134	0.714
Multipara	24	26		
Educational level				
Below junior college	27	25	0.133	0.716
Junior college and above	35	37		

CG: Control group; OG: Observation group.

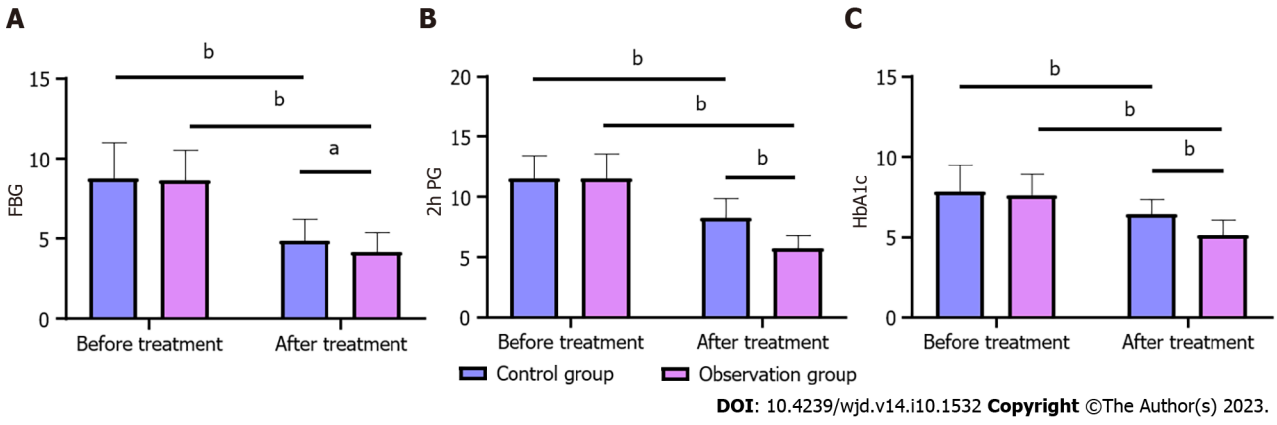

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Figure 1 Changes in blood-glucose-related indexes before and after treatment. A: Comparison of fasting blood glucose changes before and after treatment; B: Comparison of 2-h postprandial glucose changes before and after treatment; C: Comparison of glycosylated hemoglobin changes before and after treatment. $^{a}P < 0.01$; $^{b}P < 0.0001$. FBG: Fasting blood glucose; 2h PG: 2-h postprandial glucose; HbA1c: Hemoglobin.

Changes in serum-related factors before and after treatment

Compared with before treatment, Hcy level was significantly decreased in both groups after treatment ($P < 0.05$). In addition, the intergroup comparison showed that Hcy level in both groups had no significant change before treatment ($P > 0.05$), but after treatment, Hcy level in the OG was significantly lower than in the CG ($P < 0.05$) (Figure 2).

Changes in serum inflammatory cytokines before and after treatment

Compared with before treatment, TNF-α, IL-6 and CRP levels were significantly decreased in both groups after treatment ($P < 0.05$). In addition, the intergroup comparison showed that the levels of TNF-α, IL-6 and CRP in both groups had no significant change before treatment ($P > 0.05$), but after treatment, the levels of TNF-α, IL-6 and CRP in the OG were

Table 3 Comparison of therapeutic effect

Groups	CG (*n* = 62)	OG (*n* = 62)	χ^2	*P* value
Markedly effective	25 (40.32)	32 (51.61)		
Effective	19 (30.65)	25 (40.32)		
Ineffective	18 (29.03)	5 (8.06)		
Total effective rate	44 (70.97)	57 (91.94)	9.021	0.003

CG: Control group; OG: Observation group.

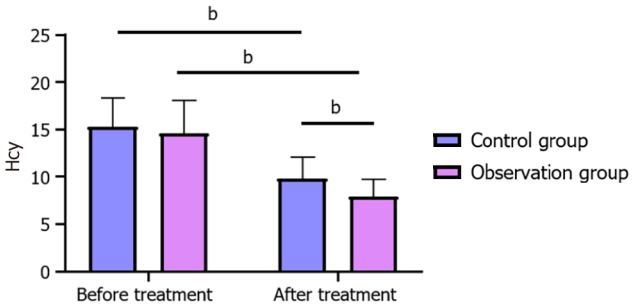

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Figure 2 Changes of homocysteine before and after treatment. $^bP < 0.0001$. Hcy: Homocysteine.

significantly lower than those in the CG ($P < 0.05$) (Figure 3).

Comparison of therapeutic effect

The total clinical effectiveness rate in the OG was significantly higher than in the CG ($P = 0.003$) (Table 3).

Comparison of adverse pregnancy outcomes and pregnancy complications

The total incidence of adverse pregnancy outcomes and pregnancy complications in the OG was significantly lower than in the CG ($P < 0.05$) (Tables 4 and 5).

DISCUSSION

Many hormones in pregnant women will change, and improper conditioning can lead to many complications. GDM is one of the more common complications[14,15]. Pregnant women in the second or third trimester produce a variety of insulin-resistant substances, such as placental lactogen, estrogen, progesterone, cortisol and placental insulinase, so that the sensitivity of pregnant women to insulin decreases with the increase of gestational age[16]. Pregnant women need more insulin to maintain blood glucose balance. For pregnant women with restricted insulin secretion, this physiological change cannot be compensated during pregnancy, which leads to an increase in blood sugar, thus aggravating the original diabetes or causing GDM[17]. GDM may be accompanied by three typical symptoms: Polydipsia, polyphagia and polyuria, and women may also experience blurred vision and abnormal touch, *etc*[18]. If GDM is not treated in time, it may have an impact on pregnant women and fetuses. GDM can lead to fetal macrosomia, fetal malformation, neonatal jaundice, neonatal respiratory distress syndrome, and increase fetal mortality[19,20]. Therefore, it is necessary to choose appropriate drugs and treat patients with GDM in time, so as to ensure the health and safety of parturients and fetuses.

At present, drugs are often used to control blood glucose. In the past, when patients were treated with biosynthetic human insulin, they were prone to hypoglycemia, so the therapeutic effect was not ideal. As a new type of rapid-acting insulin, insulin aspart has a short duration of action and peak time, takes effect rapidly, and reduces PG, which makes it a potential drug for treatment of GDM[21]. Studies have shown that insulin aspart combined with exercise diet can control the blood sugar level of patients with GDM, and ensure the health of parturients and fetuses[22]. However, long-term use of insulin can lead to resistance, thus reducing the control of blood sugar, so patients need to take corresponding hypoglycemic drugs to further control blood sugar. Metformin is a commonly used insulin-sensitizing agent that can improve insulin resistance and lower blood sugar[23]. Studies have shown that insulin aspart combined with metformin can control the blood sugar level of patients with GDM, reduce the adverse pregnancy outcomes of parturients and newborns, and play a positive role in clinical treatment[24]. In this study, insulin aspart plus metformin was used to treat patients with GDM. The total clinical effectiveness in the OG was higher than that in the CG, indicating that compared with single drug treatment, the two drugs complemented each other in combination, and significantly improved the

Table 4 Comparison of adverse pregnancy outcomes

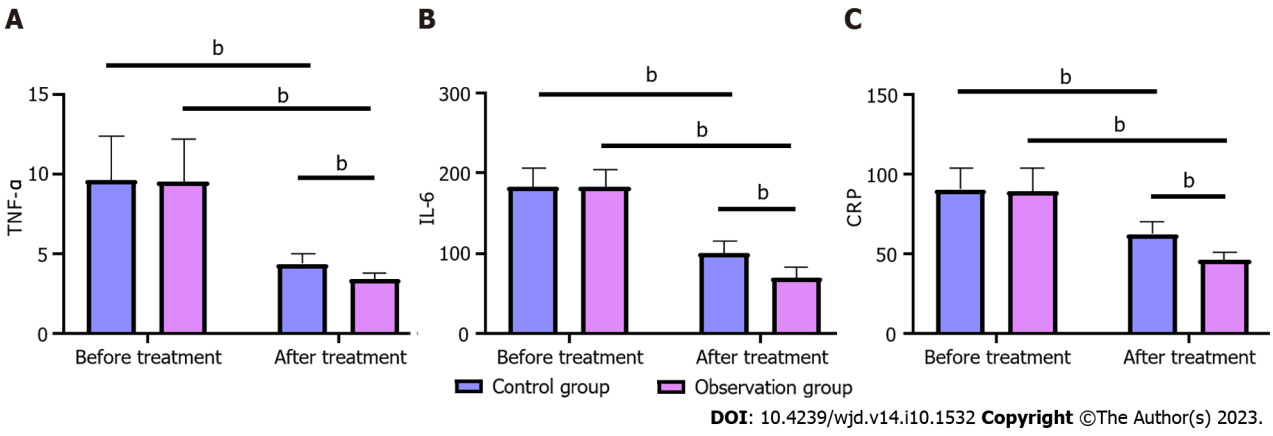
Groups	Adverse pregnancy outcomes			
	Premature delivery	Induced labor	Cesarean section	Total incidence rate
CG (n = 62)	5 (8.06)	3 (4.84)	31 (50.0)	39 (62.90)
OG (n = 62)	2 (3.23)	1 (1.61)	8 (12.90)	11 (18.33)
χ^2				26.270
P value				< 0.0001

CG: Control group; OG: Observation group.

Table 5 Comparison of pregnancy complications

Groups	Pregnancy complications				
	Pregnancy hypertension	Polyhydramnios	Hypoglycemia	Ketoacidosis	Total incidence rate
CG (n = 62)	5 (8.06)	5 (8.06)	4 (6.45)	2 (3.23)	16 (25.81)
OG (n = 62)	1 (1.61)	2 (3.23)	1 (1.61)	0	4 (6.45)
χ^2					8.585
P value					0.003

CG: Control group; OG: Observation group.



DOI: 10.4239/wjd.v14.i10.1532 **Copyright** ©The Author(s) 2023.

Figure 3 Changes in serum inflammatory cytokines before and after treatment. A: Comparison of tumor necrosis factor-α changes before and after treatment; B: Comparison of interleukin-6 changes before and after treatment; C: Comparison of C-reactive protein changes before and after treatment. $^bP < 0.0001$. TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; CRP: C-reactive protein.

therapeutic effect. The changes of blood-glucose-related indexes, Hcy and serum inflammatory cytokines were compared before and after treatment. Compared with before treatment, the levels of FBG, 2h PG, HbA1c, Hcy, TNF-α, IL-6 and CRP in both groups were significantly decreased, and the levels of FBG, 2h PG, HbA1c, Hcy, TNF-α, IL-6 and CRP in the OG were lower than those in the CG after treatment. These results indicated that the blood-glucose-related indexes, Hcy and serum inflammatory cytokines of patients receiving insulin aspart combined with metformin were significantly improved. There may be some limitations when insulin is used alone to treat GDM. Therefore, metformin combined with insulin aspart can play a significant role in lowering blood glucose and controlling blood glucose within a stable range.

At the end of the study, the adverse pregnancy outcomes and pregnancy complications were compared between the two groups. The total incidence of adverse pregnancy outcomes and pregnancy complications in the OG was lower than that in the CG, indicating that insulin aspart combined with metformin reduced the incidence of adverse pregnancy outcomes and complications in patients with GDM, with a high level of safety. In addition, some studies have shown that insulin aspart combined with metformin did not increase the risk of adverse reactions in patients GDM and fetal growth and development, and had good high safety, which is similar to our study[25].

In this study, insulin aspart combined with metformin controlled blood glucose level in patients with GDM. However, there were still some limitations to this study. First, this was a retrospective study with a small sample, so it was not as uniform as a randomized controlled trial. Second, the patients were not followed up in this study, so the long-term prognosis of the parturients and fetuses was not clear. Therefore, we hope to carry out follow-up studies in the future, so as to improve our conclusions.

CONCLUSION

Insulin aspart combined with metformin was effective in the treatment of GDM, which reduced blood-glucose-related indexes, Hcy and serum inflammatory cytokines, and reduced the risk of adverse pregnancy outcomes and complications during pregnancy. It is safe and worthy of clinical application and promotion.

ARTICLE HIGHLIGHTS

Research background

Gestational diabetes mellitus (GDM) is a type of hyperglycemia during pregnancy, which requires timely diagnosis, treatment and monitoring to avoid negative effects on maternal and infant health. In order to improve the therapeutic effect of patients with GDM, a new combination drug regimen has received extensive attention in the past few years.

Research motivation

The study was designed to investigate the effect of insulin aspart combined with metformin on inflammatory cytokine levels and overall improvement of patients with GDM. By studying the therapeutic effect and pharmacological mechanism of this new combination drug regimen, it can provide a reference for the precise treatment of patients with GDM, and a scientific basis for the protection of high-risk groups during pregnancy.

Research objectives

This study aimed to explore the efficacy of insulin aspart combined with metformin in treating GDM, and evaluate the effect of combined medication on lowering blood glucose level, and improving inflammatory response and metabolic disorder. The study revealed the advantages and limitations of the combined therapy regimen in clinical application, thus providing a scientific reference for future improvement of treatment strategies for GDM.

Research methods

This study was designed to retrospectively analyze 124 patients with GDM over a period of 2 years, divide them into two groups according to different treatment methods for analysis and comparison, and discuss the differences in blood-glucose-related indexes, serum-related factors, inflammatory cytokines, adverse pregnancy outcomes and pregnancy complications of patients with different treatment methods.

Research results

Insulin aspart combined with metformin can improve blood-glucose-related indexes (fasting blood glucose, 2-h postprandial glucose, glycosylated hemoglobin), serum-related factor (homocysteine) and serum inflammatory cytokines (tumor necrosis factor-α, interleukin-6, C-reactive protein) of patients, effectively reduce the incidence of adverse pregnancy outcomes and complications, and have a high level of safety.

Research conclusions

We studied the effectiveness of combined therapy for treating GDM and made breakthroughs in the treatment plan for this disease. These research achievements will help to more accurately determine the treatment plan for patients and promote the further development of the prevention and treatment of GDM and its complications.

Research perspectives

In follow-up studies, we hope to increase the sample size, extend the study duration, conduct follow-up, and explore the long-term prognosis of this combination therapy for both mothers and fetuses, thus improving our conclusions.

FOOTNOTES

Author contributions: Wang Y and Song M contributed equally to this study. Wang Y designed the research; Song M performed the research; Wang Y and Qi BR analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by Sanya Women and Children's Hospital Managed by Shanghai Children's Medical Center.

Informed consent statement: All patients have signed informed consent forms.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: According to the institutional policy, data for this study can be obtained from the corresponding author upon request.

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ORIGINAL ARTICLE

Retrospective Study

Establishment and evaluation of a risk prediction model for gestational diabetes mellitus

Qing Lin, Zhuan-Ji Fang

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Grade C (Good): C
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Abstract

BACKGROUND

Gestational diabetes mellitus (GDM) is a condition characterized by high blood sugar levels during pregnancy. The prevalence of GDM is on the rise globally, and this trend is particularly evident in China, which has emerged as a significant issue impacting the well-being of expectant mothers and their fetuses. Identifying and addressing GDM in a timely manner is crucial for maintaining the health of both expectant mothers and their developing fetuses. Therefore, this study aims to establish a risk prediction model for GDM and explore the effects of serum ferritin, blood glucose, and body mass index (BMI) on the occurrence of GDM.

AIM

To develop a risk prediction model to analyze factors leading to GDM, and evaluate its efficiency for early prevention.

METHODS

The clinical data of 406 pregnant women who underwent routine prenatal examination in Fujian Maternity and Child Health Hospital from April 2020 to December 2022 were retrospectively analyzed. According to whether GDM occurred, they were divided into two groups to analyze the related factors affecting GDM. Then, according to the weight of the relevant risk factors, the training set and the verification set were divided at a ratio of 7:3. Subsequently, a risk prediction model was established using logistic regression and random forest models, and the model was evaluated and verified.

RESULTS

Pre-pregnancy BMI, previous history of GDM or macrosomia, hypertension, hemoglobin (Hb) level, triglyceride level, family history of diabetes, serum ferritin, and fasting blood glucose levels during early pregnancy were de-

termined. These factors were found to have a significant impact on the development of GDM ($P < 0.05$). According to the nomogram model's prediction of GDM in pregnancy, the area under the curve (AUC) was determined to be 0.883 [95% confidence interval (CI): 0.846-0.921], and the sensitivity and specificity were 74.1% and 87.6%, respectively. The top five variables in the random forest model for predicting the occurrence of GDM were serum ferritin, fasting blood glucose in early pregnancy, pre-pregnancy BMI, Hb level and triglyceride level. The random forest model achieved an AUC of 0.950 (95%CI: 0.927-0.973), the sensitivity was 84.8%, and the specificity was 91.4%. The Delong test showed that the AUC value of the random forest model was higher than that of the decision tree model ($P < 0.05$).

CONCLUSION

The random forest model is superior to the nomogram model in predicting the risk of GDM. This method is helpful for early diagnosis and appropriate intervention of GDM.

Key Words: Gestational diabetes mellitus; Prediction model; Model evaluation; Random forest model; Nomograms; Risk factor

Core Tip: Gestational diabetes mellitus (GDM) is a common pregnancy complication, which has an important impact on maternal and child health. Early prediction of GDM can result in timely interventions in patients and improve pregnancy outcomes. This study examined various risk factors associated with GDM and established and compared two prediction models: The nomogram model and the random forest model. The random forest model has good predictive ability, which can effectively predict the risk of GDM and provide accurate references for early prevention and management of GDM.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic disease that occurs or is first discovered during pregnancy[1,2] and is a risk factor for many adverse pregnancy outcomes. International data show that by 2021, the proportion of pregnant women with GDM worldwide has reached 16.7% and continues to grow[3]. Preventing GDM has become an important challenge for global health. At present, numerous studies have been conducted worldwide to predict the likelihood of GDM[4,5], but these studies are only applicable to foreign populations, and their applicability to domestic populations is not ideal. There are relatively few studies on the risk prediction of GDM in China, which needs to be further strengthened. Therefore, the objective of this investigation is to establish a predictive model for GDM risk. By comparing the predictive efficacy of the nomogram model and the random forest model, this will provide clinicians with a more scientific and accurate risk prediction tool for GDM, promote early diagnosis and intervention of GDM, and provide pregnant women with corresponding intervention measures and health education.

MATERIALS AND METHODS

General information

A retrospective analysis of 406 pregnant women aged 22-43 years, with an average age of (31.17 ± 4.02) years, who underwent a routine prenatal examination in our hospital was conducted from April 2020 to December 2022. According to whether GDM occurred, they were divided into two groups, including the GDM group ($n = 197$) and the non-GDM group ($n = 209$).

Inclusion criteria were: (1) Normal pregnant women; and (2) natural pregnancy. Exclusion criteria were: (1) Patients with diabetes who had been diagnosed or were receiving treatment before pregnancy; (2) women who could not participate in the survey and follow-up; (3) adolescent pregnant women (< 18 years old); (4) those suffering from other chronic diseases, such as cardiovascular disease, liver disease, renal dysfunction, or malignant neoplasms; and (5) pregnant women who used hormones and immunosuppressants.

Research methods

The clinical data of early pregnancy (6-13 wk) were collected, including height, weight, pre-pregnancy body mass index (BMI), family history, hemoglobin (Hb) level, fasting blood glucose, and other indicators. Two persons were responsible for data entry and verification.

GDM diagnostic criteria

Pregnant women at the gestational age of 24 to 28 wk, underwent an oral glucose tolerance test. Glucose water (75 g) was consumed after 8 h fasting on an empty stomach and then blood glucose was measured 3 times within 2 h. A diagnosis of GDM was made if the blood glucose level measured ≥ 5.1 mmol/L, 10.0 mmol/L, or 8.5 mmol/L during the fasting, 1-h, or 2-h tests, respectively[6].

Statistical analysis

Statistical software SPSS 21.0 was utilized for data analysis. The measurement data were represented as the mean and standard deviation, and group comparisons were conducted using the *t*-test. The enumeration data were represented as number (percentage), and the comparison between groups was conducted using the χ^2 test or Fisher's exact test. A multivariate logistic regression analysis was utilized, and statistical significance was determined at the $P < 0.05$ level. Based on the machine learning method, the nomogram prediction model was established by R language, and the random forest model was established using the Random Forest package. The model's application performance was assessed using sensitivity, specificity, and the area under the receiver operating characteristic curve (ROC AUC). The AUC was compared using the Delong test.

