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REVIEW

Advanced glycation end products: Key mediator and therapeutic target of cardiovascular complications in diabetes

Savita Bansal, Archana Burman, Asok Kumar Tripathi

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Abstract

The incidence of type 2 diabetes mellitus is growing in epidemic proportions and has become one of the most critical public health concerns. Cardiovascular complications associated with diabetes are the leading cause of morbidity and mortality. The cardiovascular diseases that accompany diabetes include angina, myocardial infarction, stroke, peripheral artery disease, and congestive heart failure. Among the various risk factors generated secondary to hyperglycemic situations, advanced glycation end products (AGEs) are one of the important targets for future diagnosis and prevention of diabetes. In the last decade, AGEs have drawn a lot of attention due to their involvement in diabetic patho-physiology. AGEs can be derived exogenously and endogenously through various pathways. These are a non-homogeneous, chemically diverse group of compounds formed non-enzymatically by condensation between carbonyl groups of reducing sugars and free amino groups of protein, lipids, and nucleic acid. AGEs mediate their pathological effects at the cellular and extracellular levels by multiple pathways. At the cellular level, they activate signaling cascades *via* the receptor for AGEs and initiate a complex series of intracellular signaling resulting in reactive oxygen species generation, inflammation, cellular proliferation, and fibrosis that may possibly exacerbate the damaging effects on cardiac functions in diabetics. AGEs also cause covalent modifications and cross-linking of serum and extracellular matrix proteins; altering their structure, stability, and functions. Early diagnosis of diabetes may prevent its progression to complications and decrease its associated comorbidities. In the present review, we recapitulate the role of AGEs as a crucial mediator of hyperglycemia-mediated detrimental effects in diabetes-associated complications. Furthermore, this review presents an

overview of future perspectives for new therapeutic interventions to ameliorate cardiovascular complications in diabetes.

Key Words: Type 2 diabetes mellitus; Cardiovascular complications; Hyperglycemia; Advanced glycation end products; Reactive oxygen species; Oxidative stress; Endothelial cells; Receptor of advanced glycation end products; Anti-advanced glycation end products strategies

Core tip: Cardiovascular diseases (CVDs) in type 2 diabetes mellitus impose a clinical and an economic burden on the healthcare system. Early diagnosis of diabetes may prevent its progression to complications and decrease its associated comorbidities. The present manuscript reports the clinical relevance of estimating advanced glycation end products (AGEs) in diabetes. The deleterious effects of AGEs include many important biochemical reactions central to the development and progression of cardiovascular complications in diabetes. Therefore, AGEs are one of the important targets for future diagnosis and prevention of diabetes. The epidemiology of CVD in diabetes, AGEs as a crucial mediator of diabetic CVD, and an overview of different strategies for countering the accumulation of AGEs is discussed along with new therapeutic interventions to ameliorate their effects.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a cluster of metabolic disturbances consequent to non-utilization of glucose due to insufficient production/secretion of insulin or its resistance. T2DM poses a major threat to global health. The number of people with T2DM is increasing at an alarming rate and has become one of the leading causes of death worldwide. The upsurge is corresponding with rising obesity, aging populations, increasing urbanization, calorie dense diets, economic development, and reduced physical activity. The global prevalence of diabetes as described by the International Diabetes Federation in 2021 was estimated to be 536.6 million (10.5%) and it is projected to reach 783.2 million (12.2%) by 2045[1]. Prevalence is expected to be higher in urban areas compared to rural ones. The estimated global cost of diabetes is slated to rise from 966 billion USD in 2021 to 1054 billion USD by 2045[1,2]. Consequently, T2DM imposes both a clinical and an economic burden on the health care system. DM is a complex pathophysiological process associated with several disabling and life-threatening health problems. Since DM basically affects blood vessels, it can affect almost any part of the body. People with diabetes are at risk of developing several complications affecting the heart, eyes, kidneys, and nerves. Vascular dysfunction is the single most serious consequence of long-standing DM[3,4] resulting in debilitating morbidity and mortality due to cardiovascular diseases (CVDs)[5,6]. The CVDs that accompany DM include stroke, myocardial infarction, peripheral artery disease, and coronary thrombosis[7].

Early diagnosis of DM may prevent its progression to CVD and decrease its associated comorbidities. Persistent hyperglycemia is considered to be an important factor in the development and the progression of diabetic complications and the exact mechanism of the deleterious effects of hyperglycemia on the onset of diabetic complications is still being explored[8]. Numerous hyperglycemia-induced mechanisms have been hypothesized to account for vascular complications in T2DM. These include the hexosamine pathway, polyADP-ribose polymerase activation, protein kinase C (PKC) activation, aldose reductase-mediated polyol pathway, and enhanced formation of advanced glycation end products (AGEs)[9-11]. Among these, the AGE-mediated pathways have been explored in the last decade because of mounting evidence that AGE accumulation is the crucial factor in the progression of diabetic complications[12,13]. AGEs are heterogeneous compounds resulting from nonenzymatic reactions of reducing sugars with other biomolecules such as lipids, proteins, and nucleic acid. This nonenzymatic glycation of proteins, lipids and nucleic acids is a slow and complicated process depending on the relative concentrations of the reactants. The moderate presence of AGEs has been notice in healthy individuals whereas, its formation increased under hyperglycemic conditions[14]. The severity of the complications in T2DM through AGEs corresponds with the quantum of hyperglycemia and varies with the structural and functional changes generated in most macromolecules. Also, AGEs interact with their receptors namely the receptor of AGEs (RAGE), and trigger the activation of multiple signals that can affect cellular functions and metabolism through upregulation of inflammation and oxidative stress[15,16].