RESULTS

Sample characteristics

The comparison results of the general data in the two groups showed that there were significant differences in BMI, family history of diabetes, GDM history, macrosomia, hypertension, Hb level, triglyceride level, serum ferritin, and fasting blood glucose in the first trimester of pregnancy between the two groups ($P < 0.05$). These results are shown in Table 1.

Multivariate analysis of factors for GDM

Whether GDM occurred or not was used as the dependent variable, and the statistically significant variables in the univariate results were included in the multivariate logistic regression analysis as the independent variables, and the assignment criteria of each variable are shown in Table 2. The multivariate results showed that preconception BMI, family history of diabetes, GDM history, macrosomia, hypertension, Hb level, triglyceride level, serum ferritin, and fasting blood glucose in early pregnancy were the influencing factors of GDM as shown in Table 3 ($P < 0.05$).

Development of a first-trimester risk prediction model for GDM

Nomogram model construction: The results of multivariate logistic regression analysis were plotted into a nomogram model using R language and are shown in Figure 1. The total score was derived by assigning scores to each risk factor in the nomogram, and the corresponding probability of GDM occurring was determined using the total score and its associated probability value.

Random forest prediction model construction: Nine statistically significant indicators from univariate analysis were included in the random forest model, and the values are shown in Table 2. The results showed a fixed tree value, and when mtry = 10, the false positive rate of the model was the smallest. Based on mtry = 10, when ntree = 500, the model error was based on stability. Therefore, based on the mtry = 10 and ntree = 500 parameters, the top 5 variables in predicting the occurrence of GDM by the random forest model were serum ferritin, fasting blood glucose in the first trimester, BMI before pregnancy, Hb level and triglyceride level, as shown in Figure 2.

Comparison of the performance of the two predictive models: The nomogram model's ability to discriminate was assessed by the ROC AUC (Table 4 and Figure 3). The AUC of the random forest model was higher than that of the nomogram model ($Z = -6.104$, $P < 0.001$).

DISCUSSION

GDM is a condition that affects glucose metabolism during pregnancy. Typically, it occurs after the 27th week of gestation, although some women may develop preexisting diabetes prior to conception. The pathogenesis of GDM is complex, and its etiology is undefined[7]. In this study, after comparing the basic characteristics between pregnant women in the group with GDM and the group without GDM, the factors affecting the occurrence of GDM were obtained by multivariate logistic regression analysis, including preconception BMI, family history of diabetes, GDM history, macrosomia, hypertension, Hb and triglyceride levels, serum ferritin, and fasting blood glucose in the first trimester. These findings are essentially congruent with those of Li *et al*[8] and Tong *et al*[9].

This study revealed that pregnant women with a positive family history of diabetes exhibited a greater likelihood of GDM occurrence in comparison to their counterparts lacking such a familial history. Diabetes has a genetic predisposition, and can be passed on genetically to the next generation. Pregnant individuals who have a familial history of diabetes may possess a genetic predisposition that elevates the likelihood of the onset of GDM. A positive family history of diabetes mellitus has been established as one of the risk factors for GDM based on various national and international

Table 1 Comparison of general data between the two groups of patients, *n* (%)

Items	GDM group (*n* = 197)	Non-GDM group (*n* = 209)	Statistics	*P* value
Age (yr)	31.57 ± 3.94	30.794 ± 4.05	1.965	0.051
Body height (cm)	159.67 ± 5.91	160.38 ± 4.95	1.351	0.189
Occupation			2.246	0.134
Regular work	49 (24.87)	66 (31.58)		
No regular work	148 (75.13)	143 (68.42)		
Education level			4.790	0.091
Junior high school and below	22 (11.17)	18 (8.61)		
High school or technical secondary school	19 (9.64)	35 (16.75)		
College undergraduate and above	156 (79.19)	156 (74.64)		
Marital status			2.884	0.092
Primary marriage	169 (85.79)	166 (79.43)		
Remarriage	28 (14.21)	43 (20.57)		
Monthly income (yuan/month)			0.878	0.349
< 3000	36 (18.27)	46 (22.01)		
≥ 3000	161 (81.73)	163 (77.99)		
Family history of DM			22.357	< 0.001
Yes	49 (24.87)[b]	16 (7.66)		
No	148 (75.13)[b]	193 (92.34)		
Family history of hypertension			0.105	0.746
Yes	38 (19.29)	43 (20.57)		
No	159 (80.71)	166 (79.43)		
GDM			28.400	< 0.001
Yes	50 (25.38)[b]	13 (6.22)		
No	147 (74.62)[b]	196 (93.78)		
Parity			1.049	0.306
Plurality	91 (46.19)	86 (41.15)		
Primiparity	106 (53.81)	123 (58.85)		
PCOS			0.398	0.528
Yes	9 (4.57)	7 (3.35)		
No	188 (95.43)	202 (96.65)		
Giant infants			19.015	< 0.001
Yes	35 (17.77)[b]	9 (4.31)		
No	162 (82.23)[b]	200 (95.69)		
Pre-pregnancy weight (kg)	57.11 ± 9.58[a]	54.68 ± 7.26	2.898	0.004
Pre-pregnancy BMI (kg/m^2)	24.11 ± 4.08[b]	21.25 ± 2.63	8.439	< 0.001
History of abortion			1.106	0.293
Yes	70 (35.53)	64 (30.62)		
No	127 (64.47)	145 (69.38)		
Cesarean section history			0.878	0.349
Yes	35 (17.77)	30 (15.23)		
No	162 (82.23)	179 (84.77)		

History of preterm birth			1.872	0.171
Yes	51 (25.89)	67 (32.06)		
No	146 (74.11)	142 (67.94)		
History of stillbirth			0.212	0.645
Yes	4 (2.03)	3 (1.44)		
No	193 (97.97)	206 (98.56)		
Hypertension			14.325	< 0.001
Yes	35 (17.77)[b]	12 (5.74)		
No	162 (82.23)[b]	197 (94.26)		
Erythrocytes (× 10^{12}/L)	4.31 ± 0.41	4.27 ± 0.39	0.994	0.321
Hb (g/L)	128.77 ± 9.03[b]	121.34 ± 10.34	7.687	< 0.001
Urea (mmol/L)	2.94 ± 0.66	2.87 ± 0.65	1.079	0.281
Creatinine (μmol/L)	44.71 ± 6.81	45.38 ± 5.82	-1.070	0.285
Uric acid (μmol/L)	244.18 ± 54.53	234.62 ± 44.62	1.938	0.053
Triglyceride (mmol/L)	1.69 ± 0.56[b]	1.43 ± 0.69	4.058	< 0.001
Serum ferritin (ng/mL)	73.96 ± 18.36[b]	53.29 ± 15.30	12.350	< 0.001
First-trimester fasting hyperglycemia (mmol/L)	5.06 ± 0.47[b]	4.40 ± 0.71	10.971	< 0.001

[a]$P < 0.05$ *vs* non-gestational diabetes mellitus (GDM) group.
[b]$P < 0.001$ *vs* non-GDM group. BMI: Body mass index; DM: Diabetes mellitus; GDM: Gestational diabetes mellitus; Hb: Hemoglobin; PCOS: Polycystic ovary syndrome.

Table 2 Variable assignment

Variables	Assignment
Whether GDM occurred (dependent variable)	Yes = 1, no = 0
GDM	Yes = 1, no = 0
Hypertension	Yes = 1, no = 0
Giant infant	Yes = 1, no = 0
Family history of DM	Yes = 1, no = 0
Hb	Original value input
Pre-pregnancy BMI	Original value input
Triglyceride	Original value input
Serum ferritin	Original value input
First-trimester fasting hyperglycemia	Original value input

BMI: Body mass index; DM: Diabetes mellitus; GDM: Gestational diabetes mellitus; Hb: Hemoglobin.

studies[10-12]. If a pregnant woman is diagnosed with GDM in a previous pregnancy, she is also more likely to have GDM in subsequent pregnancies, as confirmed by studies[13]. Therefore, for pregnant women with a familial predisposition to diabetes and GDM, it is recommended that doctors pay close attention to their health during pregnancy.

This study found that hypertension plays an essential role in the progress of GDM, and studies have confirmed that hypertension is one of the factors that pose an independent risk for GDM[14]. Hypertension may lead to the onset and progression of GDM by affecting placental blood flow and insulin sensitivity, causing islet cytopenia and dysfunction. In addition, this study also found that excess preconception BMI is one of the factors that pose an independent risk for GDM. This is because overweight and obesity affect insulin metabolism and production, increasing the body's need for insulin, and thus increasing the risk of GDM[15]. Therefore, weight control before pregnancy and maintaining a normal BMI can reduce the risk of GDM. For patients with hypertension during pregnancy, surveillance and intervention should be strengthened to reduce the risk of GDM.

Table 3 Multivariate logistic regression analysis results of gestational diabetes mellitus

Items	β	SE	Wald	*P* value[a]	OR (95%CI)
Family history of DM	1.340	0.472	8.061	0.005	3.818 (1.514-9.626)
Hypertension	1.674	0.643	6.772	0.009	5.335 (1.512-18.825)
GDM	1.201	0.519	5.353	0.021	3.323 (1.201-9.192)
Giant infant	2.269	0.647	12.312	< 0.001	2.653 (1.284-5.483)
Pre-pregnancy BMI (kg/m^2)	0.233	0.055	18.059	< 0.001	1.263 (1.134-1.406)
Hb (g/L)	0.071	0.018	14.867	< 0.001	1.073 (1.035-1.112)
Triglyceride (mmol/L)	0.792	0.249	10114	0.001	2.207 (1.355-3.596)
Serum ferritin (ng/mL)	0.070	0.010	44.508	< 0.001	1.072 (1.050-1.094)
First-trimester fasting hyperglycemia (mmol/L)	1.887	0.350	29.110	< 0.001	6.602 (3.326-13.105)

[a]$P < 0.05$ was considered significant. BMI: Body mass index; DM: Diabetes mellitus; GDM: Gestational diabetes mellitus; Hb: Hemoglobin; SE: Standard error; OR: Odd ratio; CI: Confidence interval.

Table 4 Prediction performance evaluation results of the nomogram model and random forest model (%)

Prediction model		Sensitivity	Specificity	AUC (95%CI)
Nomogram model	Training set	74.1	87.6	0.883 (0.846-0.921)
	Validation set	81.0	81.2	0.850 (0.782-0.918)
Random forest model	Training set	91.4	84.8	0.950 (0.927-0.973)
	Validation set	89.7	89.7	0.918 (0.868-0.967)

AUC: Area under the curve; CI: Confidence interval.

Sissala *et al*[16] found that Hb level is a risk factor for GDM, this finding is in alignment with the outcomes of the present investigation. The reason for this is that the level of Hb may affect the diastolic blood pressure of pregnant women, thereby increasing maternal peripheral vascular resistance. This condition may reduce the stiffness of the large arteries and lead to the formation of insulin resistance, thereby increasing the risk of GDM[17,18]. Serum ferritin is a major form of intracellular iron storage, and the body's iron stores are positively correlated with Hb levels. Research has indicated that pregnant women diagnosed with GDM exhibit elevated serum ferritin levels in comparison to their non-GDM counterparts; therefore, regular measurement of Hb levels and serum ferritin levels during pregnancy can help pregnant women detect problems in a timely manner and take corresponding treatment measures. Studies have demonstrated that lipid and lipoprotein abnormalities, including elevated triglycerides, are associated with insulin resistance and type 2 diabetes, hence leading to significantly higher levels of triglycerides in GDM compared to non-GDM patients[19,20]. Therefore, monitoring blood lipid levels during pregnancy is of great clinical significance to effectively predict the onset of GDM.

In this investigation, the nomogram model and random forest model were established by applying preconception BMI, family history of diabetes, GDM history, macrosomia, hypertension, Hb and triglyceride levels, serum ferritin, and fasting blood glucose levels in the first trimester, and compared the prediction effect of the model. It was found that the AUC of GDM exhibited a value of 0.950 (95% confidence interval: 0.927-0.973), with a sensitivity rate of 91.4% and specificity rate of 84.80%. Compared with the nomogram model, it had better calibration and prediction accuracy. The reason for this may be that compared with the logistic regression model, the random forest model is not easy to overfit, has more advantages in processing high-dimensional data, and does not require feature selection.

CONCLUSION

In summary, nine indicators, including preconception BMI, family history of diabetes, GDM history, macrosomia, hypertension, Hb and triglyceride levels, serum ferritin, and fasting blood glucose level in early pregnancy, effectively predicted the incidence of GDM. In this study, the predictive model for risk assessment of GDM based on the results of multivariate analysis had a better predictive effect, and the random forest model had higher efficiency in predicting the risk of GDM, which can effectively anticipate the likelihood of developing diabetes. In pregnant women, this has important guiding significance for the prevention and treatment of GDM. However, this study only collected data in one

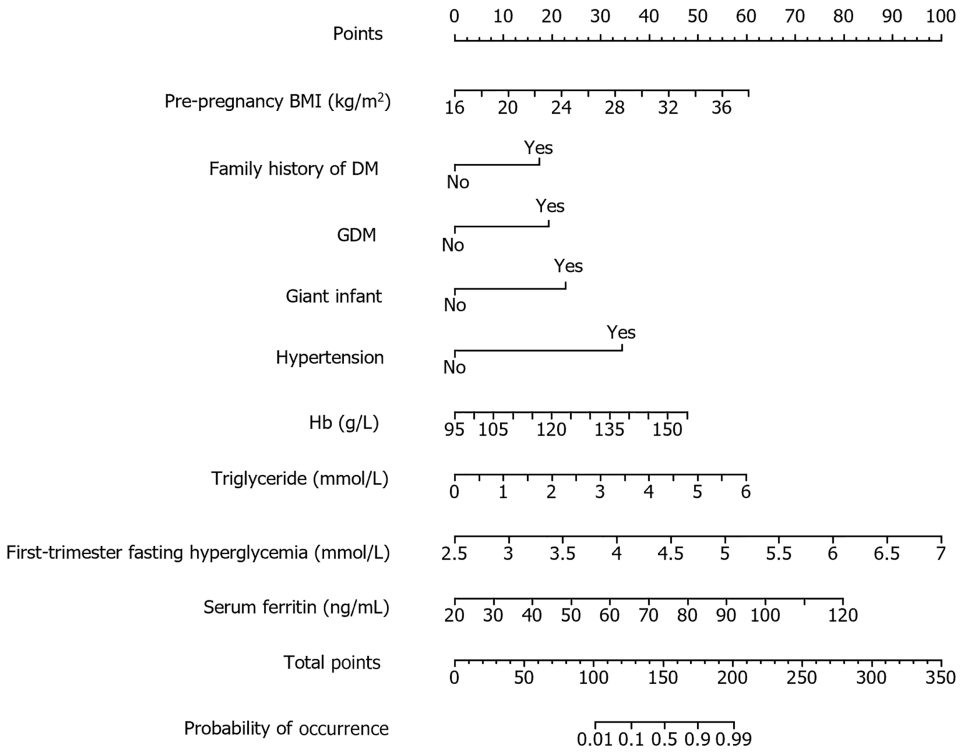

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Figure 1 Risk prediction nomogram model of gestational diabetes mellitus. BMI: Body mass index; DM: Diabetes mellitus; GDM: Gestational diabetes mellitus; Hb: Hemoglobin.

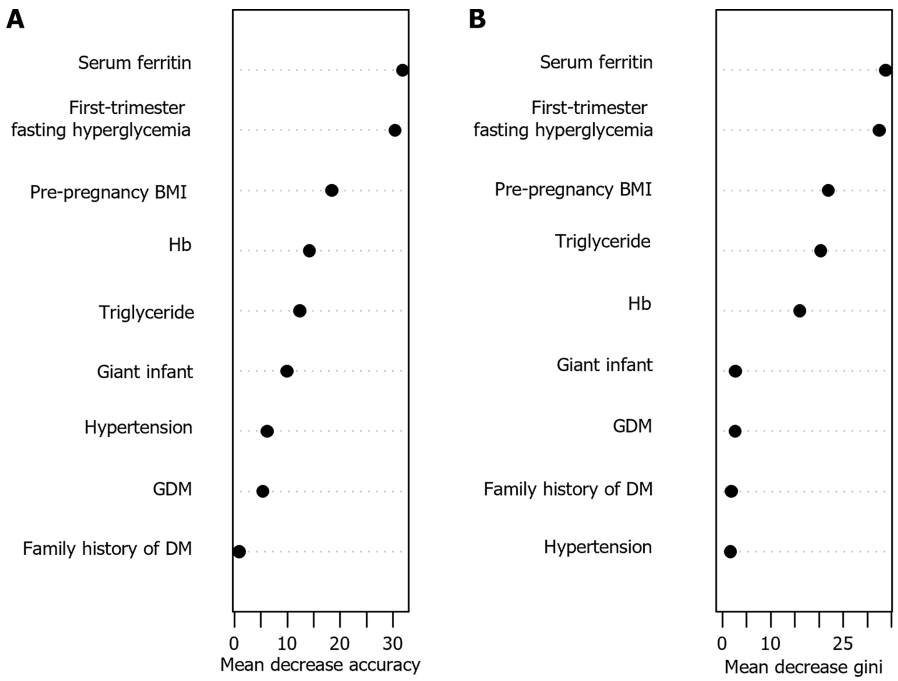

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Figure 2 Variable importance analysis of random forest model. A: The diagram shows that the value of each variable was changed into a random number, and the random forest also measured the degree of reduction in accuracy; B: The importance of each variable was compared by calculating the heterogeneous influence of each variable on the observations on each node of the classification tree. The larger the value, the greater the importance of the variable. BMI: Body mass index; DM: Diabetes mellitus; GDM: Gestational diabetes mellitus; Hb: Hemoglobin.

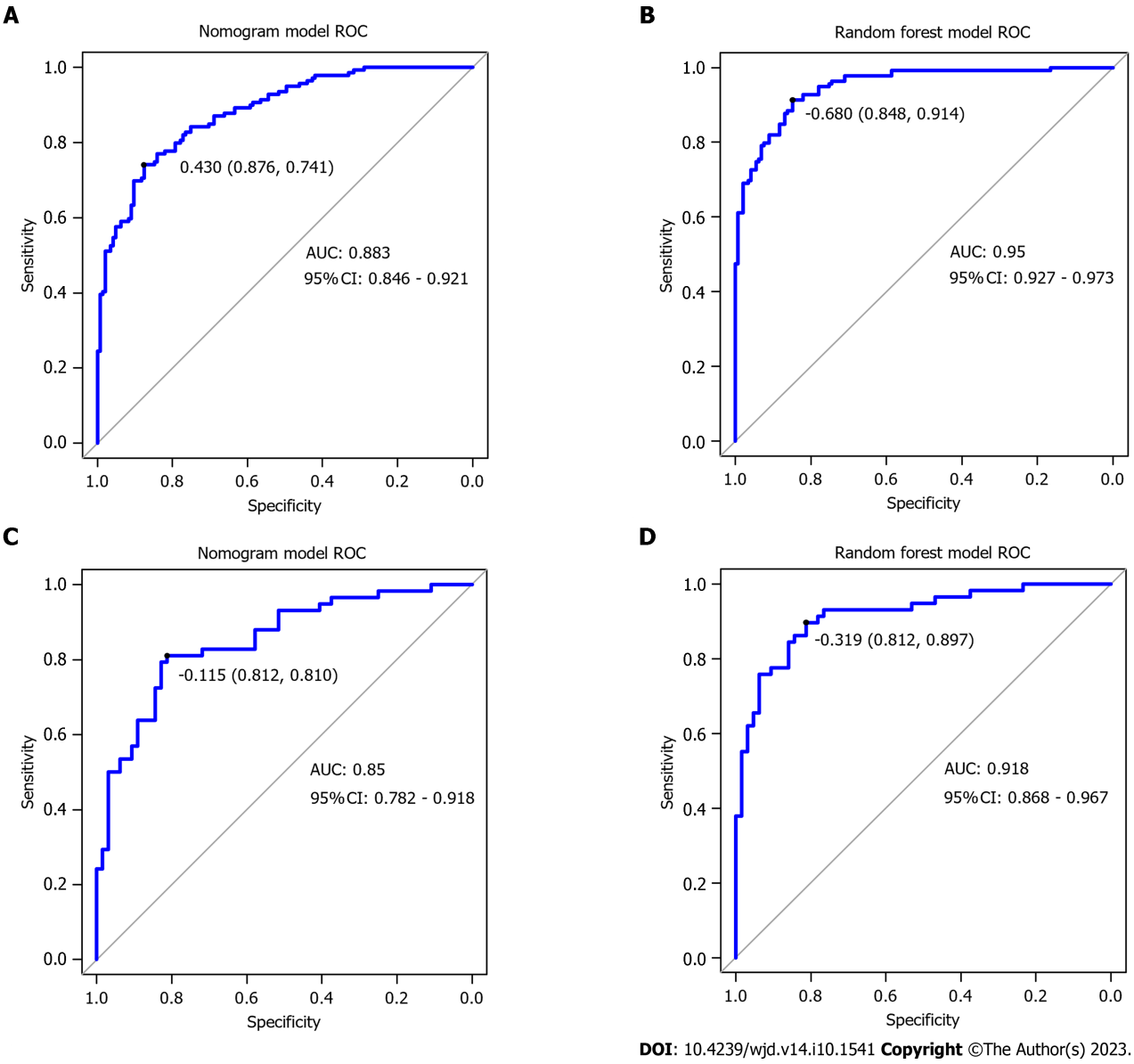

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Figure 3 Receiver operating characteristic curve of the two models for predicting gestational diabetes mellitus. A: The figure shows the receiver operating characteristic curve (ROC) curve of the training set nomogram; B: The figure shows the ROC curve of the training set random forest model; C: The figure shows the ROC curve of the validation set line graph; D: The figure shows the ROC curve of the validation set random forest model. ROC: Receiver operating characteristic curve; AUC: Area under the curve.

hospital, and the sample size was small, which had certain limitations, and it is necessary to include a larger sample size for large-scale model verification in the future to provide a reference for clinical prediction of the incidence of GDM.