The importance of AGEs in diabetic CVD is corroborated by the fact that the serum level of AGEs in T2DM CVD patients is higher compared to DM patients without CVD[17,18]. Studies have shown the association of AGEs with the prevalence as well as pathophysiological mechanisms of CVD in T2DM[19-21]. Jia *et al*[22] found that the tissue level of AGEs was independently associated with cardiac systolic dysfunction in T2DM patients with heart failure compared to T2DM patients without heart failure[22]. *In vitro* studies have shown that treatment of cardiomyocytes with AGEs for 24

h significantly reduces calcium transient in cells due to increased reactive species (RS) production[23]. Elevated serum AGEs predicted increased mortality due to CVD in Finnish women with DM who were followed up for 18 years[24]. In a recent review article by Dozio *et al*[25], the involvement of glycation in cardiovascular remodeling causing molecular, cellular and interstitial changes in the heart and vessels through different mechanisms has been demonstrated[25]. In a cross-sectional study carried out by De la Cruz-Ares *et al*[26] in 540 subjects, AGE levels and intima–media thickness of carotid arteries was consistently observed to be higher in CVD patients with T2DM[26]. Ninomiya *et al*[27] highlighted the importance of AGEs as a screening marker of atherosclerosis[27]. The AGE–RAGE axis further activates the pathological inflammation in plaques and atheromas[28]. Ren *et al*[29] identified the inhibition of prostacyclin in endothelial cells by the AGE–RAGE system, which promotes the formation of plasminogen activator inhibitor (PAI)-1 contributing to the stabilization of thrombus formation by inhibiting the fibrinolytic activity[29].

This review focuses on summarizing the clinical relevance of AGEs in CVD development and progression in T2DM. Different anti-AGE strategies are also being discussed that may become potential candidates for future preventive and therapeutic strategies in diabetic CVD.

EPIDEMIOLOGY OF CVD IN T2DM

Current trends in the epidemiology of CVD in T2DM present an underlying connection between chronic and uncontrolled T2DM and vascular complications[30]. T2DM poses a major risk for the development of CVD and T2DM-associated mortality[5]. Prevalence of coronary artery diseases, peripheral vascular diseases, and carotid artery disease has been observed in different macrovascular complications in T2DM[31]. Numerous epidemiological studies suggested that T2DM can accelerate atherosclerosis and increase the incidence of heart attacks and strokes[31,32]. Patients with T2DM have a two- to six-times higher risk of heart failure than non-T2DM patients and heart failure accounts for > 50% of deaths in T2DM patients[6,33,34]. CVD is a major comorbidity affecting about one-third of all people with T2DM. A cohort study carried out on 1.9 million people by Dinesh *et al*[35] identified T2DM as a significant risk factor for CVD, including stroke, heart failure, atherosclerosis, and myocardial infarction[35]. T2DM patients are also prone to various cardiovascular risk factors, such as hypertension, dyslipidemia, and obesity that can directly promote the occurrence of cardiovascular complications in T2DM[36,37].

A cohort study carried out by Shah *et al*[33] demonstrated that the occurrence of peripheral artery diseases and heart failure was higher in T2DM by 16.2% and 14.7%, respectively[33]. Another cohort study carried out by National Health and Nutrition Examination Survey demonstrated that T2DM increases the risk of stroke by 26.3%, hemorrhagic stroke by 50% and ischemic stroke by 50%[32,38]. An American heart report of 2014 revealed a risk of heart failure of 40% in T2DM patients compared to patients without T2DM[39]. A prospective study showed that angina, coronary angioplasty, myocardial infarction, and congestive heart failure were among the predictors of all-cause mortality in T2DM[40]. A systematic review by Vaidya *et al*[41] has shown that 15%–81% of T2DM patients have at least one cardiovascular complication[41]. Einarson *et al*[42] confirmed that CVD imposes a substantial burden on the treatment of T2DM at both patient and population levels[42]. On an average patients treated for both CVD and T2DM resulted in an additional cost ranging from $3418 to $9705 compared to T2DM alone. Given the substantial economic and health burden of CVD in T2DM patients, there is a need to understand the mechanism of T2DM–CVD relationship and early diagnosis of T2DM to prevent its devastating complications.

DIFFERENT PATHWAYS FOR AGEs FORMATION

AGEs are chemically modified complex group of heterogeneous molecules formed either exogenously or endogenously by different pathways specifically, Maillard reaction, polyol pathway, and oxidation reactions (Figure 1). The Maillard reaction was first described in 1912 by French Scientist Louis Camille Maillard as “browning reaction” due to the associated yellow–brown color change when reducing sugar was heated with amino acid[43]. The AGEs formed through the Maillard reaction secondary to hyperglycemic condition is under intense investigation since a positive correlation is found with vascular complications like CVD, retinopathy, neurodegenerative diseases and other parameters of aging[44-46]. Maillard glycation reaction is different from enzymatic N-/O-linked glycosylation of proteins since they produce crosslinked products obtained from spontaneous and nonenymatic action of reducing sugars or their derivatives on other molecules, altering the structure and function of important cellular and extracellular components[47,48]. In healthy individuals AGEs are formed minimally and are cleared efficiently from the system. Formation and accumulation of AGEs becomes more rapid and pronounced under hyperglycemic conditions, oxidative stress, inflammatory conditions, and obesity[9,16]. AGE levels are higher in aged individuals, due to either overproduction or slower clearance indicative of their pathophysiological implications[49,50]

Accrual of AGEs is a multistage process starting with covalent binding of functional groups of monosaccharides to free amino groups of proteins, lipids, and nucleic acids forming labile reversible Schiff base intermediates under a hyperglycemic environment. This reaction is reversed if the hyperglycemia abates timeously. The initial Schiff’s base transforms over a period of days to a ketoamine, called Amadori’s product. The Amadori products are more stable, but the reaction is still reversible. The most well-recognized Amadori product is glycated hemoglobin, which is widely used as a reliable marker of glycemic control. Amadori products can be degraded into a variety of dicarbonyl compounds like 3-deoxy-glucosone, glyoxal and methyl-glyoxal, which can further react with proteins to form intermediate glycation products. Yellow–brown irreversible AGEs are formed after a sequence of chemical modifications including dehydration,