ARTICLE HIGHLIGHTS

Research background

Gestational diabetes mellitus (GDM) is a common metabolic disease during pregnancy, which has adverse effects on maternal and child health. The establishment and evaluation of risk prediction models can help to identify high-risk groups early and take corresponding intervention measures to reduce the risk in pregnant women and newborns. At present, research in this field mainly focuses on the screening of predictors and the construction of models and explores their reliability and practicability. These studies provide a theoretical basis and method support for the prevention and management of gestational diabetes.

Research motivation

The purpose of this study is to establish a reliable risk prediction model for gestational diabetes to help doctors detect and treat patients with GDM. The key issues to be solved in this study include determining the best predictors and

establishing effective models. Solving these problems is of great significance for improving the diagnostic rate of early diabetes and reducing the risk of complications in pregnant women and fetuses. It will also have a positive effect on future research in this field.

Research objectives

The main objective of this study is to establish a reliable risk prediction model for GDM. The achieved goals include obtaining the risk factors of GDM, establishing a risk factor prediction model, and evaluating the model. The random forest model has a good prediction effect, which can effectively predict the risk of diabetes in pregnant women and indicate the direction for future research in this field.

Research methods

In this study, a retrospective case analysis method was adopted, and the study subjects were stratified into two groups: Those with GDM and those without GDM. According to whether GDM occurred, the general data of the two groups of pregnant women were investigated and analyzed, and we established a risk prediction model for GDM during the trimester using both the logistic regression and random forest models, and the two models were evaluated and validated. The peculiarity and novelty of the research methods lie in the adoption of machine learning methods, which greatly improve the accuracy and reliability of the model.

Research results

This study successfully established a risk prediction model for early gestational diabetes in pregnant women (random forest and nomogram model). After analyzing and screening a number of clinical factors, the random forest model had high prediction accuracy and judgment ability. This study provides strong support for early prevention and intervention of gestational diabetes in pregnant women and provides a reference value for further research in this field. In the future, it is necessary to further expand the sample size, improve the considered factors and verify the stability and applicability of the model.

Research conclusions

This study proposed a model for predicting the likelihood of developing gestational diabetes during the early stages of pregnancy and compared the predictive effects of the random forest and nomogram models. The results suggested that the random forest model can more accurately predict the risk of gestational diabetes during early pregnancy.

Research perspectives

Future research should focus on improving the risk prediction model of gestational diabetes in pregnant women and improve the accuracy and stability of the model to meet clinical needs. We should also explore new predictors, explore pathological mechanisms, and identify intervention strategies to reduce the risk of diabetes and its complications in pregnant women and improve maternal health.

FOOTNOTES

Author contributions: Lin Q designed and performed the research and wrote the paper; Fang ZJ designed the research and supervised the report.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Fujian Maternity and Child Health Hospital.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

Conflict-of-interest statement: We have no financial relationships to disclose.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of influencing factors and interaction of body weight and disease outcome in patients with prediabetes

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Abstract

BACKGROUND

The trend of prediabetes progressing to type 2 diabetes mellitus (T2DM) is prominent, and effective intervention can lead to a return to prediabetes. Exploring the factors influencing the outcome of prediabetes is helpful to guide clinical intervention. The weight change in patients with prediabetes has not attracted much attention.

AIM

To explore the interaction between body weight and the factors affecting the progression of prediabetes to T2DM.

METHODS

We performed a retrospective analysis of 236 patients with prediabetes and 50 with normal glucose tolerance (NGT), and collected clinical data and follow-up results of all patients. Based on natural blood glucose outcomes, we classified 66 patients with progression to T2DM into the disease progression (DP) group, and 170 patients without progression to T2DM into the disease outcome (DO) group. We analyzed the factors that influenced prediabetes outcome and the influence of body weight on prediabetes blood glucose outcome by unconditional logistic regression. A general linear model (univariate) was used to analyze the interaction between body weight and independent influencing factors.

RESULTS

There were 98 cases of impaired fasting glucose (IFG), 90 cases of impaired glucose tolerance (IGT), and 48 cases of coexistent IFG and IGT. The body weight, waist circumference, body mass index, fasting blood glucose, and 2 h plasma glucose of patients with IFG, IGT, and coexistent IFG and IGT were higher than those in patients with NGT ($P < 0.05$). Logistic regression analysis showed that body weight, glycosylated hemoglobin, uric acid, fasting insulin, and homeostatic model assessment for insulin resistance were independent factors affecting progression of prediabetes to T2DM ($P < 0.05$). Receiver operating characteristic curve analysis showed that the area under the curve predicted by the above indicators combined was 0.905 [95% confidence interval (CI): 0.863-0.948], which was greater than that predicted by each indicator alone. Logistic regression analysis with baseline body weight as an independent variable showed that compared with body weight 1, the odds ratio (95%CI) of body weight 3 was 1.399 (1.142-2.126) ($P = 0.033$). There was a multiplicative interaction between body weight and uric acid ($\beta = 1.953$, $P = 0.005$).

CONCLUSION

High body weight in patients with prediabetes is an independent risk factor for progression to T2DM, and the risk of progression is increased when coexisting with high uric acid level.

Key Words: Prediabetes; Type 2 diabetes mellitus; Body weight; Disease outcome; Influencing factors; Interactions; Low-carbohydrate diet

Core Tip: Progression of prediabetes to type 2 diabetes mellitus (T2DM) is severe, but effective interventions can delay or even reverse progression. High body weight is a common phenomenon in people with prediabetes. Unilateral weight-loss intervention may not be sufficient. We analyzed the interaction between body weight and the factors affecting prediabetes progression to T2DM and explored the influence of body weight and other factors, to better guide clinical intervention and reduce progression of prediabetes to T2DM.

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INTRODUCTION

Diabetes is a serious threat to public health, and its prevention and treatment are increasingly challenging[1]. Type 2 diabetes mellitus (T2DM) and its complications are increasing worldwide. According to the latest data released by the International Diabetes Federation in 2017, there were 425 million patients worldwide, and this is expected to exceed 629 million by 2045[2]. The latest epidemiological data in China show that the prevalence of DM is 11.2%, and approximately 30% of nonendocrine inpatients have DM[3]. Prediabetes, also known as impaired glucose regulation, is a state of abnormal glucose metabolism between normal glucose metabolism and DM, including impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and three states of both, with an incidence of 35.7%[4]. Clinical practice has proved that blood glucose regulation in the prediabetes stage is reversible. Early intervention can prevent prediabetes from progressing to T2DM and delay its development, which can reduce the risk of progression by 58%[5,6]. At present, clinical intervention is mainly through dietary adjustment, weight control, moderate exercise, and other ways to delay the progression of prediabetes to T2DM, and its effectiveness has been confirmed[7]. Obesity [with body mass index (BMI) as an evaluation index] is an independent risk factor for the conversion of prediabetes to T2DM, and obese prediabetes patients can benefit from weight loss. However, whether weight and its influencing factors can lead to an increase in the risk of adverse outcomes of the disease under the combined influence of prediabetes with T2DM risk factors is currently unknown and has rarely been studied. In this study, by understanding the weight status of prediabetes patients, we analyzed the factors influencing disease outcome (DO) and their interaction to provide a basis for later intervention.

MATERIALS AND METHODS

Patients

In this retrospective analysis, we selected 236 patients with prediabetes admitted to the Department of General Practice of the First People's Hospital of Wenling City from February 2019 to January 2021. Based on natural blood glucose outcomes, we classified 66 patients with progression to T2DM into the disease progression (DP) group, and 170 patients

without progression to T2DM into the DO group. All patients met the diagnostic criteria for prediabetes in the Chinese Guidelines for Diabetes Prevention and Treatment[8]: (1) IFG: Fasting blood glucose (FBG) 6.1-6.9 mmol/L and oral glucose tolerance test (OGTT) 2h plasma glucose (PG) < 7.8 mmol/L; (2) IGT: FBG < 6.1 mmol/L and OGTT 2h PG 7.8-11.1 mmol/L; and (3) IFG and IGT coexistent: FBG 6.1-6.9 mmol/L and OGTT 2h PG 7.8-11.1 mmol/L.

Inclusion criteria: (1) FBG 5.6-6.9 mmol/L, with or without 2h PG 7.8-11.0 mmol/L; (2) No serious cardiovascular, liver, kidney, and lung diseases; and (3) Complete clinical and follow-up data. Exclusion criteria: (1) Combined with severe systemic diseases, such as heart, liver, kidney or lung disease, mental illness, connective tissue disease, and bone and joint injury; (2) Pregnancy, lactation or pregnancy preparation; and (3) Lack of follow-up data. Another 50 patients with normal glucose tolerance (NGT) were selected. NGT: FBG < 6.1 mmol/L with or without OGTT 2h PG < 7.8 mmol/L.

Data collection

We consulted patients' electronic medical records, and collected clinical data and relevant test indicators at admission, including sex, age, blood glucose status, family history of DM, smoking, alcohol consumption, body weight, waist circumference, BMI, FBG, 2h PG, systolic blood pressure, diastolic blood pressure, glycosylated hemoglobin, total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid, anti-soluble liver antigen antibodies (SLA), fasting insulin (FINS), and homeostatic model assessment for insulin resistance (HOMA-IR).

Definition and detection of relevant indicators

Body weight was measured by a general practitioner (GP) using a height and weight scale. Patients were measured with an empty stomach. They removed their shoes, wore thin clothing, stood upright, feet together, shoulders and hips close to the scale. The GP lowered the horizontal plate of the scale to the top of the patient's head to read the results of height and weight. Height readings were accurate to 0.5 cm and weight readings to 0.5 kg. BMI was calculated as weight (kg)/height (m^2)[9].

Waist measurement was performed on patients with an empty stomach by a GP with an inelastic tape measure with a minimum scale of 0.1 cm. During the measurement, the patient remained upright with arms hanging down naturally and feet 25-30 cm apart. The tape measure was placed at the midpoint of the line between the anterior superior iliac spine and the line along the lower margin of the costal arch, and ran horizontally around the abdomen. The tape measure was close to the skin but not tight. The results were read at the end of the breath and were accurate to 0.1 cm.

Systolic and diastolic blood pressure was measured by a GP using a uniform mercury sphygmomanometer. Patients were prohibited from smoking and drinking coffee 30 min before the measurement and rested for 5-10 min in a quiet environment. Venous blood samples were collected in the fasting state in the morning (no intake of caloric food for at least 8 h). The blood glucose indices were determined by a HITACHI 7600-020 automatic biochemical analyzer. FPG, FINS, serum uric acid and blood lipids (TC, TG, HDL-C and LDL-C) were also measured. The homeostasis insulin resistance index (HOMA-IR) was calculated as follows[10]: HOMA-IR = (FPG × FINS)/22.5.

OGTT 2h PG: The patients took 75 g of anhydrous glucose dissolved in 250 mL water within 5 min. During the test, they did not drink any beverages, swallow, or perform strenuous exercise. The time was measured from the first mouthful of sugar water, and the venous blood was drawn 2 h after taking the sugar and was quickly examined by the hexokinase method. Glycosylated hemoglobin was determined by a Bole D-10 glycosylated swimming protein meter (high-pressure liquid chromatography).

Grouping

T2DM[11]: FBG ≥ 7.0 mmol/L with or without OGTT 2h PG ≥ 11.1 mmol/L. According to the blood glucose outcomes of prediabetes patients after a 2-year follow-up, 66 patients with progression of T2DM were classified into the DP group, and 170 patients without progression of T2DM were classified into the DO group.

Statistical analysis

Epidata3.0 software was used for double data entry and SPSS 21.0 statistical software was used for statistical analysis. The measurement data with normal distribution were expressed as mean ± SD, and the least significant difference-*t* test was used for pairwise comparison between groups. Numerical data were represented by case number (percentage) and χ^2 tests. The factors influencing prediabetes DO and the influence of body weight on prediabetes blood glucose outcome were analyzed by unconditional logistic regression. The multiplication model was used to analyze the interaction between the two influencing factors. Beta level: $\alpha = 0.05$.

RESULTS

Weight of prediabetes patients with different blood glucose status

Among 236 patients with prediabetes, there were 98 cases of IFG, 90 of IGT, and 48 of coexistent IFG and IGT. The body weight, waist circumference, BMI, FBG, and 2h PG of patients with IFG, IGT and coexistent of IFG and IGT were higher than those of patients with NGT (all $P < 0.05$) (Table 1).

Univariate analysis of the outcome of prediabetes disease

Of 236 patients with prediabetes, 66 (27.97%) developed T2DM (DP group). There were no significant differences in

Table 1 Weight of prediabetes patients with different blood glucose status

Index	NGT (50 cases)	IFG (98 cases)	IGT (90 cases)	IFG and IGT coexistent (48 cases)
Age (yr)	52.55 ± 14.67	54.68 ± 13.27[a]	52.38 ± 11.62[a]	57.75 ± 13.68[a]
Weight (kg)	61.52 ± 12.13	66.38 ± 13.35[a]	70.26 ± 10.62[a]	72.26 ± 11.62[a]
Waistline (cm)	90.37 ± 9.98	104.25 ± 12.23[a]	100.22 ± 8.56[a]	107.35 ± 11.07[a]
BMI (kg/m2)	25.87 ± 5.46	31.57 ± 4.06[a]	30.75 ± 3.39[a]	32.27 ± 3.38[a]
FBG (mmol/L)	4.46 ± 0.62	6.27 ± 0.75[a]	5.58 ± 0.36[a]	6.48 ± 0.82[a]
2h PG (mmol/L)	5.16 ± 1.08	5.87 ± 0.77[a]	8.82 ± 1.17[a]	9.35 ± 1.12[a]

[a]Indicates the same index compared with normal glucose tolerance, $P < 0.05$.

NGT: Normal glucose tolerance; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; BMI: Body mass index; FBG: Fasting blood glucose; 2h PG: 2h postprandial blood glucose.

gender, age, family history of diabetes, FBG, diastolic blood pressure, TC, HDL-C and LDL-C between the DP and DO groups ($P > 0.05$). In addition, glucose status, history of smoking, drinking, body weight, waist circumference, BMI, 2h PG, systolic blood pressure, glycosylated hemoglobin, TG, uric acid, SLA, FINS, and HOMA-IR difference were statistically significant ($P < 0.05$) (Table 2).

Multivariate analysis of DOs in patients with prediabetes

We took whether to progress to T2DM as the dependent variable and the index of $P > 0.05$ in the above single-factor analysis as the independent variable, which were inserted into the logistic regression model for analysis. Table 3 shows the assignment of the data in the model. Body weight, glycosylated hemoglobin, uric acid, FINS, and HOMA-IR were independent factors affecting progression of prediabetes to T2DM ($P < 0.05$) (Table 4). Receiver operating characteristic (ROC) curve analysis of body weight, glycosylated hemoglobin, uric acid, FINS, and HOMA-IR predicted prediabetes progression to T2DM, and showed that the area under the curve (AUC) predicted by the above indices combined was 0.905 [95% confidence interval (CI): 0.863-0.948], which was higher than predicted by each index separately (Figure 1, Table 5).

Analysis of the influence of body weight on DO in patients with prediabetes

Whether progressed to T2DM was used as the dependent variable, and baseline body weight [body weight 1 (35-60 kg), body weight 2 (60-80 kg), body weight 3 (80-100 kg)] was the independent variable. Logistic regression analysis was performed by adjusting blood glucose status, smoking history, drinking history, waist circumference, BMI, 2h PG, systolic blood pressure, glycosylated hemoglobin, triglycerides, uric acid, SLA, FINS and HOMA-IR. Body weight was a risk factor for prediabetes progression to T2DM. Compared with body weight 1, the odds ratio (OR) (95%CI) of body weight 3 was 1.399 (0.142-1.126) ($P = 0.083$) (Table 6).

Analysis of interaction between body weight and independent influencing factors

Taking the best cut-off value of each index as the boundary, we converted the data of body weight, glycosylated hemoglobin, uric acid, FINS and HOMA-IR into binary variables. Whether progressed to T2DM was used as the dependent variable and weight by glycosylated hemoglobin, weight by uric acid, weight by FINS, and weight by HOMA-IR as the fixed factors, the interaction analysis showed that there was a multiplicative interaction between weight and uric acid ($\beta = 1.953$, $P = 0.005$) (Table 7).

DISCUSSION

There has been significant progression of prediabetes to T2DM in recent years[12]. According to our study, 27.97% of prediabetes patients developed T2DM. The progression to T2DM was highest in patients with coexistent IFG and IGT, which is consistent with the findings of Wu *et al*[13]. We found that most patients with prediabetes had IFG or IGT, and coexistent IFG and IGT accounted for 20%. Further analysis showed that body weight, waist circumference, BMI, FBG and 2h PG were higher in patients with IFG, IGT, and coexistent IFG and IGT than in patients with NGT, which is similar to previous results[14].

Our logistic regression analysis showed that body weight (> 71.75 kg), glycosylated hemoglobin (> 6.25%), uric acid (> 289.5 mmol/L), FINS (> 6.25 mL/mL) and HOMA-IR (> 1.35) were independent risk factors for prediabetes progression to T2DM ($P < 0.05$). ROC curve analysis showed that the AUC predicted by combination of the above indicators was 0.905 (95%CI: 0.863–0.948), which was greater than that predicted by each indicator alone, indicating that the above indicators had high efficacy in predicting the progression of prediabetes to T2DM, suggesting that high levels of these indicators increase the risk of prediabetes progression to T2DM. Our logistic regression analysis, with T2DM progression as the dependent variable and baseline body weight as the independent variable, showed that the OR (95%CI) of those with

Table 2 Univariate analysis of the outcome of prediabetes disease

Data	DP group (n = 66)	DO group (n = 170)	$t/\chi^2/Z$	*P* value
Gender			0.143	0.705
Male	39 (59.09)	105 (61.76)		
Female	27 (40.91)	65 (38.24)		
Age			< 0.001	0.988
< 60 yr	42 (63.64)	108 (63.53)		
≥ 60 yr	24 (36.36)	62 (36.47)		
Blood glucose status			14.639	0.001
IFG	16 (24.24)	82 (48.24)		
IGT	28 (42.42)	62 (36.47)		
IFG and IGT coexistent	22 (33.33)	26 (15.29)		
Family history of diabetes			0.279	0.598
Yes	6 (9.09)	12 (7.06)		
No	60 (90.91)	158 (92.94)		
Smoking history			4.561	0.033
Yes	20 (30.30)	30 (17.65)		
No	46 (69.70)	140 (82.35)		
Drinking history			5.457	0.019
Yes	26 (39.39)	41 (24.12)		
No	40 (60.61)	129 (75.88)		
Weight, kg (mean ± SD)	74.59 ± 11.19	66.91 ± 11.86	4.535	< 0.001
Waist circumference, cm (mean ± SD)	106.84 ± 10.31	101.98 ± 10.95	3.110	0.002
BMI, kg/m2 (mean ± SD)	32.37 ± 3.58	30.41 ± 3.75	0.074	0.941
FBG, mmol/L (mean ± SD)	5.98 ± 0.73	6.08 ± 0.75	0.926	0.355
2h PG, mmol/L (mean ± SD)	8.12 ± 1.83	7.54 ± 1.84	2.177	0.031
Systolic blood pressure (mmHg)	128 ± 21	122 ± 20	2.040	0.043
Diastolic blood pressure (mmHg)	81 ± 11	80 ± 10	0.670	0.503
Glycosylated hemoglobin (%)	6.28 ± 0.53	5.89 ± 0.33	6.794	< 0.001
TC (mmol/L)	4.76 ± 1.17	4.64 ± 1.06	0.758	0.449
TG (mmol/L)	1.58 ± 0.32	1.42 ± 0.47	2.544	0.012
HDL-C (mmol/L)	1.25 ± 0.27	1.21 ± 0.32	0.899	0.370
LDL-C (mmol/L)	1.88 ± 0.53	1.85 ± 0.41	0.463	0.644
Uric acid (μmol/L)	3.43 ± 0.76	3.20 ± 0.87	2.067	0.040
SLA (μmol/L)	325.10 ± 75.04	300.22 ± 80.23	2.176	0.031
FINS (μU/mL)	5.96 ± 1.57	5.11 ± 1.19	6.016	< 0.001
HOMA-IR	1.67 ± 0.45	1.21 ± 0.39	7.782	< 0.001

Results presented as *n* (%), unless indicated otherwise. DP: Disease progression; DO: Disease outcome; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; BMI: Body mass index; FBG: Fasting blood glucose; 2h PG: 2h postprandial blood glucose; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; SLA: Anti-soluble liver antigen antibodies; FINS: Fasting insulin; HOMA-IR: Homeostatic model assessment for insulin resistance.

Table 3 Assignment table

Independent variable	Assignment
Blood glucose status	1 = IFG, 2 = IGT, 3 = IFG and IGT coexist
Smoking history	1 = Yes, 2 = No
Drinking history	1 = Yes, 2 = No
Weight	Measured value
Waist circumference	Measured value
BMI	Measured value
2h PG	Measured value
Systolic blood pressure	Measured value
Glycosylated hemoglobin	Measured value
TG	Measured value
Uric acid	Measured value
SLA	Measured value
FINS	Measured value
HOMA-IR	Measured value

IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; BMI: Body mass index; 2h PG: 2h postprandial blood glucose; TG: Triglycerides; SLA: Anti-soluble liver antigen antibodies; FINS: Fasting insulin; HOMA-IR: Homeostatic model assessment for insulin resistance.

Table 4 Logistic regression analysis of disease outcomes in prediabetes patients

Independent variable	β	SE	Wals	*P* value	OR	95%CI
Blood glucose status			1.138	0.566		
Blood glucose status (1)	0.034	0.958	0.001	0.972	1.035	0.158-6.771
Blood glucose status (2)	0.588	0.648	0.825	0.364	1.801	0.506-6.415
Smoking history	0.916	0.486	3.553	0.059	2.499	0.964-6.479
Drinking history	0.341	0.457	0.555	0.456	1.406	0.574-3.445
Weight	0.066	0.020	11.128	0.001	1.068	1.028-1.110
Waist circumference	0.041	0.022	3.427	0.064	1.042	0.998-1.089
BMI	0.006	0.060	0.010	0.920	1.006	0.895-1.131
2h PG	0.150	0.204	0.538	0.463	1.162	0.778-1.734
Systolic blood pressure	0.015	0.010	2.213	0.137	1.016	0.995-1.036
Glycosylated hemoglobin	2.542	0.599	18.014	< 0.001	12.705	3.928-41.092
TG	0.527	0.528	0.997	0.318	1.694	0.602-4.772
Uric acid	0.007	0.003	7.217	0.007	1.007	1.002-1.012
SLA	0.001	0.003	0.226	0.635	1.001	0.996-1.007
FINS	0.503	0.169	8.872	0.003	1.653	1.188-2.301
HOMA-IR	2.224	0.547	16.561	< 0.001	9.245	3.167-26.984
Constant (quantity)	-38.654	6.686	33.420	< 0.001	< 0.001	-

BMI: Body mass index; 2h PG: 2h postprandial blood glucose; TG: Triglycerides; SLA: Anti-soluble liver antigen antibodies; FINS: Fasting insulin; HOMA-IR: Homeostatic model assessment for insulin resistance; OR: Odds ratio; CI: Confidence interval.

Table 5 Receiver operating characteristic curve analysis of weight, glycosylated hemoglobin, uric acid, fasting insulin, homeostatic model assessment for insulin resistance in predicting progression of prediabetes to type 2 diabetes mellitus

Independent variable	AUC	95%CI	Specificity	Sensitivity	Optimum break value
Weight	0.699	0.620-0.778	0.729	0.758	71.75
Glycosylated hemoglobin	0.726	0.645-0.806	0.882	0.515	6.25
Uric acid	0.590	0.512-0.668	0.424	0.788	289.5
FINS	0.666	0.583-0.750	0.835	0.500	6.25
HOMA-IR	0.798	0.736-0.859	0.647	0.818	1.35
Collaborative forecasting	0.905	0.863-0.948	-	-	

AUC: Area under the curve; FINS: Fasting insulin; HOMA-IR: Homeostatic model assessment for insulin resistance; CI: Confidence interval.

Table 6 Analysis of the influence of weight on disease outcome in patients with prediabetes

Model	Weight 1	Weight 2		Weight 3	
		OR (95%CI)	*P* value	OR (95%CI)	*P* value
Model 1	1	1.210 (1.082-2.532)	0.001	1.366 (1.180-2.743)	0.005
Model 2	1	1.233 (1.085-2.640)	0.005	1.357 (1.166-3.768)	0.008
Model 3	1	1.164 (1.041-1.662)	0.011	1.399 (1.142-2.126)	0.033

No variable adjusted in model 1; model 2 adjusted blood glucose status, smoking history, drinking history, waist circumference and body mass index (BMI); model 3 adjusted blood glucose status, smoking history, drinking history, waist circumference, BMI, 2h postprandial blood glucose, systolic blood pressure, glycosylated hemoglobin, triglycerides, uric acid, anti-soluble liver antigen antibodies, fasting insulin, homeostatic model assessment for insulin resistance; weight 1 is 35-60 kg, weight 2 60-80 kg, and weight 3 is 80-100 kg. OR: Odds ratio; CI: Confidence interval.

Table 7 Analysis of the interaction between body weight and independent influencing factors

Independent variable	β	SE	Wals	*P* value	OR	95%CI
Weight	2.664	0.52	26.23	< 0.001	14.356	5.179-39.795
Glycosylated hemoglobin	2.772	0.606	20.948	< 0.001	15.987	4.878-52.390
Weight by glycosylated hemoglobin	-0.828	0.82	1.021	0.312	0.437	0.088-2.178
Constant	-3.082	0.457	45.408	< 0.001	0.046	-
Weight	2.453	0.565	18.86	< 0.001	11.625	3.842-35.174
Uric acid	1.887	0.578	10.664	0.001	6.6	2.127-20.484
Weight by uric acid	1.953	0.719	1.758	0.005	0.386	0.094-1.577
Constant	-2.923	0.459	40.545	0	0.054	-
Weight	2.883	0.565	26.066	< 0.001	17.86	5.906-54.009
FINS	2.578	0.622	17.189	< 0.001	13.174	3.894-44.570
Weight by FINS	-0.797	0.833	0.916	0.339	0.451	0.088-2.305
Constant	-3.229	0.51	40.113	< 0.001	0.04	-
Weight	3.31	1.08	9.39	0.002	27.375	3.296-227.343
HOMA-IR	3.067	1.049	8.55	0.003	21.471	2.749-167.718
Weight by HOMA-IR	-1.463	1.15	1.619	0.203	0.231	0.024-2.205
Constant	-4.29	1.007	18.159	< 0.001	0.014	-

FINS: Fasting insulin; HOMA-IR: Homeostatic model assessment for insulin resistance; OR: Odds ratio; CI: Confidence interval.

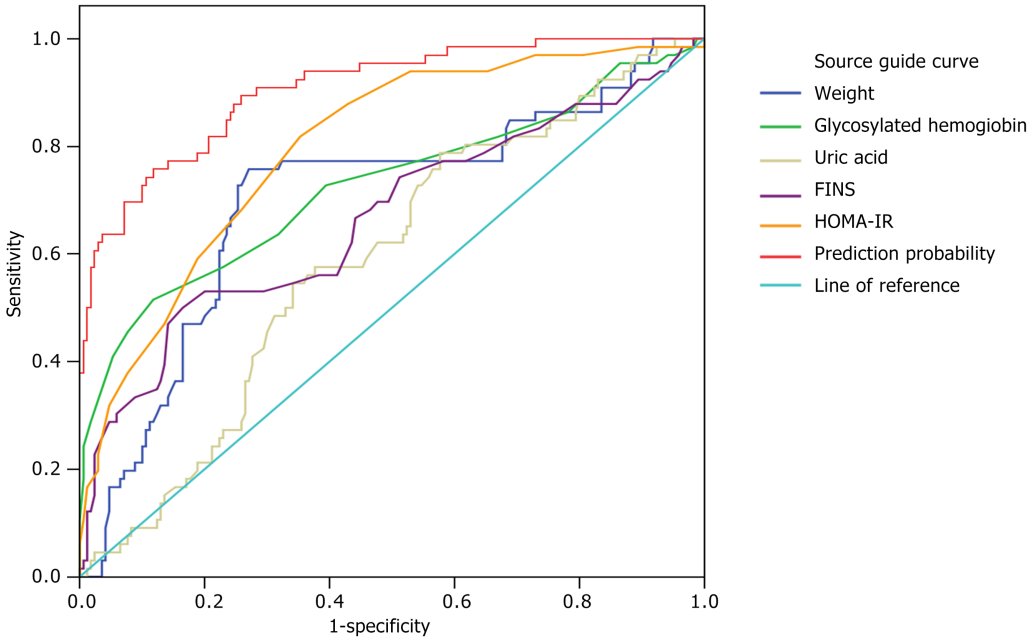

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Figure 1 Receiver operating characteristic curves of body weight, glycosylated hemoglobin, uric acid, fasting insulin, and homeostatic model assessment for insulin resistance predict progression of prediabetes to type 2 diabetes mellitus. FINS: fasting insulin; HOMA-IR: Homeostatic model assessment for insulin resistance.

weight 80-100 kg was 1.399 (1.142-2.126) (P = 0.033), compared with those with weight ranging from 35 to 60 kg. The risk of prediabetes progression to T2DM was increased by 1.399 times with high body weight based on low body weight.

Prediabetes is an early stage of glucose metabolism disorder, in which glucose regulation function is impaired, accompanied by insulin resistance and lipid metabolism disorder[15]. Being overweight or obese increases the risk of diabetes, and our study did not show the risk effect of BMI on progression to T2DM, which may be because BMI did not reflect the actual content and distribution of body fat. Although BMI may be normal, the body may have ectopic fat deposition and metabolic disorders[16]. Being overweight or obese is an important factor in predicting self-underestimation of body mass in prediabetes, and overweight people tend to underestimate self-body mass[17]. Only 10% of overweight DM patients judged their body weight correctly[18]. High body weight in prediabetes patients with improper control of body mass increases the risk of progression to T2DM. Obesity is associated with metabolic dysfunction and overnutrition. Weight gain often means increased BMI, which is closely related to changes in adipocyte secretion, release of inflammatory mediators, chronic inflammation, and insulin resistance[19]. For patients with DM, 5%-10% weight loss can improve their health status, reduce the level of glycosylated hemoglobin, improve cardiovascular disease risk factors, and reduce the use of antidiabetic, antihypertensive and lipid-regulating drugs[20].

The progression of prediabetes is reversible, and effective intervention is important for the outcome of patients with prediabetes[21]. Weight loss can reduce or even reverse ectopic deposition and reduce progression of prediabetes to T2DM. At present, the main clinical intervention for prediabetes is lifestyle intervention, supplemented by drug intervention. Lifestyle intervention mainly includes diet, exercise, body mass, and dietary intervention is divided into diet control and nutritional supplementation[22]. Through long-term control of total dietary calories and restriction of various types of energy intake, such as fat and sugar, weight loss can be achieved and postprandial hyperglycemia can be reduced, thus reducing the burden on pancreatic islet beta cells, improving the function of beta cells, and improving HOMA-β, to correct the disorder of glucose metabolism[11]. In recent years, many patients with DM in western countries have been affected by various dietary programs, such as low-carbohydrate diet, a very low-carbohydrate diet, and a Mediterranean diet to reduce weight and improve blood sugar. In particular, a low-carbohydrate diet has the most obvious effect on weight loss, which has been widely confirmed in some clinical experiments, including obesity, metabolic disorders, and risk of cardiovascular events[23]. There are also many domestic and foreign studies on low-carbon diets, and it has been preliminarily confirmed that a low-carbon diet can reduce body weight and the level of glycosylated hemoglobin[24]. Griauzde *et al*[18] showed that carbohydrate-restricted diets benefit patients with obesity and T2DM and can be used as a potential tool to support individual patients' weight loss and metabolic health. Therefore, we suggest that dietary intervention programs represented by a low-carbon diet can reduce body weight and body fat accumulation in prediabetes patients with high body weight. At the same time, regular monitoring of blood glucose and adjustment of the program are conducive to better weight loss, and to delay or even reverse the course of prediabetes. However, it should be noted that weight loss intervention is not appropriate in patients with severe organ diseases, malnutrition, and age > 55 years.

Our interaction analysis showed that there was a multiplying interaction between body weight and uric acid, but no interaction between body weight and glycosylated hemoglobin, FINS and HOMA-IR, suggesting that for prediabetes

patients with T2DM, the higher the body weight, the higher the uric acid level. The levels of glycosylated hemoglobin, FINS and HOMA-IR were not related to body weight. Obesity is a condition in which body weight exceeds the normal standard and body fat is accumulated excessively or distributed abnormally. Obesity is associated with elevated blood uric acid, and hyperuricemia is associated with obesity[25]. Obesity caused by high body weight is related to genetic and environmental factors. Such people often have an unreasonable diet and lack of exercise, resulting in accumulation of body fat, which can be accompanied by disorders of purine metabolism or uric acid excretion, increasing uric acid levels, the end product of purine metabolism. In addition, regular intake of too much high-purine food, such as seafood, animal viscera, or long-term drinking of beer, may lead to increased purine metabolism in the body, resulting in increased uric acid level, and thus manifested as disorders of uric acid metabolism[26]. Uric acid is associated with obesity[27]. Therefore, we suggest that prediabetes patients with high body weight can undertake comprehensive treatment through behavior, diet, and exercise, adopt a healthy lifestyle and reasonable eating habits, to reduce weight, avoid elevated uric acid, and reduce the possibility of prediabetes progressing to T2DM. However, this study has its limitations, that is, the sample size in this study is insufficient, and there may be selective bias leading to biased research results. In addition, we selected the study sample from a single center, and the research results can only reflect the population of this center. It is unknown whether it is widely applicable to the population of other centers. Therefore, multi-center and larger sample size studies are needed to further verify these findings.

CONCLUSION

High body weight in patients with prediabetes is an independent risk factor for progression to T2DM, and high body weight coexisting with high uric acid level increases the risk of T2DM progression. Clinically, patients with high body weight and high uric acid should be vigilant, and timely clinical intervention measures should be taken to reduce the risk of prediabetes progressing to T2DM.

ARTICLE HIGHLIGHTS

Research background

The high incidence of diabetes mellitus (DM) is a serious threat to public health. There have been many reports on its influencing factors, but few studies on the influence of body weight on the progression from prediabetes to type 2 diabetes mellitus (T2DM), and the interaction between body weight and various influencing factors has not been reported.

Research motivation

The phenomenon of high weight, waist circumference, and body mass index is common in prediabetes patients, and there are many factors affecting the progression of prediabetes to T2DM. Unilateral weight control cannot reduce this risk, and it is necessary to understand the interaction between weight and other factors.

Research objectives

The purpose of this study was to explore the weight status of patients with prediabetes and analyze the interaction between weight and other disease outcome (DO) factors, so as to guide clinical intervention and reduce the risk of prediabetes progressing to T2DM.

Research methods

A retrospective analysis of 236 patients with prediabetes and 50 patients with normal glucose control was performed. Clinical data and follow-up results of all patients were collected. The influencing factors (including body weight) of prediabetes DO were analyzed by logistic regression, and the interaction between body weight and independent influencing factors was analyzed by a general linear model (univariate).

Research results

Body weight, glycosylated hemoglobin, uric acid, fasting insulin (FINS), and homeostatic model assessment for insulin resistance (HOMA-IR) were independent factors affecting the progression of prediabetes to T2DM ($P < 0.05$). There was a multiplicative interaction between weight and uric acid ($\beta = 1.953$, $P = 0.005$).

Research conclusions

Body weight has a significant effect on prediabetes progression to T2DM, and coexistent high body weight and high uric acid increase the risk of progression to T2DM.

Research perspectives

From the perspective of high body weight as a risk factor for prediabetes progression to T2DM, the interaction between body weight and other risk factors (including glycosylated hemoglobin, uric acid, FINS and HOMA-IR) was discussed, and low carbon diet and weight loss were proposed to reduce the risk of progression and guide clinical intervention.

FOOTNOTES

Author contributions: Li YY designed and performed the research and wrote the paper; Lin XY designed the research and supervised the report; Tong LP, Wu XD, Lin D, and Lin Y provided clinical advice.

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ORIGINAL ARTICLE

Observational Study

Characteristics of glucose change in diabetes mellitus generalized through continuous wavelet transform processing: A preliminary study

Yoichi Nakamura, Shinya Furukawa

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Abstract

BACKGROUND

The continuous glucose monitoring (CGM) system has become a popular evaluation tool for glucose fluctuation, providing a detailed description of glucose change patterns. We hypothesized that glucose fluctuations may contain specific information on differences in glucose change between type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), despite similarities in change patterns, because of different etiologies. Unlike Fourier transform, continuous wavelet transform (CWT) is able to simultaneously analyze the time and frequency domains of oscillating data.

AIM

To investigate whether CWT can detect glucose fluctuations in T1DM.

METHODS

The 60-d and 296-d glucose fluctuation data of patients with T1DM (n = 5) and T2DM (n = 25) were evaluated respectively. Glucose data obtained every 15 min for 356 d were analyzed. Data were assessed by CWT with Morlet form (n = 7) as the mother wavelet. This methodology was employed to search for limited frequency glucose fluctuation in the daily glucose change. The frequency and enclosed area (0.02625 scalogram value) of 18 emerged signals were compared. The specificity for T1DM was evaluated through multiple regression analysis using items that demonstrated significant differences between them as explanatory variables.

RESULTS

The high frequency at midnight (median: 75 Hz, cycle time: 19 min) and middle frequency at noon (median: 45.5 Hz, cycle time: 32 min) were higher in T1DM *vs* T2DM (median: 73 and 44 Hz; P = 0.006 and 0.005, respectively). The area of the > 100 Hz zone at midnight to forenoon was more frequent and larger in T1DM *vs* T2DM. In a day, the lower frequency zone (15-35 Hz) was more frequent and the area was larger in T2DM than in T1DM. The three-dimensional scatter diagrams, which consist of the time of day, frequency, and area of each signal after CWT, revealed that high frequency signals belonging to T1DM at midnight had a loose distribution of wave cycles that were 17-24 min. Multivariate analysis revealed that the high frequency signal at midnight could characterize T1DM (odds ratio: 1.33, 95% confidence interval: 1.08-1.62; P = 0.006).