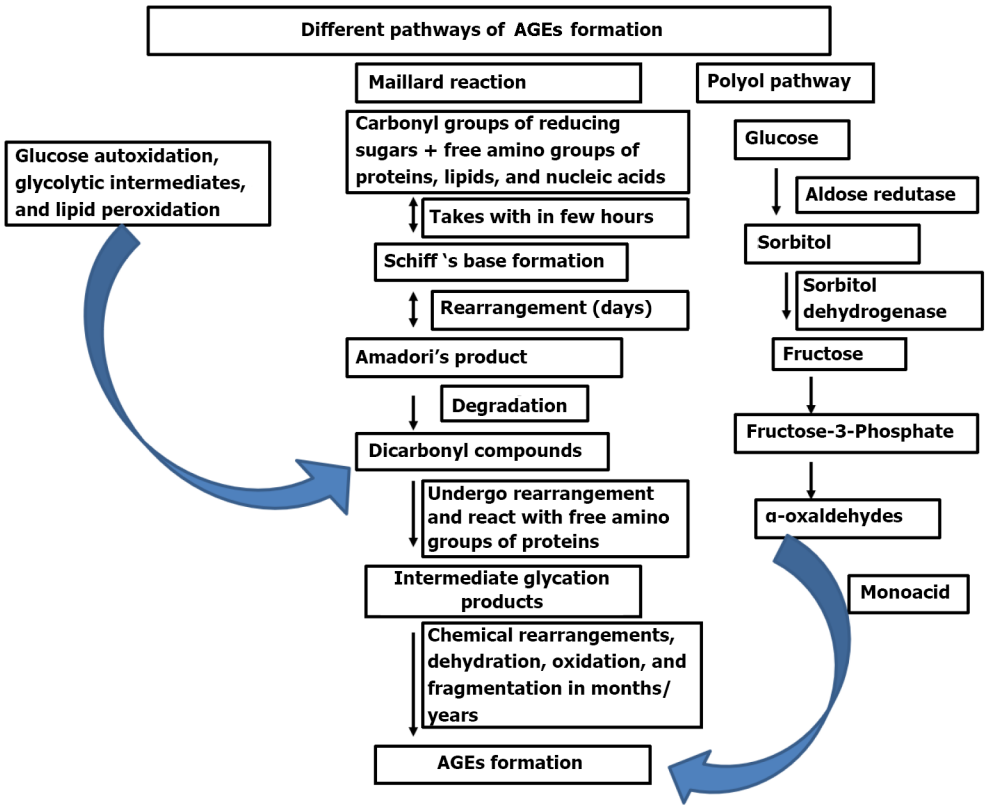

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Figure 1 Pathways for endogenous advanced glycation end products formation. Formation of AGEs occurs through different pathways. Maillard reaction which occurs at three stages: (1) Covalent binding of reducing sugars to free amino groups of proteins, lipids, and nucleic acid resulting in reversible Schiff base formation within hours; (2) it undergoes chemical rearrangement over a period of days to form a more stable Amadori product (the reaction is still reversible); and (3) Amadori's products can be degraded into many reactive dicarbonyl compounds undergoing chemical rearrangements leading to the formation of irreversible AGEs. These spontaneous rearrangements are slow and often taking months to years but enhanced in presence of oxidative stress, and metal ions. Autoxidation of glucose and the peroxidation of lipids into dicarbonyl derivatives also results in AGEs formation. Monosaccharides glycolytic intermediates and dicarbonyl compounds formed during glycolysis also play an important role in AGEs formation. Polyol pathway, where glucose is converted to sorbitol by the enzyme aldose reductase and then sorbitol is converted to fructose by the action of sorbitol dehydrogenase. Fructose metabolites are converted into α-oxaldehydes and interact with monoacids to form AGEs. AGEs: Advanced glycation end products.

oxidation, and fragmentation reactions (Figure 1). These spontaneous rearrangements are normally slow, often taking months to years. Nevertheless, the presence of oxidative stress, metal ions, and other catalysts can substantially increase the post-Amadori formation of AGEs. They are stable and accumulate inside and outside the cells and some of them have fluorescent properties[9,12,16].

Besides the Maillard reaction, other pathways such as the Hodge pathway, Namiki pathway and Wolff pathway can also result in AGEs formation, through autoxidation interactions of Amadori products, monosaccharides (glucose, fructose, ribose and glyceraldehyde) with amino acids and lipids[16,51-53]. Besides monosaccharides, the reactive products formed during glycolysis can also form AGEs by attacking proteins and other components. Some of the important glycolytic intermediates identified in AGEs formation are glyoxal, methylglyoxal, glucose-6-phosphate, triose phosphates, glyceraldehydes-3-phosphate and dihydroxy-acetone phosphate and 3-deoxyglucosone[54,55]. Auto-oxidation of glucose, reaction between glycolipid and arginine/lysine also results in AGEs formation through glyoxal and methyl-glyoxal production[56,57]. The Polyol pathway where, enzymatically formed metabolites of glucose like sorbitol and fructose also contributes significantly to AGEs formation[58,59]. The free ribose formed during the degradation of nucleic acid also represents the main source of pentosidine formation[60].

Also, sugars vary in their susceptibility to the Maillard reaction, where D-glucose is less reactive and D-fructose is more reactive sugar as demonstrated in both thermally processed food and *in vivo* conditions[53,61,62]. Temperature also has a significant effect on early glycation product formation, where high temperature (120–180C) accelerates the Maillard reaction in processed food, and the same reaction for Amadori's product formation *in vivo* conditions require much longer time[63].