CONCLUSION

CWT might be a novel tool for differentiate glucose fluctuation of each type of diabetes mellitus using CGM data.

Key Words: Continuous glucose monitoring; Pathophysiology; Fourier, Pseudo-frequency; Contour map; Scalogram matrix

Core Tip: In the present study, we hypothesized that continuous wavelet transform differentiates glucose fluctuation according to the type of diabetes mellitus. Type 1 diabetes mellitus (T1DM) was characterized by a rapid change (cycle of a 17-24-min interval at midnight). T2DM was characterized by a broad wave (cycle of a 41-96-min interval during a day). Plotting at the three-dimensional scattergram consisting of time, frequency, and an enclosed area of interest revealed that the data of T1DM on the high frequency zone (60-85 Hz) at midnight dispersed into the allocated box, although the glucose fluctuation of T2DM was aligned regularly.

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INTRODUCTION

The levels of blood glucose change during a day because they are controlled by several factors (*e.g.*, a hormonal network, dietary habits, glucose intake, exercise). With the development of continuous glucose monitoring (CGM) systems[1], such changes can be easily and continuously detected in clinical settings[2]. They are occasionally constituted from various waves with complex forms. Therefore, the properties of those waves are able to decompose any signals following elementary functions that are well concentrated in time and frequency.

Recently, the continuous wavelet transform (CWT) method was utilized for the analysis of oscillating data obtained from clinical diagnostic tools, such as those produced by electroencephalography[3,4], electromyography[5,6], electroretinography[7], phonocardiography[8,9], ultrasound sonoelastography[10], and electrocardiography including a longitudinal wave[5,11-14]. This type of processing has epochal merit for simultaneously exploring the time and frequency domains, although Fourier transform is unable to analyze a time domain[15-17].

When considering the pathophysiology of representative abnormal glucose dynamics, type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) exhibit marked differences. T1DM is an autoimmune disease characterized by β-cell destruction. T2DM is a complex metabolic disorder, in which the pathophysiology involves an interaction between genetic predisposition and environmental triggers. Based on this knowledge, it was hypothesized that daily glycemic variation may provide insight into the different fluctuation patterns of blood glucose according to the etiologies. Therefore, this study evaluated whether CWT could differentiate signals in blood glucose fluctuation between the two DM groups using CGM data.

MATERIALS AND METHODS

Study population

Data were obtained from consecutive 5 outpatients with T1DM and 25 outpatients with T2DM, who visited the Specified Clinic of Soyokaze CardioVascular Medicine and Diabetes Care (Matsuyama, Ehime, Japan) from December 1, 2017 to June 30, 2018. In the present study, the inclusion criteria were: Patients receiving any diabetic therapy; and age > 20 years. The exclusion criteria were: Presence of a malignancy and history of treatment in the previous 5 years; liver dysfunction with transaminase levels > 100 IU/L; renal dysfunction with estimated glomerular filtration rate < 30 mL/min; implantation of a pacemaker; occurrence of acute coronary syndrome in the previous 2 mo; and pregnancy.

Furthermore, 8 outpatients treated for hypertension or dyslipidemia with normal glucose fluctuation applied through an in-hospital communication sheet supplied by the clinical study team. In addition to those volunteers, two healthy volunteers who applied *via* an invitation on the website homepage of the clinic were also included. Their data were utilized in this study as a reference to determine the normal glucose levels through CWT processing. All subjects provided written informed consent for their participation in this study. This study was approved by the ethics committee of Ehime University (approval No. 1711001).

Data collection and statistical calculation of glucose variance

A sensor of the flash glucose monitoring system (FreeStyle Libre Pro®; Abbott, Chicago, IL, United States) was attached to the back of the upper arm of all subjects. The memorized text document data obtained from subcutaneous tissue every 15 min over a period of 14 d were converted to comma-separated values files. These data were transformed through CWT processing. The 60-d data of 5 patients with T1DM and 296-d data obtained from 25 patients with T2DM were evaluated. Glucose data of a total of 356 d were employed in this analysis, because this evaluation tool was used to search for a limited frequency glucose fluctuation into the daily glucose change.

CWT

Wavelet transform decomposes a signal into a series of dilated and translated versions of the mother wavelet function [17]. The form of the CWT of a signal is defined by the following formula.

$$c_{a,b} = \int_R x(t)\frac{1}{\sqrt{a}}\psi * (\frac{t-b}{a})dt$$

$$\psi(x) = \pi^{-1/4}\cos(7x)e^{-x^2/2}$$

In this study, $\psi(x)$ was nominated as a Morlet form, using wave number 7 as the mother wavelet. This process was performed using OriginPro® version 2018 (OriginLab Co., Northampton, MA, United States). This function computes the real continuous wavelet coefficient of $x(t)$ for each given scale presented in the scale vector a and each position b from 1 to 96 during 24 h. The obtained scalogram matrix by CWT was presented in the form of a contour diagram. In case of data loss due to a sensor error, the data of that day were excluded from the analysis. Consequently, this application assigned a pseudo-frequency with a cycle of 1 Hz wave over a 24-h period. The signals that emerged on the contour diagram were divided into 18 areas according to the time and frequency zone, which corresponded to the peak scalogram value. The frequency zone was defined as follows: 60-85 Hz, high frequency signal (P1-P3); 35-55 Hz, middle frequency signal (P4-P8); > 100 Hz, super-high frequency signal (P9-P11); and 15-35 Hz, lower frequency signal (P12-P18). If the enclosed area at the 0.02625 scalogram value fused to another area of different points, those signal data were adopted at the point that showed the highest scalogram value. The other area points, which had a lower scalogram value, defined defect data because those borderlines could not be fixed.

Signal characteristics of T1DM

The frequency at a point that showed the peak scalogram value was compared between the groups to clarify the specific glucose fluctuation in T1DM. The area enclosed at the scalogram value of 0.02625 on the contour diagram was also evaluated. Subsequently, the relationships of factors exhibiting significant differences with the specific glucose fluctuation in T1DM were determined through multivariate analysis.

Statistical analysis

The statistical methods used in this study were reviewed by Data Seed Inc., a consulting company specializing in biostatistics (https://dt-seed.com, info@dt-seed.com). Age, body mass index, hemoglobin A1c levels, and daily dose of insulin used were compared between the T1DM and T2DM groups using the Mann-Whitney U test. All frequencies and areas, which emerged through CWT in the two groups, were also evaluated using the Mann-Whitney U test. The statistically calculated data of mean glucose and mean amplitude of glucose excursion (MAGE) were converted to natural logarithm, because they were obtained based on an approximate normal distribution. Because of a normal distribution, those indices together with log mean glucose, standard deviation, percent coefficient of variation, and log MAGE were evaluated using the unpaired t-test. Sex, medications, and number of signals obtained through CWT were assessed using the Fisher's exact test. For the selection of possible factor characterized in T1DM glucose fluctuation, logistic regression analysis was employed using factors that showed significant differences between the two groups as explanatory variables. $P < 0.05$ was considered statistically significant.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to include additional statistical functions frequently used in biostatistics [18].

RESULTS

The characteristics of subjects and medications used in both diabetes groups, as well as data of subjects without diabetes (reference), are summarized in Table 1. The average data for glucose change did not show a significant difference between the groups. However, significant differences between the two groups were recorded for the standard deviation, percent coefficient of variation, and log MAGE. The representative contour diagram that emerged from glucose

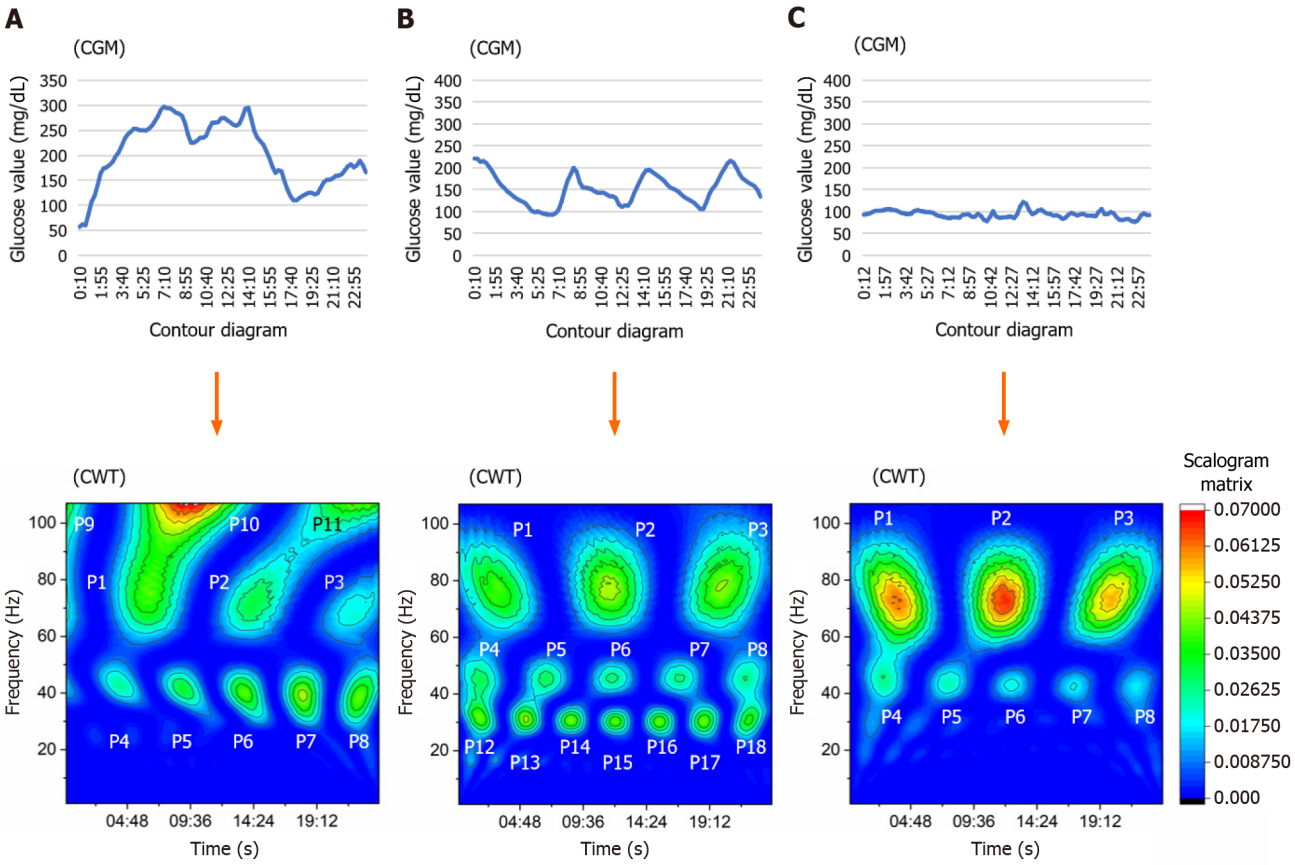

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Figure 1 Representative image of the contour diagram converted through continuous wavelet transform of continuous glucose monitoring data associated with both diabetes groups, including a subject without diabetes. The upper panels indicate the continuous glucose monitoring data of each group. The bottom panels indicate the contour diagram after continuous wavelet transform (CWT) processing. The CWT produced 18 signals from the continuous glucose shift. The signals were divided according to the time and frequency zone, which corresponded to the peak scalogram value. P1-P3, P4-P8, P9-P11, and P12-P18 belonged to a high frequency zone (about 60-85 Hz; indicating a wave period of 17-24 min), middle frequency zone (35-55 Hz; indicating a wave period of 26-41 min), super-high frequency zone (> 100 Hz; indicating a wave period < 14 min), and low frequency zone (15-35 Hz; indicating a wave period 41-96 min), respectively. A: Type 1 diabetes mellitus; B: Type 2 diabetes mellitus; C: A subject without diabetes as a reference. T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; CGM: Continuous glucose monitoring; CWT: Continuous wavelet transform.

fluctuation after conversion through CWT is shown in Figure 1. The T1DM group showed some signals on the super-high frequency zone (rate: 20% at P9, 27% at P10) in contrast with the T2DM group (rate: 7% at P9, 11% at P10) (P = 0.003 and P = 0.003, respectively). Signals of the T2DM group appeared more frequently on the lower frequency zone (*i.e.*, 15-35 Hz on the contour map, indicating a time cycle of 41-96 min) throughout the day (Table 2). The median frequency of P1 signal in the T1DM group was 75 Hz (quartile: 72-78 Hz), indicating a time cycle of 19 min. This value was higher than that noted in the T2DM group [median: 73 Hz (quartile: 71–75 Hz)] (P = 0.006). The wave period of this range signals in T1DM was 18-20 min. Moreover, the median frequency of P6 signal in the T1DM group was 45.5 Hz (quartile: 44-46.25 Hz), indicating a time cycle of 32 min. Signals that emerged on the middle frequency range around noon each day were higher than those observed in the T2DM group [median: 44 Hz (quartile: 42-45 Hz)] (P = 0.005) (Table 3). The area of P9 and P10 points of the T1DM group was larger than that of the T2DM group, although both groups exhibited less emergence in that frequency zone compared with other zones. The area of the lower frequency zone, which was positioned at P12-P17, was smaller and less frequent in the T1DM group *vs* the T2DM group (Table 4).

The three-dimensional (3D) scatter diagrams, which consist of a time of a day, a frequency, and an area of each signal after CWT, are demonstrated in Figure 2. Subjects without diabetes showed three high frequency signals (P1-P3) and five middle frequency signals (P4-P8) regularly distributed in a similar interval during 24 h. Occasionally, some cases exhibited signals in the low frequency zone. The distribution of T2DM was similar to that observed in subjects without diabetes, although each signal zone expanded toward a time (x-axis) and an area (y-axis) direction; the frequency fluctuation (z-axis) was small for all signals. Furthermore, signals that emerged on the low frequency zone were increased, whereas other signals of the super-high frequency zone were observed in the glucose fluctuation of patients with T2DM in a few days. By contrast, the 3D scatter diagram of T1DM showed a destroyed distribution pattern, particularly in the frequency width of the P1 signal. Consequently, the borderline of each signal disappeared, complicating the differentiation of signals.

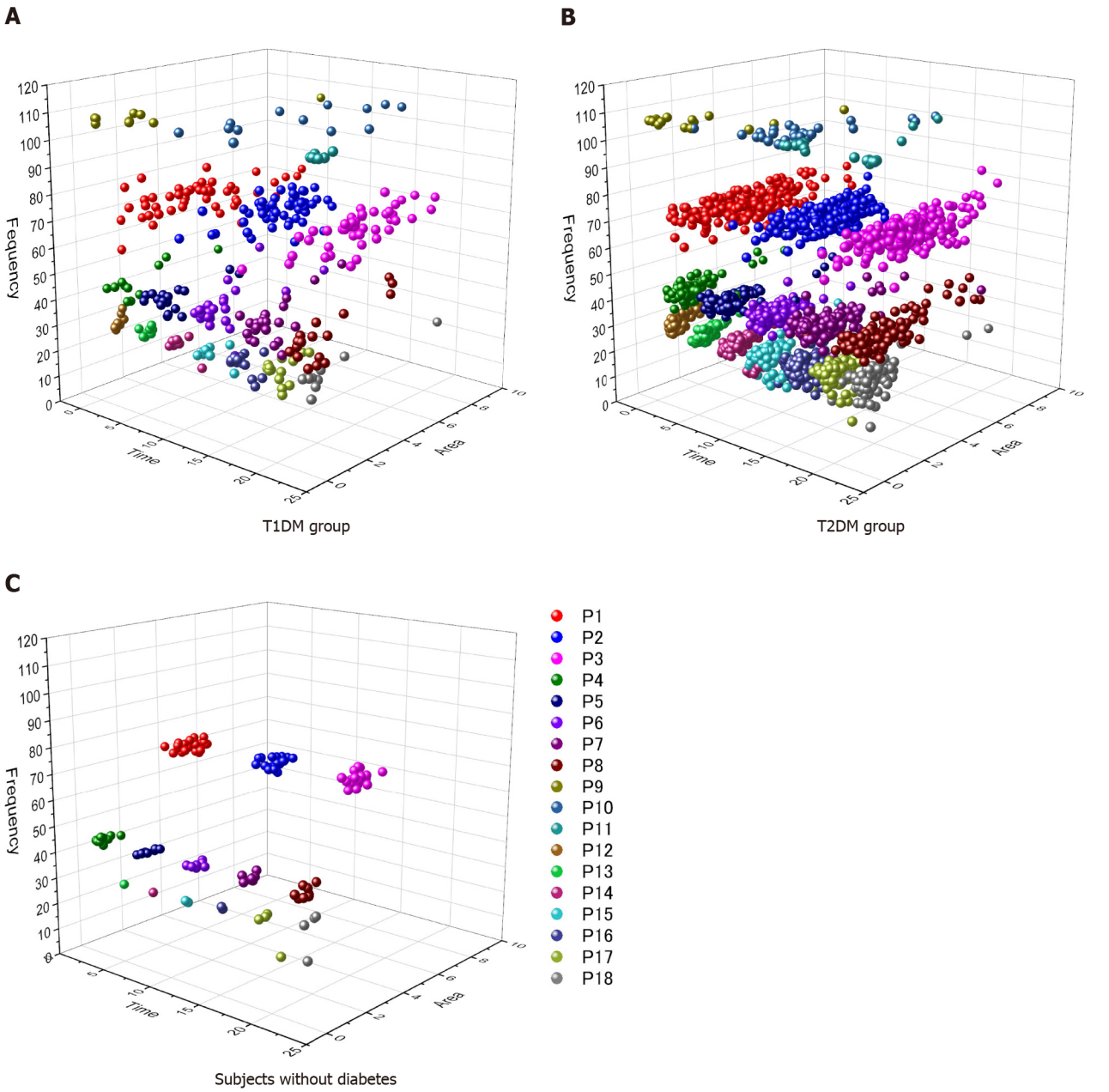

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Figure 2 Comparison of the three-dimensional scattering diagram between groups. The x-axis indicates time during a day; the y-axis indicates the area enclosed at the 0.02625 scalogram value; the z-axis indicates a pseudo-frequency determined after continuous wavelet transform processing. The wave cycles of P1 signals belonging to type 1 diabetes mellitus (T1DM) were distributed during 17-24 min. The loose distribution of P1 signal wave length characterized T1DM. A: Type 1 diabetes mellitus group; B: Type 2 diabetes mellitus group; C: Subjects without diabetes.

In the multivariate analysis, the area data of P13, P14, and P15 were removed because the value of the variance inflation factor was > 5. Furthermore, the area data of P9, P12, and P16 were also removed because those items had a large 95% confidence interval (CI) (1.33 × 10^{-16} to 1.90 × 10^{12} at P9, 0.08-50.4 at P12, and 0.01-213 at P16) (Supplementary Table 1). Consequently, the frequency of P1 and P6 signals and the area of P10 and P17 signals were nominated as explanatory variables. Logistic regression analysis revealed that the frequency of the P1 signal could characterize the specific T1DM distribution [odds ratio (OR) = 1.33, 95%CI: 1.08-1.62; P = 0.006] (Table 5). In both analyses with or without a large CI at P9, P12, and P16, those results indicated the frequency of P1-characterized T1DM glucose fluctuation.