Exogenous formation of AGEs through glyco-oxidation and lipo-oxidation reactions formed from heating food at high temperature and chemical processing, tobacco smoke components and other pollutants also contributes to the chemical load of AGEs. Blood and tissue AGE levels have been consistently observed to be higher in smokers and in patients on high AGEs diets compared to non-smokers and controls on low AGE diets[64-67]. Ingestion of exogenous AGEs has been shown to exacerbate diabetic complications like CVD in animal models, hence their role needs further exploration[68,69].

TYPE OF AGEs

Due to variety of precursors and numerous pathways of nonenzymatic reactions, the AGEs are diverse in their chemical structure and properties. AGEs comprise a large number of chemical structures like N-carboxy-methyl-lysine (CML), pyrraline, pentosidine, cross-linked AGEs include GOLD [glyoxal-derived lysine dimer, 1,3-di(*N*_-lysino imidazolium salt], MOLD [methylglyoxal-derived lysine dimer, 1,3-di(*N*_-lysino)-4-(methyl-imidazolium salt], DOLD [3-deoxy-glucosone-derived lysine dimer, 1,3- di(*N*_-lysino)-4 (2,3,4-trihydroxybutyl)imidazolium salt], *etc*.[16,70-72]. The best biochemical and immunohistochemically characterized AGEs found in humans are pentosidine, carboxyl methyl lysine and methylglyoxal, which accumulate and can potentially be used as biomarkers[73,74]. CML is the most well-characterized AGE demonstrated in DM patients with CVD[75]. Structure and function of matrix proteins are modified with variable loss of function due to the aggregation of these adducts. Some of these AGEs have native fluorescence which can be used for their identification and quantification.

AGEs AND DIABETIC-CARDIOVASCULAR COMPLICATIONS

AGEs formed secondary to hyperglycemic conditions are gaining prominence as the underlying mechanism of CVD complications in T2DM. DM patients are known to have 20%–30% more circulating AGEs compared to controls, whereas DM patients with CVD complications have up to 40%–100% higher levels of AGEs[17,76]. The AGEs remain significantly high even after correction of variables such as duration of diabetes, sex, and age in T2DM patients with complications compared to those without complications[77,78]. Statistical analyses have also shown the association of AGEs level with the development and severity of atherosclerosis in DM patients[79,80]. Clinical reports have indicated that serum AGE levels can act as important marker or predictor of heart failure and CVD mortality in T2DM since their deposition has been detected in atherosclerotic plaques and heart muscles[81,82].

The deleterious effects of AGE-mediated cardiovascular complications in T2DM involve various pathological changes such as plaque formation, arterial stiffening, and generalized endothelial dysfunction aided by prothrombotic gene expression[83-85]. These detrimental effects of AGEs can be explained at the cellular and extracellular level as shown in Figure 2.

AGE–RAGE axis in cardiovascular complications

At the cellular level, AGEs mediate their effects through interaction with their receptors, especially RAGE. RAGE is recognized by multiple ligands and has been localized on endothelial cells, vascular smooth muscle cells (VSMCs), immune cells and many others[86]. The presences of RAGE on multiple cells indicate its involvement in pathways affecting the vascular system in diabetes[87]. AGE–RAGE interaction activates signaling cascades leading to enhanced production of reactive oxygen species (ROS), oxidative stress, inflammation, adhesion molecule expression, endothelin-1, PAI-1, tumor necrosis factor (TNF)-α, chemoattraction of inflammatory cells, smooth muscle and fibroblast proliferation, autophagy, and apoptosis[88-90]. AGE–RAGE interaction modulates the cellular properties that possibly promote proinflammatory and procoagulant gene pathways through stimulation of signaling molecules such as extracellular signal-regulated kinase (ERK)1/2, p21RAS, mitogen-activated protein kinase (MAPK), nuclear factor (NF)-κB, cdc42/rac, and Janus kinase (JAK)/STAT and adversely affect the cardiovascular health in diabetes[91,92]. Cipollone *et al*[93] have studied the association of AGE–RAGE interaction and RAGE overexpression in human diabetic plaque macrophages by an increased inflammatory reaction, cyclooxygenase-2/prostaglandin E synthase-1 expression that may contribute to plaque destabilization through induction of metalloproteinase expression[93]. Also, the AGE–RAGE system activates inflammation in plaques and atheromas. Therefore, therapeutic approaches are now targeting the AGE-RAGE system to prevent the development of atherosclerosis[94].

Glycation of cellular and extracellular components in diabetic CVD

AGEs are also involved in the covalent modifications and crosslinking of serum and extracellular matrix (ECM) proteins, lipids and nucleic acid leading to perturbation of their structure and functions. Proteins of ECM have slow turnover rate and longer half-life which make them more prone to glycation reaction and crosslinking under hyperglycemic conditions. Modification of ECM proteins and crosslinking interferes with cell–matrix and matrix–matrix interactions, leading to profibrotic action, decreased elasticity, increased stiffness and narrowing of vessels and other hallmarks of atherosclerosis [14,95]. Cellular proteins also undergo the nonenzymatic glycation reaction by glucose and its derivatives like glucose-6-phosdphate, glyceraldehyde-3-phosphate, dihydroxyacetone-phosphate, GO, and MGO. Cellular AGEs have also been known to activate signaling pathways further impacting the diabetic vascular complications[96]. AGEs also induce crosslinking of intracellular proteins that participate in Ca^{2+} homeostasis resulting in cardiomyocyte dysfunction[97]. AGE–RAGE interaction is also found to be associated with decreased Ca^{2+} levels by upregulated ryanodine receptor which is involved in maintaining ionic balance during systolic and diastolic phases[98].

Development of cardiovascular complications in T2DM is also associated with increased incidence of low-density lipoprotein (LDL) oxidation, glycation of paraoxonase (PON)1, and high-density lipoprotein (HDL)[99]. Oxidation of LDL in arterial walls is the primary step in initiation and progression of atherosclerosis by foam cell formation. Recent studies have reported that glycated LDL can evade recognition by LDL receptors and can attach to arterial walls[100]. Non-enzymatic glycation of LDL is also responsible for impairment of hepatic receptor-mediated uptake and its removal. As a result, AGE-modified LDL is trapped in the subendothelium, causing its retention in the aortic wall where it is internalized by macrophages resulting in foam cell formation[101-103]. Glycation of LDL also makes it more vulnerable to

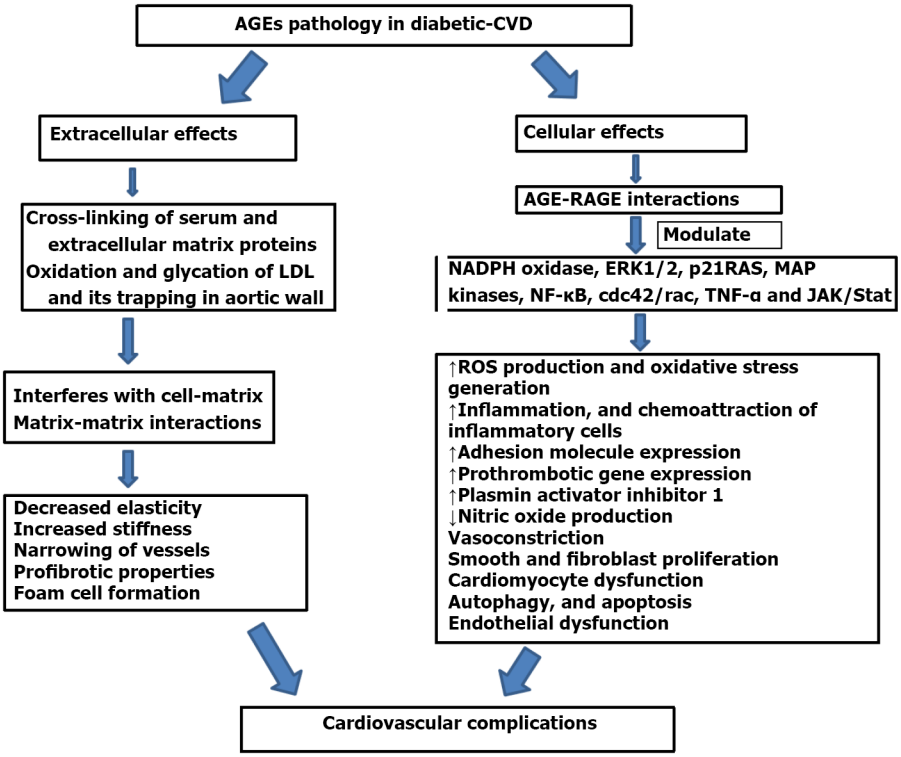

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Figure 2 Advanced glycation end product-mediated diabetic cardiovascular complications. AGEs mediate their pathological effects at the cellular and extracellular level by multiple pathways. At the cellular level, they activate signaling cascades *via* RAGE and initiate a complex series of intracellular signaling leading to reactive oxygen species generation, oxidative stress development, inflammation, adhesion molecule expression, endothelin-1, plasmin activator inhibitor 1, tumor necrosis factor alpha, chemoattraction of inflammatory cells, smooth muscle and fibroblast proliferation, autophagy, and apoptosis. AGE–RAGE interaction modulate the cellular properties through stimulation of signaling molecules such as ERK 1/2, p21RAS, MAPK, NF-B, cdc42/rac, and Janus kinase/STAT and adversely affects the cardiovascular health in diabetes. AGEs also causes covalent modifications and crosslinking of serum and ECM proteins, altering their structure, stability, and functions. Modification of ECM proteins and cross-linking interferes with cell–matrix and matrix–matrix interactions, affecting the matrix–cell signaling and leading to profibrotic action, decreased elasticity, increased stiffness, narrowing of vessels, and other hallmarks of atherosclerosis. VCAM1: Vascular cell adhesion molecules; JAK: Janus kinase; RAGE: Receptor for advanced glycation end products; NADPH: Nicotinamide adenine dinucleotide phosphate oxidase; NF-κB: Nuclear factor-B; AGEs: Advanced glycation end products; MAPK: Mitogen-activated protein kinase; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor ; ERK: Extracellular signal-regulated kinase; LDL: Low-density lipoprotein; ECM: Extracellular matrix.

crosslinking with collagen in the arterial wall. Elevated lipid-linked AGEs in LDL have also been noticed in T2DM patients[104]. Glycation of HDL also influences inflammation and affects the removal of cholesterol, leading to the development of atherosclerosis[105]. PON1 is an HDL-associated enzyme with antiatherogenic properties that protects LDL and cell membranes from oxidation. Glycation of PON1 is found to decrease its activity in DM, leading to the development of premature atherosclerosis[17,106,107].