DISCUSSION

The present evaluation of 356-d glucose data demonstrated that CWT processing can detect the specific glucose wave form of T1DM with regard to the onset time and time cycle in the contour map. It revealed that the P1 signal wave length was broadly distributed during a 17-24 min interval at midnight. This finding indicated that the cycle of glucose change

Table 1 Background characteristics of patients with diabetes (*n* = 30) and subjects without diabetes (*n* = 10)

Characteristic	T1DM group	T2DM group	*P* value	Subjects without diabetes
Days evaluated, *n*	60	296	-	23
Age, yr	50 (43-66)	61 (48-71)	0.419[a]	60 (47.5-72.3)
Sex as female/male, *n*	2/3	7/18	0.622[b]	4/6
BMI in kg/m^2	28.3 (26.0-39.3)	26.0 (22.5-28.6)	0.229[a]	22.9 (21.7-27.2)
HbA1c, %	8.8 (8.6-9.3)	7.6 (6.9-9.0)	0.220[a]	5.4 (5.4-5.5)
Log MG	5.09 ± 0.32	5.11 ± 0.30	0.579[c]	4.61 ± 0.08
SD	56.26 ± 18.63	44.60 ± 20.29	< 0.001[c]	11.58 ± 2.37
%CV	34.85 ± 11.85	25.53 ± 7.43	< 0.001[c]	11.56 ± 2.66
Log MAGE	4.58 ± 0.40	4.41 ± 0.42	0.003[c]	3.17 ± 0.27
Medication, *n*				
Metformin	0	5	0.556[b]	N/A
DPP-4 inhibitor	0	21	0.001[b]	N/A
α-GI	0	3	1.000[b]	N/A
Thiazoline	0	14	0.045[b]	N/A
SGLT2 inhibitor	0	4	1.000[b]	N/A
SU	0	0	1.000[b]	N/A
GLP-1 RA	0	5	0.556[b]	N/A
Insulin	5	16	0.286[b]	N/A
Total insulin dose in U	37 (34-38)	8 (0-20)	0.008[a]	N/A
Ultra-rapid in U	21 (18-26)	0 (0-11)	0.030[a]	N/A
Lasting in U	16 (11-20)	2 (0-14)	0.022[a]	N/A

[a]Mann-Whitney *U* test.
[b]Fisher's exact test.
[c]Unpaired *t*-test.
BMI: Body mass index; CV: Coefficient of variation; DPP-4: Dipeptidyl peptidase 4; GI: Glucosidase inhibitor; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; HbA1c: Hemoglobin A1c; MAGE: Mean amplitude of glucose excursion; MG: Mean glucose; N/A: Not applicable; SD: Standard deviation; SGLT2: Sodium-glucose co-transporter type 2; SU: Sulfonylurea; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

in T1DM was irregular and involved different waves around a 19 min interval at midnight. On the other hand, T2DM was characterized by low frequency signals distributed during a 39-85 min cycle that emerged frequently, and those areas increased during 1 d.

The CWT represents the time-frequency space of a signal as a matrix with magnitude values that can be readily visualized in the form of a heat map to reveal important features, transient effects, and anomalies[17]. T1DM showed super-high frequency signals from midnight to forenoon with high probability. Furthermore, the distribution of P1 signals in the T1DM group showed differences in time, area, and frequency on the contour map after CWT processing. However, the distribution in the T2DM group was similar to that observed in subjects without diabetes. This observation suggested that T1DM exhibits complex and short glucose changes. Those rapid and varied glucose changes at midnight might reflect the presence of the dawn phenomenon or Somogyi effect. Notably, a regular signal appearance observed after CWT may indicate preserved basal insulin secretion. By contrast, increased signals on the low frequency zone were frequently noted in the T2DM group. This finding suggested that slow glucose change components were included in the CGM glucose data. However, the reason underlying this finding could not be determined in this study. It is hypothesized that the results might reflect the effects of medications or the pathophysiology of insulin resistance.

Glucose variability in T1DM is largely due to the lack of or diminished insulin secretion. The frequency of fluctuation might be an important phenomenon when considering differences in the pathophysiology of diabetes. Previous studies have reported increases in several statistical calculation markers of T1DM such as the standard deviation of blood glucose change, percent cyclic variation, and MAGE[19,20]. Those indices are calculated based on the amplitude of the glucose value. However, CWT processing discovered the object wave of interest from daily glucose change; furthermore, this method could detect the time when the target wave presented during a day. This is fundamentally different from conventional statistical indices. Unfortunately, CWT could not reverse original data; therefore, it could not detect the amplitude width of the glucose wave, although the value of the scalogram could detect the wave power.

Table 2 Prevalence rate of emerging items on the contour map treated by a continuous wavelet transform between the type 1 diabetes mellitus and type 2 diabetes mellitus groups, *n* = 356

Time zone	Position	Frequency zone	Prevalence rate, %		
			T1DM group	T2DM group	*P* value
Midnight					
	P9	Super-high	20	7	0.003
	P1	High	85	88	0.527
	P4	Middle	20	34	0.047
	P12	Low	13	26	0.032
	P13	Low	15	32	0.008
Daytime					
	P10	Super-high	27	11	0.003
	P2	High	88	93	0.299
	P5	Middle	32	39	0.311
	P6	Middle	40	43	0.670
	P7	Middle	42	48	0.478
	P14	Low	15	33	0.005
	P15	Low	15	35	0.001
Night					
	P11	Super-high	13	10	0.491
	P3	High	83	94	0.014
	P8	Middle	42	50	0.321
	P17	Low	25	43	0.014
	P18	Low	22	41	0.005

T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Recently, it was reported that the use of artificial intelligence and CWT may improve the accuracy of atrial fibrillation detection through electrocardiography (10 s)[14]. This proposed evaluation method based on CGM data may be able to accurately and promptly diagnose pathogenesis through the use of deep learning after CWT processing.

Limitation

In the present study, it was not possible to remove the effects of medications on glucose fluctuation owing to the small sample size. To exclude such bias and identify the specificity for T1DM glucose fluctuation, a large number of patients are required because the degree of impaired β cells differs depending on the stage. Furthermore, T2DM had a different pathophysiology, such as an insulin resistance or a decrease of insulin secretion. Glucose fluctuations differ between days. Therefore, when the pathophysiology of diabetes is assessed, it is important to determine whether glucose data from several days were averaged or data from a single day were used. In this study, the latter approach was employed. Furthermore, this analysis could not determine the amplitude of the target wave form, although the duration of a wave period was obtained because CWT could not reverse original data after processing.

CONCLUSION

The contour diagram obtained through CWT demonstrated that fluctuation in the high frequency wave, indicating a time cycle of 17-24 min at midnight, could characterize T1DM based on glucose transition. The scatter diagram of signals demonstrated that the distribution pattern in T1DM was destroyed, although T2DM exhibited a similar pattern to that observed in subjects without diabetes. The present method may contribute to the differentiation of glucose fluctuations according to the etiology of DM.

Table 3 Comparison of frequency on the contour map treated by a continuous wavelet transform between the type 1 diabetes mellitus and type 2 diabetes mellitus groups, *n* = 356

Time zone	Position	Frequency zone	T1DM group			T2DM group			*P* value
			Min	Median	Max	Min	Median	Max	
Midnight									
	P9	Super-high	106	108	108	106	107	108	0.433
	P1	High	61	75	85	61	73	80	0.006
	P4	Middle	39	45	53	38	45	56	0.265
	P12	Low	29	30.5	38	28	32	36	0.634
	P13	Low	29	30	36	27	31	35	0.965
Daytime									
	P10	Super-high	106	108	108	106	107	108	0.100
	P2	High	66	75	84	59	74	81	0.088
	P5	Middle	37	45	50	37	44	51	0.418
	P6	Middle	33	45.5	58	37	44	51	0.005
	P7	Middle	35	45	54	33	44	57	0.225
	P14	Low	25	30	33	18	30	35	0.895
	P15	Low	25	30	32	17	30	37	0.885
	P16	Low	25	30.5	33	20	30	36	0.725
Night									
	P11	Super-high	107	108	108	105	107	108	0.004
	P3	High	65	75	85	59	74	86	0.104
	P8	Middle	36	45	54	37	44	53	0.893
	P17	Low	25	28.5	33	17	29	36	0.395
	P18	Low	26	33	35	17	31	37	0.166

Max: Maximum; Min: Minimum; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Table 4 Comparison of area on the contour map treated by a continuous wavelet transform between the type 1 diabetes mellitus and type 2 diabetes mellitus groups, *n* = 356

Time zone	Position	Frequency zone	T1DM group			T2DM group			*P* value
			Min	Median	Max	Min	Median	Max	
Midnight									
	P9	Super-high	0.00	0.00	8.70	0.00	0.00	5.34	0.008
	P1	High	0.00	3.01	8.99	0.00	2.75	8.14	0.866
	P4	Middle	0.00	0.00	5.06	0.00	0.00	5.67	0.111
	P12	Low	0.00	0.00	0.60	0.00	0.00	4.01	0.043
	P13	Low	0.00	0.00	0.65	0.00	0.00	1.83	0.011
Daytime									
	P10	Super-high	0.00	0.00	8.32	0.00	0.00	6.81	0.001
	P2	High	0.00	3.96	5.87	0.00	3.65	6.43	0.267
	P5	Middle	0.00	0.00	3.32	0.00	0.00	5.23	0.249
	P6	Middle	0.00	0.00	5.77	0.00	0.00	3.70	0.812

	P7	Middle	0.00	0.00	5.29	0.00	0.00	5.50	0.348
	P14	Low	0.00	0.00	0.95	0.00	0.00	3.91	0.005
	P15	Low	0.00	0.00	1.42	0.00	0.00	4.40	0.003
	P16	Low	0.00	0.00	1.63	0.00	0.00	2.22	0.020
Night									
	P11	Super-high	0.00	0.00	1.07	0.00	0.00	6.48	0.257
	P3	High	0.00	3.39	8.38	0.00	3.75	9.18	0.258
	P8	Middle	0.00	0.00	5.09	0.00	0.00	6.70	0.163
	P17	Low	0.00	0.00	2.02	0.00	0.00	2.47	0.031
	P18	Low	0.00	0.00	7.09	0.00	0.00	7.08	0.059

Max: Maximum; Min: Minimum; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Table 5 Logistic regression analysis for the identification of characteristics of type 1 diabetes mellitus with selected factors, *n* = 356

Selected item	Odds ratio	95%CI		*P* value
		Lower	Upper	
Frequency of P1 signal	1.33	1.08	1.62	0.006
Frequency of P6 signal	0.84	0.63	1.12	0.232
Area of P10 signal	1.24	0.72	2.14	0.432
Area of P17 signal	1.24	0.29	5.29	0.771

CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Recently, the continuous glucose monitoring (CGM) system was readily accepted in the clinical setting. Although that system provides details of the glucose fluctuation that occur during a day, occasionally, a lot of vague data might confuse the interpretation of a glucose shift. Continuous wavelet transform (CWT) is a novel approach for analyzing oscillating data in the case of clinical field. That methodology is able to analyze time domain and frequency domain simultaneously, although Fourier transforms are limited to the analysis of frequency domain.

Research motivation

When the glucose change during a day can replace a waveform, the glucose fluctuation includes some waveform in the glucose change. We hypothesized the specific waveform of type 1 diabetes mellitus (T1DM) might be present because glucose change pattern might be different from T2DM due to a different etiology. The CWT is an available method to explore the target substance into the objects through analyzing oscillating data.

Research objectives

The present study evaluated 60-d glucose fluctuation data obtained from T1DM patients (n = 5) and 296-d data from T2DM patients (n = 25).

Research methods

The data obtained every 15 min from a flash glucose monitoring system during 14 d were converted through the CWT process. In the present study, Morlet form (n = 7) was employed as the mother wavelet. The produced scalogram matrix by CWT was converted to the contour diagram. Through this process, the waveform obtained from CGM divided 18 segment signals, that is, 3 super-high frequency (> 100 Hz) zones, 3 high frequency (60-85 Hz) zones, 5 middle frequency (35-55 Hz) zones, and 7 low frequency (15-35 Hz) zones. The frequency and an enclosed area at 0.02625 scalogram value obtained from those emerged signals were compared between the T1DM and T2DM groups at 18 segments. To identify the specificity of T1DM, a statistical approach was applied. The explanatory variables of a logistic regression analysis model were the nominated items, which were significantly different between groups.

Research results

In the T1DM group, super-high frequency signals at midnight and forenoon emerged more frequently. On the other hand, the prevalence rate of low frequency signals in a day in the T2DM group was increased. The high frequency signal at night and middle frequency signal also emerged frequently in the T2DM group. The frequency of the high frequency signal at midnight and the middle frequency signal at noon in the T1DM group were higher than those of the T2DM group. The areas of low frequent zone in a day in the T2DM group were significantly higher than those of the T1DM group. In multivariate analysis, some data were excluded because of the variance inflation factor and a large 95% confidence interval (CI). Finally, the fine waveform presented in the high frequency signal zone at midnight showed the characteristic wave pattern of T1DM (odds ratio = 1.33, 95%CI: 1.08-1.62; P = 0.006).

Research conclusions

Through the contour diagram after CWT processing, the fine waveform indicating a time cycle of 17-24 min at midnight had characterized the glucose fluctuation of T1DM. However, the low frequency signals emerged frequently in T2DM in 1 d.

Research perspectives

Confirming the accuracy of present study required a lot of data to be obtained from both groups. If an artificial intelligence including deep learning is available in this analyzing system, it will obtain the results rapidly and correctly because this manual process takes a lot of time, even though it is a 1 d data calculation. Furthermore, this novel approach will be available to research the relationship between the diabetic complications and any specific waveform and might select medications according to the patients' conditions to decease any diabetic complications.

FOOTNOTES

Author contributions: Nakamura Y was the guarantor, designed the study, performed the acquisition, analysis and interpretation of the data, and drafted the manuscript; Furukawa S participated in the study design, data interpretation, and manuscript drafting.

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META-ANALYSIS

Indirect comparison of efficacy and safety of chiglitazar and thiazolidinedione in patients with type 2 diabetes: A meta-analysis

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Abstract

BACKGROUND

Chiglitazar is an emerging pan-agonist of all peroxisome proliferator activated receptors (PPAR)-α, δ and γ, and has therapeutic potential for type 2 diabetes (T2D). However, to date, no clinical studies or meta-analyses have compared the efficacy and safety of chiglitazar and traditional PPAR-γ agonist thiazolidinediones (TZDs). A meta-analysis concerning this topic is therefore required.

AIM

To compare the efficacy and safety of chiglitazar and TZD in patients with T2D.

METHODS

PubMed, Medline, Embase, the Cochrane Central Register of Controlled Trials, *Reference Citation Analysis* and *Clinicaltrial.gov* websites were searched from August 1994 to March 2022. Randomized controlled trials (RCTs) of chiglitazar or TZD *vs* placebo in patients with T2D were included. Indirect comparisons and sensitivity analyses were implemented to evaluate multiple efficacy and safety endpoints of interest.

RESULTS

We included 93 RCTs that compared TZD with placebo and one that compared chiglitazar with placebo. For efficacy endpoints, the augmented dose of chiglitazar resulted in greater reductions in hemoglobin (Hb)A1c [weighted mean difference (WMD) = -0.15%, 95% confidence interval (CI): -0.27 to -0.04%], triglycerides (WMD = -0.17 mmol/L, 95%CI: -0.24 to -0.11 mmol/L) and alanine aminotransferase (WMD = -5.25 U/L, 95%CI: -8.50 to -1.99 U/L), and a greater increase in homeostasis model assessment-β (HOMA-β) (WMD = 17.75, 95%CI: 10.73-24.77) when compared with TZD treatment. For safety endpoints, the risks of hypoglycemia, edema, bone fractures, upper respiratory tract infection, urinary tract infection, and weight gain were all comparable between the augmented dose of chiglitazar and TZD. In patients with baseline HbA1c ≥ 8.5%, body mass index ≥ 30 kg/m^2 or diabetes duration < 10 years, the HbA1c reduction and HOMA-β

increase were more conspicuous for the augmented dose of chiglitazar compared with TZD.

CONCLUSION
Augmented dose of chiglitazar, a pan-activator of PPARs, may serve as an antidiabetic agent with preferable glycemic and lipid control, better β-cell function preserving capacity, and does not increase the risk of safety concerns when compared with TZD.

Key Words: Chiglitazar; Thiazolidinedione; Glycemic control; β-cell function; Drug safety

Core Tip: This is the first indirect meta-analysis comparing efficacy and safety of chiglitazar and thiazolidinediones (TZDs). In patients with type 2 diabetes, compared with TZDs, chiglitazar induced favorable glycemic and lipidemic control, preserved β-cell function, without increasing safety concerns.

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INTRODUCTION

Thiazolidinediones (TZDs) are hypoglycemic agents for type 2 diabetes (T2D) that characteristically alleviate insulin resistance (IR) to improve glycemic control[1]. TZDs are able to activate the peroxisome proliferator activated receptors (PPARs), which are mainly distributed in adipose tissue[2]. They also enhance sensitivity to insulin in target tissues through multiple downstream mechanisms including promoting fatty acid storage in adipose tissue and reducing free fatty acids (FFAs)[3], releasing insulin-sensitizing adipokines such as adiponectin[4], and suppressing excretion of IR-inducing cytokines such as tumor necrosis factor (TNF)-α[5]. Therefore, TZDs are effective in patients with traits of IR[6].

In previous clinical trials in patients with T2D, besides the favorable glycemic control[7], TZD also decreased the index of homeostasis model assessment of insulin resistance (HOMA-IR)[8], which indicated improved insulin sensitivity. However, the potential adverse events of TZD (including edema[9], heart failure[10], bone fracture[11], weight gain[2,9] and hepatic injury[12]) raised concerns. It has been reported that TZD lead to overactivation of PPAR-γ, which accelerates weight increase through facilitating adipocyte differentiation[1], and promotes water–sodium retention *via* more epithelial sodium channel expression in kidney tubules[13]. Other detrimental adverse effects including increased risks of bone fracture and heart failure were also found related to selective and excess PPAR-γ activation[1,13].

Due to the safety concerns, further applications of TZD in T2D treatment are therefore limited and whether the specific benefits of TZD outweigh the risks remains controversial. However, chiglitazar, a pan-agonist of PPAR-α, PPAR-δ and PPAR-γ[14], has been developed as a promising agent with improved therapeutic efficacy and safety by activation of multiple PPARs[15]. PPAR-α is mainly expressed in skeletal muscle and liver which regulates fatty acid metabolism[16], and its activation is associated with improved lipid profiles[17]. PPAR-δ is distributed widely in somatic cells, whose activation participates in elevated insulin sensitivity[18] and reverses metabolic abnormalities[15]. PPAR-α activation might also be associated with a reduced risk of heart failure[19], while PPAR-δ agonists have been reported to alleviate diabetic osteoporosis by promoting macrophage polarization[20].

Subsequently, with comprehensive activation of PPAR subtypes, chiglitazar may outperform TZD in terms of efficacy and safety in the management of T2D. However, to our knowledge, there have been no head-to-head randomized clinical trials (RCTs) directly comparing the efficacy and safety of chiglitazar and TZD. Hence, we conducted an indirect comparison meta-analysis using the data from RCTs comparing chiglitazar and TZD with placebo in patients with T2D.

MATERIALS AND METHODS

Study design and registration

This systematic review and indirect meta-analysis was conducted in line with the criteria of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol[21]. Registration has been accomplished on International Prospective Register of Systematic Reviews (PROSPERO) platform as CRD42022334206.

Data sources and searches

In conformation with the recommendations in the Cochrane Handbook for Systematic Reviews for Meta-analysis, we implemented a systematic literature retrieval in Pubmed, Medline, Embase, Cochrane Central Register of Controlled

Trials, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and *Clinicaltrial.gov* websites for RCTs of chiglitazar or TZD treatment with placebo comparator in patients with T2D, which were published between August 1994 and March 2022. The search strings were as follows: Chiglitazar, pioglitazone, rosiglitazone, troglitazone, englitazone, thiazolidinedione, TZD, randomized controlled trial, placebo, efficacy, safety, T2D. The references in retrieved articles were also screened to thoroughly identify available and eligible RCTs.

Study selection and data extraction

The inclusion criteria of this indirect meta-analysis were: (1) Studies conducted in patients with T2D; (2) studies comparing chiglitazar or TZD with placebo; and (3) studies with reports of efficacy or safety outcomes. Two investigators (CL and ZL) independently screened articles by titles, abstracts and full text, excluded duplicate and ineligible studies, evaluated the quality and risk of bias with the Cochrane risk of bias tool, and extracted data from eligible studies. The collected data included: Study design (drug exposure, study duration, sample size in experimental and control arms); publication information (first author and publication year); baseline characteristics of patients [age, baseline hemoglobin (Hb)A1c, body mass index (BMI), sex ratio, ethnicity, and diabetes duration]; efficacy parameters [changes in HbA1c, fasting blood glucose (FBG), HOMA-IR, HOMA-β, total triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)]; and safety parameters (measurements of weight gain; incidence of hypoglycemia, edema, heart failure, bone fracture, upper respiratory tract infection, and urinary tract infection). Required data were primarily abstracted from the original articles or attached supplementary materials. The *Clinicaltrials.gov* website was subsequently searched if data were not available in articles and supplementary materials. Discrepancies were resolved by reaching a consensus with another joint investigator (XC).