AGEs and oxidative stress in diabetic-CVD

T2DM patients are exposed to high oxidative stress, increased reactive species (RS) generation, and decreased antioxidant defense mechanism. Hyperglycemia-induced ROS generation unveils the pathophysiology of CVD in T2DM and increased production of ROS triggers the inflammatory cascades responsible for the pathogenesis of cardiovascular complications[108,109]. The level of transcription factors such as TNF-α and NF-κB is modulated by increased RS production mediated signal transduction pathways enhancing the proinflammatory events including inflammatory adhesion molecules, interleukin (IL)-6, IL-1, and cytokines[110-112]. The AGE–RAGE interaction is also involved in increased RS generation through stimulation of certain signaling mediators like ERK, phospholipase A2, phophoinositide 3-kinase activation, activation of NADPH oxidase, inducible NO synthase (NOS), PKC and p38 MAPK[113-115]. Increased ROS production by mitochondria also triggers the inflammatory cascades in DM and prolonged exposure to high levels of ROS leads to oxidation, peroxidation and glyoxidation reactions resulting in increased oxidative stress markers such as protein carbonyl, oxidation of thiol group, lipid peroxidation, advanced oxidation protein products, and 8-OHdG[17,116]. Oxidative injury to biomolecules has also been observed in tissues and blood of diabetics with high AGEs concentration[117,118]. *In vitro* and *in vivo* studies have reported that increased ROS production by AGE–RAGE interaction causes DNA damage that induces endothelial cell death by triggering the apoptotic pathway[119,120].

AGEs and endothelial cell dysfunction

Endothelial dysfunction is the hallmark for the development of cardiovascular complications in T2DM. The presence of RAGE on the endothelial cell surface suggests its relevance in endothelial dysfunction by interacting with AGEs in T2DM.

Lowered NO production, increased ROS generation, and enhanced expression of adhesion molecules, chemokines and cytokines are the hallmarks of endothelial dysfunction[121]. These conditions lead to inflammation, vasoconstriction, oxidative stress, myofibroblast migration, and proliferation inside the endothelial layer of vessels; all of which play a vital role in the development and progression of vascular complications in T2DM[122]. Under hyperglycemic condition endothelial cell proteins such as fibroblast growth factor and mitochondrial proteins undergo nonenzymatic glycation reactions affecting the vascular properties of cells by increased superoxide production, altering mitogenic and endothelial NOS (eNOS) activity[123,124].

Serum level of AGEs is negatively associated with the extent of endothelium-dependent vasodilation in T2DM patients [125]. NO acts as an antiatherogenic factor due to its effective vasodilatory, anti-inflammatory, and antiproliferative activities[110,126]. Increased ROS production by AGEs is one of the reasons for inactivation of NO as well their conversion to peroxynitrite form, thereby affecting the integrity of endothelial cells. Formation and accumulation of AGEs inside the endothelial cells is also found to be associated with reduced eNOS gene expression and increased eNOS mRNA degradation[126]. AGE–RAGE interaction on endothelial cells also results in enhanced production of asymmetric dimethylarginine, which is an endogenous inhibitor of eNOS and is one of the strongest marker of cardiovascular disease progression[127]. AGEs are also involved in NO quenching and inactivation of endothelium-derived NO[88]. Uhlmann *et al*[128] reported a significant reduction in NO production in AGE-treated cells *in vitro*. Their results implied that AGEs have a role in the modulation of NO activity in diabetic pathophysiology[128]. Ren *et al*[29] demonstrated the involvement of AGEs in reducing eNOS expression and NO bioavailability by increasing the oxidative stress development through activation of p38 and ERK1/2 in human coronary artery endothelial cells *in vitro*[29]. Therefore, accumulation of AGEs and AGE–RAGE interaction has an important impact on the pathogenesis of diabetic-CVD by affecting the vasodilating properties of endothelial cells. The AGE–RAGE axis also provokes the expression of p22hox and gp91hox, which are reduced form of NADPH oxidase in endothelial cells and causes its dysfunction[28].

Involvement of AGEs has also been noticed in the production of vascular endothelial growth factor (VEGF) by endothelial cells and thereby involved in atheroma formation. The activation of NF-κB by AGEs increases the secretion of VEGF (that prevent the repair of endothelial lesions resulting in atherogenesis), stimulates the differentiation of monocyte to macrophages and the accumulation of oxidized LDL in the vasculature leading to foam cell formation[29,129]. AGE–RAGE involvement has also been observed to inhibit the prostacyclin production and generation of PAI-1 in endothelial cells[130]. Formation and accumulation of AGEs have also been implicated in platelet activation and aggregation, stimulation of procoagulant activity, thrombus formation, and endothelial cell damage mediated by upregulation of protease-activated receptor-1 and -2 potentiates thrombin[131,132]. Decreased endothelial progenitor cell (EPC) function and mobilization poses a major risk for developing cardiovascular complications in T2DM[133]. AGE–RAGE interaction augments the apoptotic pathways and suppresses the migration and tube formation of late EPC by downregulation of Akt and cyclooxygenase-2[134]. Glycation of Arg-Gly-Asp motif of fibronectin by AGEs results in impairment of vascular repair by inhibiting EPC adhesion, migration, and spreading[134].

Vascular complications are also characterized by the adhesion and transmigration of monocyte into the subendothelial space. AGE–RAGE interactions enhance this process by activation of proinflammatory molecules such as NF-κB, which causes the overexpression of proinflammatory genes and adhesion proteins that aid monocyte adhesion to endothelial cells[103,135,136]. Foam cells and fatty streak formation take place in the vessel wall by monocyte and oxidized lipid at the adhesion site. These fatty streaks mature into advanced lesions with a fibrous cap that can dislodged resulting in an infarct or a stroke[137]. These observations suggest that AGEs have a definitive role in development and progression of vascular injuries observed in diabetes.