Risk of bias assessment

The risk of bias in enrolled RCTs was assessed with the Cochrane Collaboration tool[22]. The evaluating measurements included random sequence generation, allocation concealment, blinding of participants and care-givers, missing outcome data, selective outcomes reporting, and other bias. Each domain was evaluated by degrees of the existing risks of bias, including "definitely yes", "probably yes", "definitely no", "probably no" according to the instruction[22].

Data synthesis and analysis

The primary efficacy endpoint was defined as indirect comparison of changes in HbA1c after treatment with chiglitazar or TZD in comparison with placebo. The indirect comparisons for other efficacy parameters (including FBG, HOMA-IR, HOMA-β, TG, LDL-C, HDL-C, ALT and AST) were interpreted as exploratory efficacy endpoints. The primary safety endpoint was defined as indirect comparison of the incidence of hypoglycemia after treatment with chiglitazar or TZD in comparison with placebo. Indirect comparisons for the incidence of other adverse events including edema, heart failure, bone fracture, upper respiratory tract infection, and urinary tract infection, and measurement of weight gain were interpreted as exploratory safety endpoints. Subgroup analyses with regard to baseline characteristics including age, baseline HbA1c, BMI, male percentage, predominant ethnicity, diabetes duration, follow-up duration, and monotherapy or combination therapy were performed to further characterize the influences of these potentially associated factors on the outcomes. Caucasian predominance was defined as the percentage of Caucasian > 50% of the participants. Correspondingly, Asian predominance was defined as the percentage of Asian > 50% of the participants. Meanwhile, we also conducted subgroup analyses concerning different TZD subtypes in indirect comparisons for changes in HbA1c and TG to further compare the efficacy between chiglitazar and different subtypes of TZD. Meta-regression analyses evaluating the potential correlation between baseline characteristics (including age, male percentage, BMI, diabetes duration, study duration, and baseline HbA1c) and the study outcomes were also conducted in the TZD treatment group (since the chiglitazar treatment group only involved one RCT, when the meta-regression analysis could not be implemented).

Prior to producing an indirect estimate of the treatment effect of chiglitazar *versus* TZD, we primarily checked the adequacy of such synthesis[23,24]. Homogeneity of the results from the placebo group as a common comparator for the indirect comparison was first evaluated among included studies. Whether the treatment effects were sufficiently homogeneous to be pooled within each comparison of chiglitazar *vs* placebo and TZD *vs* placebo was evaluated. We also qualitatively assessed the trials for patient characteristics and design features for comparability, based on which, the subsequent sensitivity analyses were performed to control the potential confounding effects.

To perform the indirect comparison, we firstly calculated the pooled treatment effect estimates of chiglitazar *vs* placebo and TZD *vs* placebo through regular meta-analysis statistical methods. Afterwards, the indirect comparison was implemented by synthesizing the pooled treatment effect estimates of each treatment group compared with placebo. Results of continuous variables in this indirect meta-analysis were presented as the weighted mean difference (WMD) with 95% confidence intervals (CIs). For discontinuous variables, the risk ratios (RRs) with 95%CIs were calculated and rendered. The heterogeneity of the included studies was evaluated by Higgins I^2 statistics. $I^2 \geq 50\%$ represented a high level of heterogeneity; otherwise, a low level of heterogeneity level was considered. A random-effects model was uniformly adopted for data analyses. Publication bias was assessed with the funnel plot. Statistical significance was considered at $P < 0.05$. Statistical analyses were principally completed by Review Manager version 5.3 (Nordic Cochrane Center, Copenhagen, Denmark) and STATA version 12.0 (Stata Corp., College Station, TX, United States).

RESULTS

Characteristics and quality assessments of included studies

There were 94 RCTs included in this meta-analysis, including one comparing chiglitazar with placebo (166 participants in the chiglitazar arm *vs* 202 in the placebo arm), and 93 comparing TZD with placebo (15580 participants in the TZD arm *vs* 14706 in the placebo arm). The RCT of chiglitazar investigated two doses, where 32 mg and 48 mg were defined as the standard and augmented doses, respectively. The TZDs involved in this meta-analysis included pioglitazone, rosiglitazone and troglitazone. The selection and inclusion process of eligible studies is summarized in the flow chart (Figure 1).

Baseline characteristics of included studies are recorded in Supplementary Table 1. The quality assessments were conducted with Cochrane instruments (Supplementary Table 2), which indicated low overall risks of bias in included studies. There was one RCT with high risk of frequent missing data, while all RCTs were with low risks in inadequate randomization sequence generation, inadequate allocation concealment, selective outcome reporting, masking patients and caregivers, and masking outcome assessors. The publication bias was evaluated by funnel plots, which displayed even distributions in most of the endpoints but an asymmetric distribution for the endpoint of edema (Supplementary Figure 1).

Indirect comparisons of effects of augmented dose of chiglitazar versus TZD on efficacy endpoints

For glycemic control, compared with placebo, chiglitazar (WMD = -1.05%, 95%CI: -1.10 to -1.00%) and TZD (WMD = -0.90%, 95%CI: -1.00 to -0.79%) significantly reduced HbA1c in patients with T2D (Supplementary Figure 2). The indirect comparison indicated a greater reduction in HbA1c with the augmented dose of chiglitazar compared with TZD (WMD = -0.15%, 95%CI: -0.27 to -0.04%). Both chiglitazar (WMD = -1.55 mmol/L, 95%CI: -2.08 to -1.09 mmol/L) and TZD (WMD = -2.05 mmol/L, 95%CI: -2.32 to -1.77 mmol/L) were associated with significantly reduced FBG level when compared with placebo. The reduction in FBG was comparable between the augmented dose of chiglitazar and TZD (WMD = 0.50 mmol/L, 95%CI: -0.04 to 1.03 mmol/L).

With respect to lipid profiles, chiglitazar (WMD = -0.38 mmol/L, 95%CI: -0.40 to -0.36 mmol/L) and TZD treatment (WMD = -0.21 mmol/L, 95%CI: -0.27 to -0.15 mmol/L) were effective in lowering TG levels in patients with T2D compared with placebo. The indirect comparison indicated greater TG reduction with chiglitazar compared with TZD (WMD = -0.17 mmol/L, 95%CI: -0.24 to -0.11 mmol/L). Although chiglitazar and TZD were both associated with increased LDL-C compared with placebo, greater LDL-C elevation was observed in patients with augmented dose chiglitazar compared with TZD (WMD = 0.13 mmol/L, 95%CI: 0.09 to 0.17 mmol/L). Both chiglitazar (WMD = 0.09 mmol/L, 95%CI: 0.086 to 0.094 mmol/L) and TZD (WMD = 0.10 mmol/L, 95%CI: 0.08 to 0.11 mmol/L) contributed to elevated HDL-C levels compared with placebo. Such effects on HDL-C were comparable between augmented dose of chiglitazar and TZD (WMD = -0.01 mmol/L, 95%CI: -0.02 to 0.14 mmol/L).

Although the effectiveness of reducing HOMA-IR index was validated in patients treated with augmented dose chiglitazar (WMD = -0.94, 95%CI: -0.99 to -0.89) and TZD (WMD = -1.81, 95%CI: -2.30 to -1.33) compared with placebo, chiglitazar might underperform with respect to HOMA-IR reduction compared with TZD (WMD = 0.87, 95%CI: 0.38-1.37). However, chiglitazar was associated with a profound elevation in HOMA-β index compared with placebo (WMD = 16.64, 95%CI: 16.23-17.05), which was not observed in patients with TZD treatment compared with placebo (WMD = -1.11, 95%CI: -8.12 to 5.90). The indirect comparison further indicated the superiority of chiglitazar in HOMA-β improvement (WMD = 17.75, 95%CI: 10.73-24.77) over TZD.

For liver enzymes, compared with placebo, chiglitazar treatment was associated with significantly decreased ALT (WMD = -6.60 U/L, 95%CI: -9.19 to -4.01 U/L) and AST level (WMD = -3.00 U/L, 95%CI: -4.66 to -1.34 U/L). TZD was associated with significantly decreased ALT level (WMD = -1.35 U/L, 95%CI: -8.32 to -0.62 U/L) but did not significantly change AST level (WMD = -0.03 U/L, 95%CI: -6.44 to -6.40 U/L) in patients with T2D. By indirect comparison, the augmented dose of chiglitazar outperformed TZD for ALT reduction (WMD = -5.25 U/L, 95%CI: -8.50 to -1.99 U/L), whereas chiglitazar and TZD exhibited similar effects on AST levels (WMD = -2.98 U/L, 95%CI: -9.61 to 3.65 U/L) (Figure 2).

Sensitivity analyses showed that chiglitazar reduced HbA1c more prominently compared with TZD in patients with age ≥ 60 years (WMD = -0.30%, 95%CI: -0.41 to -0.18%), baseline HbA1c ≥ 8.5% (WMD = -0.44%, 95%CI: -0.58 to -0.30%), BMI ≥ 30kg/m^2 (WMD = -0.24%, 95%CI: -0.40 to -0.08%), and duration of diabetes < 10 years (WMD = -0.16%, 95%CI: -0.31 to -0.02%) (Supplementary Table 3). The increase in HOMA-β after chiglitazar treatment was significantly greater than that after TZD treatment in patients with baseline HbA1c ≥ 8.5% (WMD = 26.36, 95%CI: 8.80-43.93), BMI ≥ 30 kg/m^2 (WMD = 29.42, 95%CI: 19.34-39.50) and duration of diabetes < 10 years (WMD = 26.36, 95%CI: 8.80-43.93) (Supplementary Table 3). Sensitivity analyses of TZD subtypes indicated that the greater reduction in HbA1c in patients treated with augmented dose of chiglitazar *vs* TZD was mainly shown by comparison between chiglitazar 48 mg once daily and rosiglitazone 4 mg once daily (WMD = -0.39 %, 95%CI: -0.67 to -0.11 %). The greater reduction in TG after treatment by chiglitazar was mainly shown by comparison between chiglitazar 48 mg once daily and rosiglitazone 4 mg once daily (WMD = -0.58 mmol/L, 95%CI: -0.86 to -0.30 mmol/L) as well as comparison between chiglitazar 48 mg once daily and rosiglitazone 8 mg once daily (WMD = -0.22 mmol/L, 95%CI: -0.36 to -0.08 mmol/L) (Supplementary Table 3).

Indirect comparisons of the effects of augmented dose of chiglitazar vs TZD on safety endpoints

Compared with placebo, chiglitazar did not increase the risk of hypoglycemia (RR = 2.43, 95%CI: 0.45-13.12), which was elevated in patients with TZD treatment (RR = 1.72, 95%CI: 1.48-2.01) (Supplementary Figure 3). However, the indirect comparison suggested a non-significant difference in risk of hypoglycemia between chiglitazar and TZD treatment (RR = 1.42, 95%CI: 0.26-7.68). Both chiglitazar (WMD = 2.50 kg, 95%CI: 1.93-3.07 kg) and TZD (WMD = 2.15 kg, 95%CI: 1.51-2.79

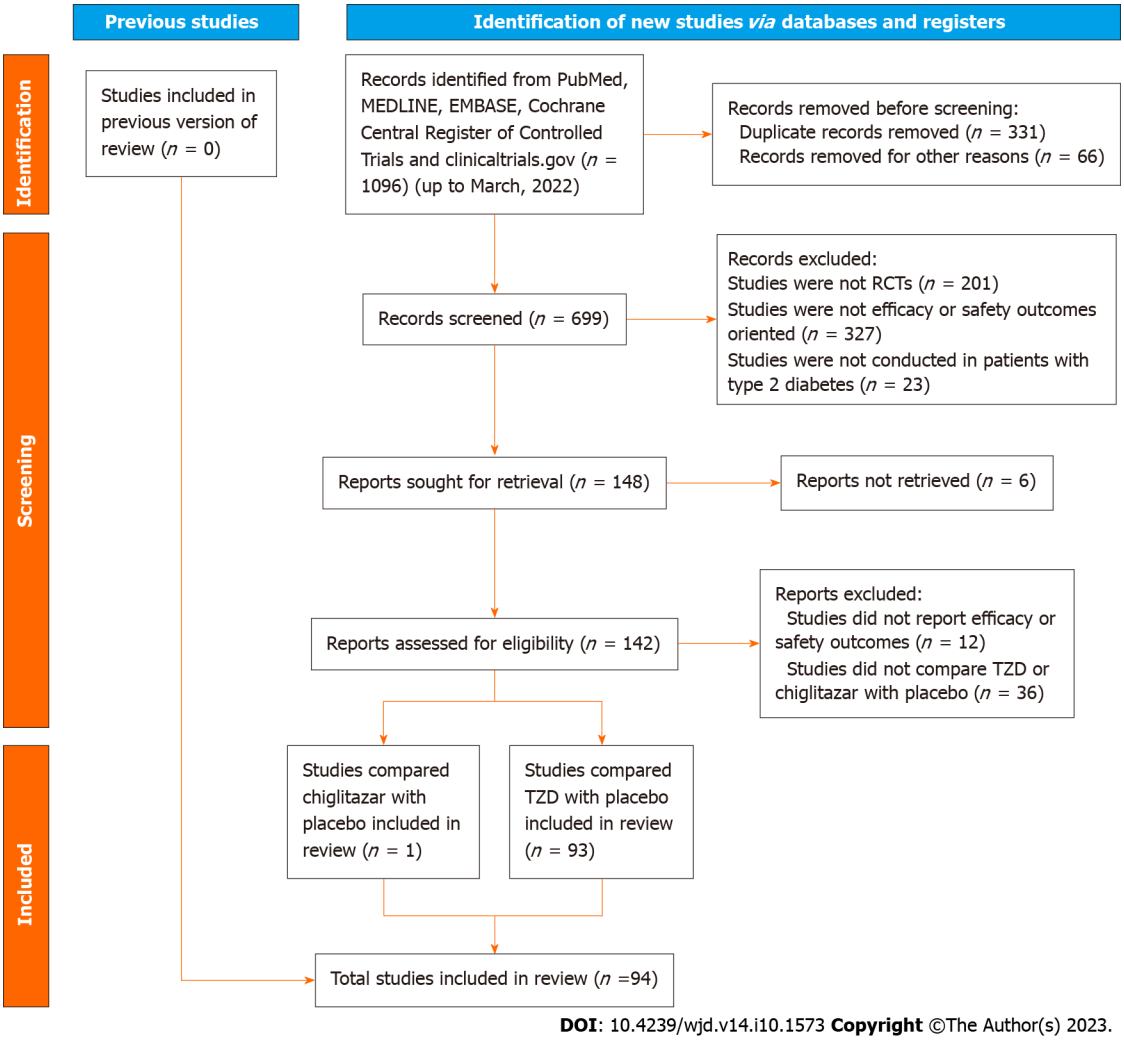

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Figure 1 Flow chart of this indirect meta-analysis.

kg) were associated with significantly increased body weight compared with placebo, but the weight gain was comparable between chiglitazar and TZD treatment in patients with T2D (WMD = -0.04 kg, 95%CI: -0.16 to 0.08 kg). Although heart failure was defined as an exploratory safety endpoint in this research, since no case of heart failure was reported in the chiglitazar or placebo treatment arms, we were unable to conduct an indirect comparison of the incidence of heart failure after treatment with chiglitazar or TZD (Figure 3). Compared with placebo, chiglitazar (RR = 20.67, 95%CI: 1.20-355.40) and TZD (RR = 2.04, 95%CI: 1.72-2.42) were both associated with significantly elevated risks of edema in patients with T2D. The risk of edema was comparable between chiglitazar and TZD (RR = 10.18, 95%CI: 0.59-175.98). The incidence of other adverse events, including bone fractures, upper respiratory tract infection and urinary infection, was comparable between chiglitazar/TZD and placebo, when indirect comparison also indicated a non-significant difference between chiglitazar and TZD treatment (Figure 3). Subgroup analyses of safety endpoints also conferred negative findings (Supplementary Table 3).

Indirect comparison of effects of standard dose of chiglitazar versus TZD on efficacy and safety endpoints

In patients treated with standard dose of chiglitazar, we observed significantly decreased HbA1c, FBG, TG, HOMA-IR index and ALT, and significantly elevated LDL-C, HDL-C and HOMA-β index compared with placebo, which was consistent with the results of treatment with augmented dose of chiglitazar. However, the indirect comparison suggested comparable change of HbA1c, TG and ALT levels after treatment with chiglitazar or TZD in comparison with placebo in patients with T2D. For safety endpoints, compared with placebo, standard dose of chiglitazar was not associated with increased risk of hypoglycemia. The increased risk of edema with augmented dose of chiglitazar became non-significant after treatment with standard dose of chiglitazar. Indirect comparison indicated comparable risks of safety concerns between standard dose of chiglitazar and TZD treatment, which was consistent with the results of the indirect compassion between augmented dose of chiglitazar and TZD treatment. The detailed results are shown in Supplementary Figure 4.

Meta-regression analyses

Meta-regression analyses showed that in patients under TZD treatment, male percentage (β = 0.011, 95%CI: 0.002-0.021, *P*

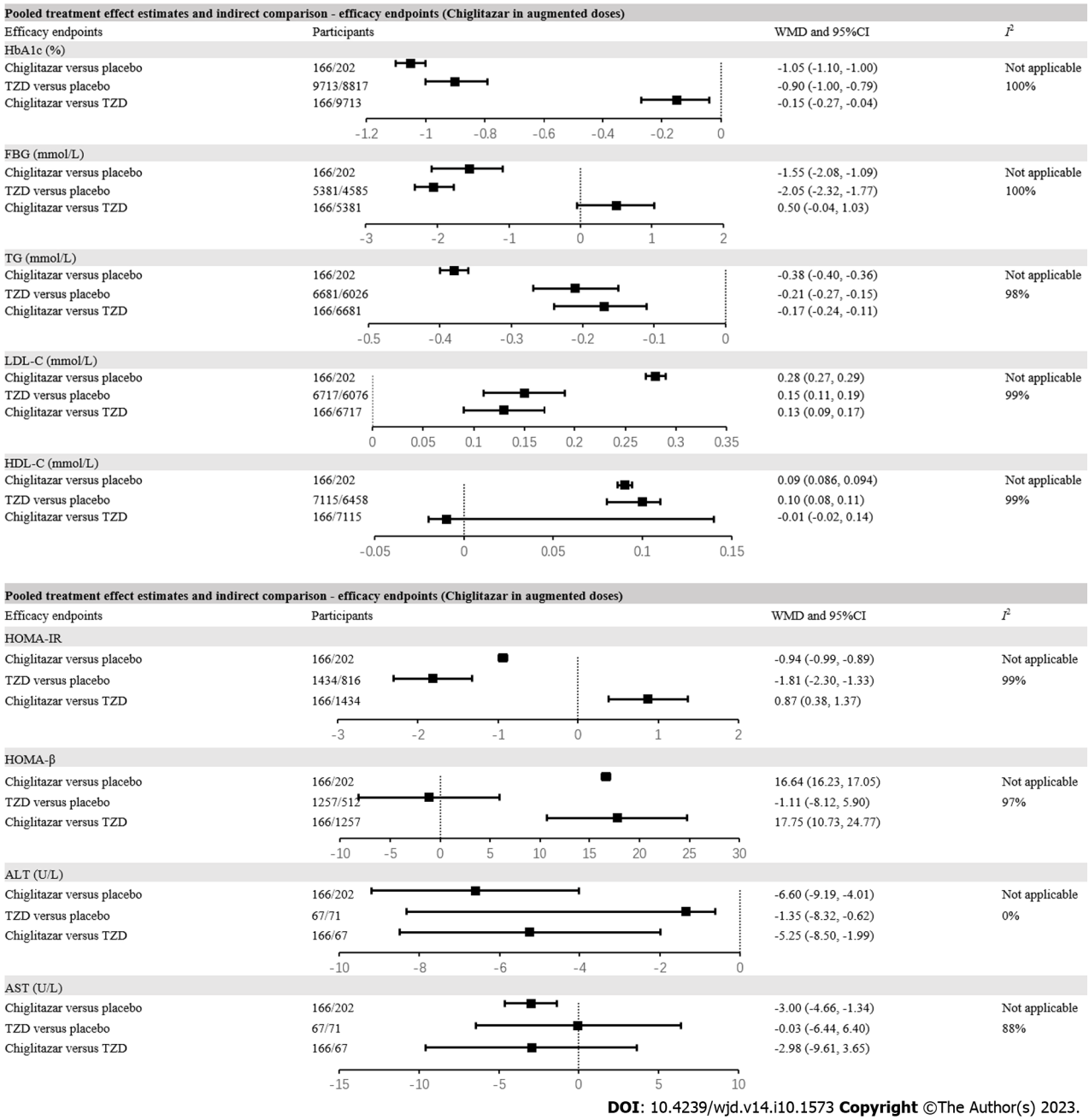

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Figure 2 The forest plot exhibiting pooled effect estimates and indirect comparison between chiglitazar and thiazolidinediones on efficacy endpoints including hemoglobin A1c, fasting blood glucose, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, homeostasis model assessment of insulin resistance, homeostasis model assessment of β cell function, alanine aminotransferase and aspartate aminotransferase. HbA1c: Hemoglobin A1c; FBG: Fasting blood glucose; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-β: Homeostasis model assessment of β cell function; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RR: Risk ratios; 95%CI: 95% confidential intervals; TZD: Thiazolidinedione.

= 0.019) and baseline HbA1c (β = -0.320, 95%CI: -0.427 to -0.212, *P* = 0.0001) were significantly correlated with the change in HbA1c, when baseline HbA1c (β = -0.578, 95%CI: -0.768 to -0.388, *P* = 0.0001) and BMI (β = -0.249, 95%CI: -0.442 to -0.055, *P* = 0.013) were significantly correlated with changes in FBG and TG, respectively. Male percentage also exhibited a significant linear association with the change in LDL-C (β = -0.006, 95%CI: -0.012 to -0.0001, *P* = 0.046), and baseline HbA1c showed a significant linear association with the change in HOMA-IR (β = -0.573, 95%CI: -1.112 to -0.034, *P* = 0.039) (Supplementary Table 4).

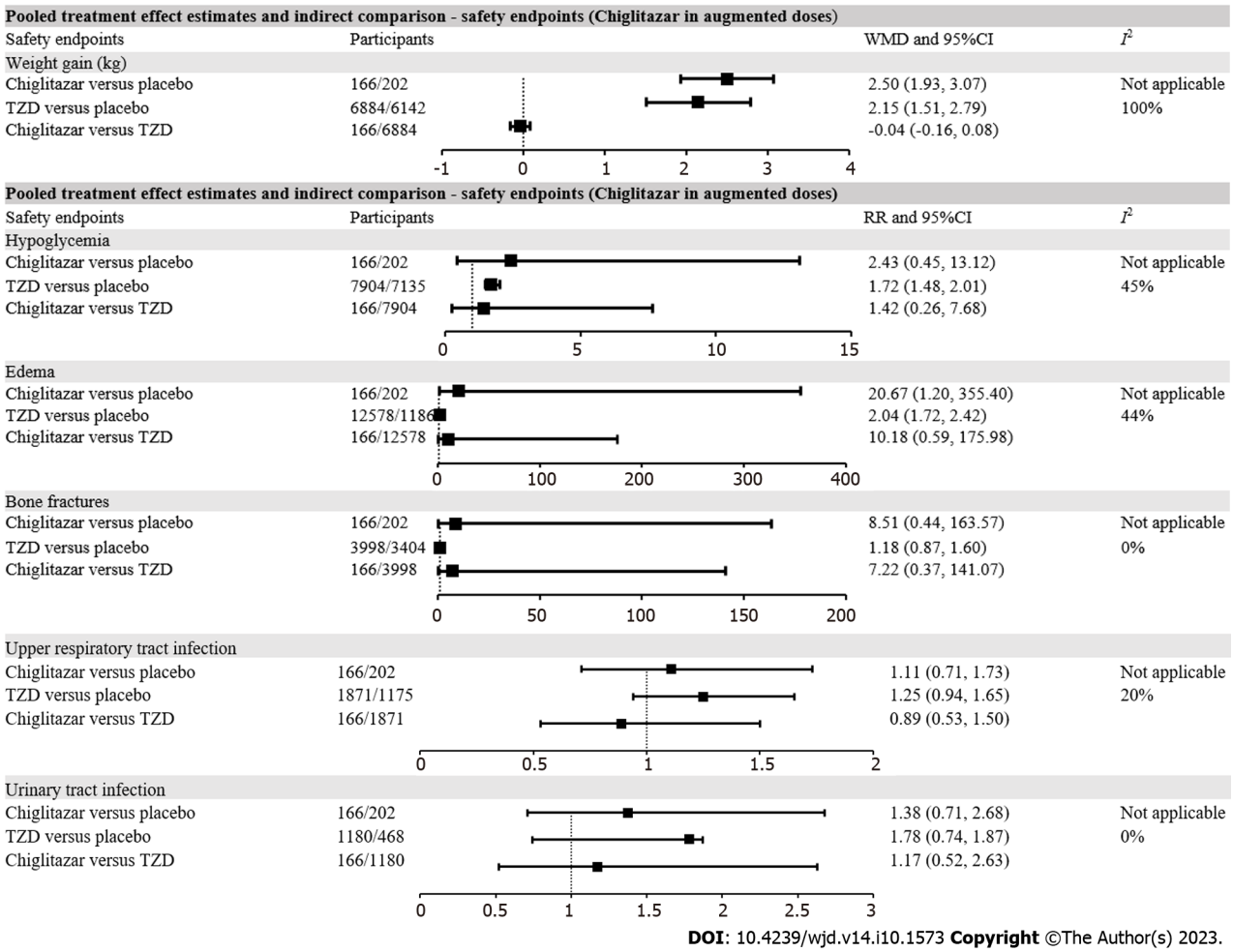

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Figure 3 The forest plot exhibiting pooled effect estimates and indirect comparison between chiglitazar and thiazolidinediones on safety endpoints including weight gain, hypoglycemia, edema, bone fractures, upper respiratory tract infection and urinary tract infection. HbA1c: Hemoglobin A1c; FBG: Fasting blood glucose; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-β: Homeostasis model assessment of β cell function; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RR: Risk ratios; 95%CI: 95% confidential intervals; TZD: Thiazolidinedione.

DISCUSSION

To our knowledge, this is the first comprehensive meta-analysis comparing the efficacy and safety of chiglitazar and TZD. According to this meta-analysis, augmented doses of chiglitazar outperformed TZD treatment for HbA1c, TG and ALT reduction and HOMA-β index elevation, and conferred greater LDL-C elevation and less HOMA-IR reduction in patients with T2D. For safety endpoints, the risks of hypoglycemia, edema, heart failure, bone fractures, upper respiratory tract infection and urinary tract infection, and weight gain were all comparable between augmented doses of chiglitazar and TZD. Further sensitivity analyses indicated that in patients with age ≥ 60 years, baseline HbA1c ≥ 8.5%, BMI ≥ 30 kg/m^2 or diabetes duration < 10 years, the reduction in HbA1c and improvement in HOMA-β were more conspicuous with augmented doses of chiglitazar compared with TZD.

Chiglitazar and TZD, as hypoglycemic agents, both lowered blood glucose level with mutual pivotal mechanisms of activating PPAR-γ[14,25]. PPAR-γ activation could ameliorate hyperglycemia by enhancing glucose transporter-1 and -4 of adipocytes, which facilitated glucose ingestion in adipose tissues[26]. Therefore, PPAR-γ activation mediated glucose lowering effects in both chiglitazar and TZD. However, since chiglitazar acted as a pan-agonist of PPAR-α, PPAR-δ and PPAR-γ, the hypoglycemic capacity of chiglitazar may also be derived from the activation of other PPARs. PPAR-α was distributed widely in liver, skeletal muscle, heart and adipose tissues, and its activation accelerated fatty acid uptake and oxidation and lipoprotein assembly[27], which resulted in decreased FFA and TG levels and fat accumulation. The lipid-modulating effects of PPAR-α activation attenuated lipidic toxicity for β cells[28] and inhibited gluconeogenesis from excess lipids[29], which improved overall glycemic control. PPAR-α activation was also reported to promote glucose metabolism and ketogenesis[27], which increased glucose consumption and thereby lowered blood glucose. Activation of PPAR-δ facilitated glucose metabolism through the pentose phosphate pathway[25] and increased basal metabolic rate [29] to reduce blood glucose. PPAR-α and PPAR-δ activation improved β-cell function[30,31], which lowered glycemia independent of IR remission[27]. The details are elaborated in the next section.

Apart from their hypoglycemic effects, chiglitazar and TZD reduced the serum TG level, for which PPAR-γ activation served as the mutual mechanism. Activation of PPAR-γ was associated with lipid uptake, lipid droplet formation, and adipocyte differentiation[25,44] in adipose tissues, as well as lipid oxidation in skeletal muscle and liver, which resulted in decreased circulating FFA and TG levels[32]. PPAR-γ activation promoted synthesis of bio-active proteins including fat-specific protein 27 and monoacylglycerol O-acyltransferase 1, which participated in lipid uptake and storage[29,33]. PPAR-γ activation also increased preadipocyte differentiation and functionalization, thus accelerating lipogenesis and consumption of lipids[34].

In our study, the augmented doses of chiglitazar outperformed TZD with respect to TG reduction. The enhanced hypolipidemic effects of chiglitazar may also have been derived from activation of PPAR-α and PPAR-δ. PPAR-α was identified as a regulator of lipid metabolism, whose activation increased lipid uptake and transport, fatty acid oxidation, lipoprotein assembly and TG accumulation in the liver[27]. PPAR-α activation also facilitated cytochrome P4504A production, which participated in hydroxylation of fatty acids and thereby reduced TG synthesis[35]. The PPAR-α agonists fibrates lowered TG levels and have been extensively used in patients with dyslipidemia[36], which confirms the hypolipidemic activity of PPAR-α activation. PPAR-δ activation was associated with fatty acid transport, lipid oxidation and decreased fatty acid release[25], and fat combustion and thermogenesis contributed to overall lipid reduction. Mice treated with PPAR-δ agonists had significantly lowered TG levels[37], indicating PPAR-δ activation had the potential to improve TG profiles. Therefore, chiglitazar may result in greater TG reduction compared with TZD, and the additional hypolipidemic effects may be derived from PPAR-α and PPAR-δ activation.

We found that chiglitazar and TZD treatment was associated with elevated LDL-C and HDL-C concentrations, which was more pronounced with augmented doses of chiglitazar compared with TZD. It was indicated that PPAR-α and PPAR-γ activation could facilitate reversed cholesterol transportation and lipoprotein exchange, and therefore increased plasma LDL-C and HDL-C levels[38]. Activation of either PPAR resulted in significant HDL-C elevation in previous *in vivo* experiments[39-41], whereas the changes in LDL-C under PPAR agonist treatment were inconsistent[42,43]. The underlying mechanisms have also not been fully demonstrated, and further investigations on the correlations between PPARs and cholesterol are required.

The activation of PPAR-α, PPAR-δ and PPAR-γ was associated with ameliorated nonalcoholic fatty liver disease *via* improved lipidemic and glycemic control[29]. The transfer of fat and lipids from viscera to peripheral tissues was facilitated by PPAR-α activation, which also relieved steatosis of hepatocytes[27]. We observed significantly decreased ALT levels after treatment with augmented doses of chiglitazar compared with TZD. The greater ALT reduction with chiglitazar may also have resulted from alleviated liver injuries with the favorable lipidemic, glycemic control and fat distribution through additional activation of PPAR-α and PPAR-δ.

IR and attenuation of β-cell function have been identified as the central pathophysiology of T2D; therefore, ameliorating IR and postponing β-cell failure have become important strategies in retarding T2D progression[44]. PPAR-γ activation contributed to adipocytes remodeling by virtue of facilitating apoptosis of visceral insulin-resistant adipocytes and generation of subcutaneous insulin-sensitive adipocytes[45]. It was also demonstrated that PPAR-γ activation lowered secretion of adipocytokines and chemokines, which contributed to IR[46]. PPAR-γ activation also prevented β-cell dysfunction by improving glycemic control and lipid metabolism, which attenuated glucotoxicity and lipotoxicity in islets[47,48]. PPAR-γ activation also inhibited the production of inflammatory cytokines, including TNF-α, interleukin (IL)-1 and IL-6, which mitigated islet inflammation and preserved β-cell function[49,50].

PPAR-α and PPAR-δ agonists improved insulin sensitivity in *in vitro* studies[51-53]. The insulin-sensitizing effects of PPAR-α and PPAR-δ were mostly circuitous and not as well-established as those of PPAR-γ. Since the interactions to PPAR-α, PPAR-δ and PPAR-γ of chiglitazar were generally balanced, the stimulating intensity to PPAR-γ might be relatively decreased when compared with TZD[25]. Therefore, the relief of IR by chiglitazar might also have been attenuated when compared with that of TZD. Although PPAR-γ activation was potentially able to preserve β-cell function as noted above, we observed comparable HOMA-β index alteration between TZD treatment and placebo. However, HOMA-β index was significantly elevated by chiglitazar treatment at both standard and augmented doses when compared with placebo and TZD. According to previous researches, HOMA-β index elevation may be attributed to the activation of PPAR-α and PPAR-δ. PPAR-α activation was associated with islet adaptation to starvation, which enhanced glucose utilization and insulin secretion[54]. Glucose-induced insulin secretion was also promoted by PPAR-α activation [55], especially in response to hyperglycemia[56]. PPAR-α activation stimulated insulin secretion through inhibition of Ca^{2+} signaling[57]. The islet-preserving effects of PPAR-δ have also received extensive attention. Many studies have indicated that PPAR-δ activation significantly improved islet function in mice, with the potential of elevating β-cell mass [58], alleviating β-cell lipoapoptosis[59], and reducing inappropriate baseline secretion[60]. Favorable glycemic and lipidemic control, and ameliorated chronic inflammatory states derived from PPAR-α and PPAR-δ activation may also participate in preservation of β-cell function[44]. However, the effects of PPAR-γ, PPAR-α and PPAR-δ activation on β-cell function have not been fully characterized. Further research on the specific mechanisms of preservation of β-cell function by chiglitazar and PPAR activation is required.

Although TZD significantly improved glycemic and lipidemic control and relieved IR, the clinical utilization of TZD was limited by the increased risk of adverse events. The adverse events related to TZD were primarily hypoglycemia[10], weight gain[9], edema[9], congestive heart failure[10], and bone fracture[11]. Since chiglitazar may ameliorate the centralized and excess PPAR-γ activation presented in TZD[22], and potentially exert beneficial effects through PPAR-α and PPAR-δ activation, it was expected that the safety risks could be attenuated in chiglitazar treatment in contrast to TZD. However, in this meta-analysis, we observed significantly increased risks of weight gain and edema with both chiglitazar and TZD compared with placebo. Subsequent indirect comparisons exhibited comparable risk of hypoglycemia, weight gain, edema, bone fracture, upper respiratory tract infection and urinary tract infection between chiglitazar and TZD. The safety of PPAR-α and PPAR-δ activation was not shown[61]. Clinical trials of chiglitazar were

rare, which made it difficult to thoroughly evaluate safety outcomes. Further researches are required to comprehensively assess the safety features and potential mechanisms in chiglitazar.

A number of baseline characteristics are potentially associated with the effects of chiglitazar and TZD in patients with T2D, including age, sex, glycemic control status (baseline HbA1c), BMI and diabetes duration. According to the meta-regression analysis, male percentage, BMI and baseline HbA1c were linearly associated with several glycemic and lipidemic control outcomes. The potential influence of these baseline characteristics on study results should therefore be cautiously considered when interpreting the outcomes of this study. Meanwhile, in this indirect comparison meta-analysis, reduction in HbA1c and improvement of HOMA-β index were more prominent for treatment with augmented doses of chiglitazar compared with TZD for patients with baseline HbA1c ≥ 8.5% (poorly controlled diabetes), BMI ≥ 30 kg/m^2 (obese) or diabetes duration < 10 years (short T2D duration).

In patients with poorly controlled diabetes and frequent hyperglycemia, the systematic metabolic disorders appeared to be more severe[62]. Chiglitazar outperformed TZD in improving lipid profiles and accelerating glucose consumption [49,56]. Therefore, chiglitazar could have achieved better glycemic control and protection of β-cell function through better relief of metabolic disorders, which improved glucose consumption and decreased lipotoxicity to islets.

For patients with obesity, the lipid-modifying effects of chiglitazar may have synergistically improved glycemic control [44]. It would be more effective for chiglitazar to preserve β-cell function in obese patients as their β-cell function was generally better than that in patients who were non-obese[63]. Furthermore, compared with long-established T2D, the severities of metabolic turbulence, glycemic or lipidemic disorder, and deterioration of β-cell function were lower in patients with shorter diabetes duration, which were more reversible with chiglitazar treatment[63].

This study had some limitations. Firstly, this research was based on the statistical approach of indirect comparison. Secondly, since the RCTs had different study designs and populations, the resultant endogenous heterogeneity should not be ignored. To control the heterogeneity, we implemented multiple sensitivity analyses concerning underlying associated factors to minimize the confounding effects. Moreover, there was only one eligible RCT investigating chiglitazar available for the indirect comparison, when the sample size and data abundance were limited. Considering the potential bias, the results and conclusions in this indirect comparison meta-analysis should be interpreted with caution. The comparison should be updated with enriched RCT data of chiglitazar in the future. There was no heart failure event reported in the RCT of chiglitazar; therefore, the indirect comparison of heart failure incidence between chiglitazar and TZD was not possible in this study. More investigations evaluating safety outcomes of chiglitazar, especially heart failure, are still needed.

CONCLUSION

Through pan-activation of PPAR-α, PPAR-δ and PPAR-γ, chiglitazar may serve as a promising therapeutic agent for T2D with preferable glycemic and lipid control, additional β-cell function preservation, and favorable tolerance for augmented doses when compared with TZD.

ARTICLE HIGHLIGHTS

Research background

Chiglitazar as a pan-agonist of peroxisome proliferator activated receptor (PPAR)-α, δ and γ, has the potential to induce better glycemic and lipidemic control than the PPAR-γ agonist thiazolidinediones (TZDs) in patients with type 2 diabetes (T2D).

Research motivation

Currently, there are no clinical studies or meta-analyses comparing the efficacy and safety of chiglitazar and TZD. A meta-analysis is required to further address this topic.

Research objectives

To compare the efficacy and safety of chiglitazar and TZD in patients with T2D.

Research methods

Randomized controlled trials (RCTs) of chiglitazar or TZD *vs* placebo in patients with T2D were retrieved. Indirect comparisons and sensitivity analyses were implemented to evaluate the efficacy and safety endpoints of interest.

Research results

We included 93 RCTs comparing TZD with placebo and one comparing chiglitazar with placebo. For efficacy endpoints, the augmented dose of chiglitazar, compared with TZD, resulted in greater reductions in hemoglobin A1c, triglycerides and alanine aminotransferase levels, and greater homeostasis model assessment of β cell function elevation. For safety endpoints, the risks of hypoglycemia, edema, bone fractures, upper respiratory tract infection, urinary tract infection, and weight gain were all comparable between the augmented dose of chiglitazar and TZD.

Research conclusions

Chiglitazar, a pan-activator of PPARs, may exhibit preferable glycemic and lipid control, and β-cell function preservation, with no additional safety concerns with augmented doses compared with TZD in patients with T2D.

Research perspectives

Chiglitazar has potential for T2D treatment. However, more investigations evaluating safety outcomes of chiglitazar, especially heart failure, are still needed.

FOOTNOTES

Author contributions: Ji LN and Cai XL were responsible for the study concept and designed the systematic review protocol; Lin C and Li ZL performed the study selection and data extraction; Lin C and Li ZL performed the statistical analyses; Lin C, Li ZL and Cai XL prepared the outlines and wrote the manuscript; All authors contributed to the critical revision of manuscript drafts.

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