AGEs and VSMC modifications

Recently researchers have identified the phenotype transformation of VSMCs into macrophages during cardiovascular pathology[138]. *In vitro* studies have shown the effects of AGEs on increased proliferative activity and production of fibronectin in cultured SMCs. Transforming growth factor-β might act as a mediator in AGE-induced fibronectin production in SMC through AGE–RAGE interactions[139]. *In vivo*, the effect of AGEs on the growth of SMCs has also been noticed and is mediated by increased production of cytokines or growth factors[140]. Expansion of neointima is a unifying feature of atherosclerosis. Significant decreased in neointimal expansion, SMC proliferation, migration, and expression of ECM proteins have been demonstrated in homozygous RAGE-null mice. These data highlight the involvement of the AGE–RAGE axis in modulating the SMC properties and suggesting an important pharmaceutical target for suppression of neointima expansion[44,140]. VSMC phenotype transformation and calcification is one of the main pathological manifestations of atherosclerosis[141]. Recently Bao *et al*[142] showed the effect of AGEs on VSMC-derived foam cell formation and phenotype transformation. They identified the effect of CML on decreased expression of VSMC markers and increased expression of macrophage markers. They also noticed the involvement of AGEs in SMC migration and the secretion of proinflammatory factors[142]. Xing *et al*[143] explained the associated mechanism of phenotype transformation of VSMCs to macrophages by AGEs during atherosclerosis. They noticed that AGEs induced activation of RAGE/TLR4/FOXC2 signaling in macrophages with high expression of delta-like ligand (Dll)4 during M1 polarization. These altered macrophages promoted phenotype conversion of VSMC through Dll4/Notch pathway after cell-to-cell contact[143].

ANTI-AGEs THERAPIES

The deleterious effects of AGEs in the development and progression of diabetic vascular complications have driven the

focus of pharmacological intervention towards attenuating the effects of AGEs. Although lifestyle modification, better glycemic control, regular physical activity, smoking cessation, restriction of AGE-rich diet have been reported to reduce the availability of precursors for glycation reactions and AGEs formation in T2DM[144-146]. A plethora of studies over the last few decades have been dedicated to in searching for pharmacological agents capable of interfering with glycation reactions and their sequelae. The underlying mechanism of action of these proposed drugs are based on AGEs inhibitors, AGEs crosslink breakers, detoxifying the dicarbonyls intermediates, and AGE–RAGE signaling blockers (Figure 3)[147, 148]. No AGE-modifiers have been approved as drugs as yet, although some AGE-associated medications are in clinical and preclinical testing. Phytochemicals having antioxidant and anti-inflammatory properties have the potential to arrest the detrimental effects of AGEs and downstream consequences of the AGE–RAGE pathway[149].

Inhibition of endogenous AGEs formation

The first drug that was discovered to impede endogenous AGE formation was aminoguanidine with a guanidine group that is capable of trapping α-dicarbonyl product of early glycation reactions and thereby preventing the subsequent reactions with proteins[150,151]. Bolton *et al*[152] demonstrated the role of aminoguanidine in reducing proteinuria and progression to retinopathy, however due to its side effects, it is unlikely to be used for therapeutic purposes[152]. Compounds structurally related to aminoguanidine such as ALT-946 and OPB-9195 have been developed and tested as potential drugs. ALT-946 therapy was found to reduce renal AGE accumulation, and reduce albumin excretion in animal models[153]. OPB-9195 is an antagonist of peroxisome proliferator-activated receptor-γ and inhibits the glycoxidation and lipoxidation reactions. In animal models, OPB-9195 decreased the progression of nephropathy, lowered the blood pressure, and the serum level of AGEs[154,155]. LR-90 is another aromatic compound with anti-AGE properties due to its metal-chelating ability and its interaction with dicarbonyl compounds. It affords renoprotection such as improved renal albuminuria, reduction of connective tissue growth factors, fibronectin and collagen deposition in experimental model of type 1 and type 2 nephropathy[156]. TM2002 is a powerful AGE inhibitor that has transition metal-chelating properties and is nontoxic. It improves renal and cardiac lesions, and decreases infarct volume in different animal models[157,158]. Benfotiamine is a prodrug of thiamine monophosphate with AGE-lowering properties, mediated through preventing dicarbonyl formation[159,160]. In a pilot study, Brownlee *et al*[150] observed that treatment along with α-lipoic acid improved complications in patients with type 1 or type 2 DM. Pyridoxamine also intervenes in the glycation process by blocking the transformation of Amadori products into AGEs[161]. They have the ability to trap ROS, thereby blocking the oxidative degradation of Amadori intermediates and preventing the formation of AGEs[162,163].

Preformed AGEs breakers

Among the deleterious effects of AGE accumulation, crosslinking of ECM is of prominence and results in cardiovascular stiffness. Phenylthiazolium bromide was the first reported AGE crosslink breaker that is not stable in aqueous solution [164]. Several of its derivates have now been derived, such as ALT-711 or alageberium, and have the ability to break AGE crosslinks. The precise mechanism of their action relies on reaction with carbonyl groups present in AGE crosslinks and cleavage of carbon–carbon bonds. Application of alageberium in animal models has proved to be effective in reducing large artery stiffness and blood vessel fibrosis, attenuating atherosclerosis, diabetic nephropathy, and hypertension[165, 166]. The role of aptamers has been explored in biomedical and pharmaceutical industries[167]. Aptamers are a group of short and single-stranded DNA or RNA molecules with the ability to bind with high affinity/specificity to a variety of proteins. DNA aptamers raised against AGEs bind and ameliorate AGE-associated effects[168]. These specific DNA aptamers can become novel therapeutic agents for AGE-related pathologies.

AGE–RAGE signaling blockers/RAGE antagonists

In vitro and *in vivo* studies have confirmed that AGE–RAGE axis is one of the major pathways for diabetic vascular complications. Therefore, it would be an ideal target to prevent the development and progression of complication in T2DM. Pharmacological agents that focus on the AGE–RAGE axis could function through different means such as inhibiting the RAGE expression, altering the AGE–RAGE signaling or by raising the blood level of soluble RAGE (sRAGE) to trap AGEs. sRAGEs are formed by alternative gene splicing of *RAGE* gene or proteolytic cleavage of membranous RAGE. Administration of sRAGE has shown to decrease albuminurea, glomerulosclerosis and diabetic CVD [169,170]. Statin and thiazolindinediones have been shown to ameliorate RAGE expression in conjugation with increased sRAGE[171,172]. The proposed underlying mechanisms of statin and thiazolindinediones have also been described. Activation of peroxisome proliferator-activated receptor-γ can inhibit the phosphorylation of ERK1/2 and downregulate NF-κB, thereby lowering the expression of inflammatory cytokines and RAGE[173,174]. Other molecules such as glucagon-like peptide (GLP)-1 and its analog exendin also decrease RAGE expression through suppressing NF-κB and decreasing ROS production by inhibiting NADPH oxidase activity[175,176]. Studies have also reported the involvement of GLP-1 and exendin in reducing activation of the AGE–RAGE axis and its associated complications such as atherosclerosis and diabetic cardiomyopathy *etc*[177,178]. RAGE inhibitors FPS-ZM1 and PF-04494700 had neuroprotective effects against ischemic brain injury in a rat model and β-amyloid structures in clinical trials for Alzheimer's disease[179, 180]. The effect of FPS-ZM1 as a RAGE inhibitor is associated with decreased inflammation and oxidative stress by targeting other ligands of RAGE such as S100, high-mobility group protein 1, and amyloid β-protein[180-183]. The promising effect of RAGE blockers such as FPS-ZM1 and PF-04494700 in neurodegenerative diseases provides the rationale to study their effects in T2DM patients.

AGEs and hypoglycemic drugs

The effects of many hypoglycemic drugs have also been studied in the context of decreasing AGE level and ameliorating

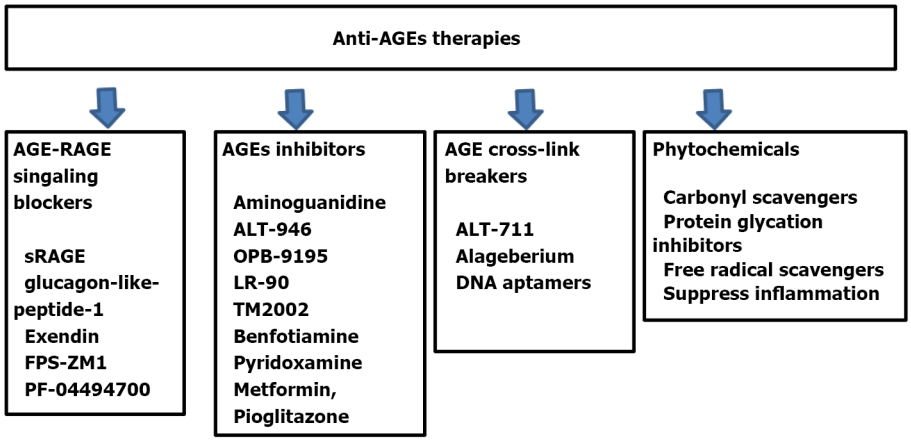

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Figure 3 Anti-advanced glycation end product therapeutic strategies. Anti-AGE therapies target multiple pathways based on AGE-mediated effects in type 2 diabetes mellitus and associated complications. These include inhibitors of AGE formation, AGE crosslink breakers, and AGE–RAGE for AGE signaling blockers. The uses of phytochemicals having antioxidant and anti-inflammatory properties are also providing options to arrest the detrimental effects of AGEs by reducing peroxidative inflammatory reactions through carbonyl scavengers, protein glycation inhibitors and free radical scavengers which can reduce oxidative stress. RAGE: Receptor for advanced glycation end products; AGEs: Advanced glycation end products; sRAGE: Soluble RAGE.

the effects of AGE–RAGE axis. Prasad and Tiwari[169] have reported the effects of rosiglitazone in inhibiting the AGE–RAGE interaction and found elevated sRAGE levels[169]. Similar results have been reported in a randomized placebo-controlled study of 111 patients with T2DM CVD, where increased sRAGE and decreased inflammatory markers were reported after 6 mo of rosiglitazone treatment[184]. Effects of glimepiride beyond glycemic control have been reported in reduction of toxic glyceraldehyde-derived AGE levels and increased colony-stimulating factors to potentially repair tissue damage in T2DM patients[185]. Metformin treatment inhibits development of adverse myocardial structural and functional changes by inhibiting the production and accumulation of AGEs[186,187]. Metformin also inhibits the AGE-induced VSMC proliferation[188]. Animal and *in vitro* models have shown the efficacy of dipeptidyl peptidase-4 inhibitors such as sitagliptin, cilizytin, vildagliptin and linalgliptin in inhibiting glycosylation, downregulating the levels of AGEs, RAGE and oxidative stress markers, and decreasing the expression of VCAM-1, PAI-1, and ICAM-1[189-192]. GLP analog liraglutide was also found to ameliorate atherogenesis by inhibiting AGE-induced expression of RAGE in a mouse model[193].

CONCLUSION

T2DM imposes both clinical and economic burdens on the healthcare system. Recent reports have confirmed that CVD represents a substantial burden on the treatment of T2DM at both patient and population level. The pathophysiology of hyperglycemia in T2DM is closely associated with AGEs formation, accumulation, and their deleterious effects. The adverse effects of AGE accumulation include many important biochemical reactions that are central to the development and progression of cardiovascular complications in T2DM. AGE-mediated cardiovascular complications show many pathological changes such as plaque formation, arterial stiffening, neointimal proliferation, vasoconstriction, oxidation of LDL, and endothelial dysfunction. The probable mechanisms through which AGEs exert their detrimental effects include increased ROS generation, oxidative stress development, decreased NO production and its inactivation, inflammation, adhesion molecule expression, crosslinking of proteins, and prothrombotic gene expression. AGE–RAGE interactions also alter the cellular properties by promoting proinflammatory and procoagulant pathways acting through modulation of signaling molecules such as ERK1/2, cdc42/rac, p21RAS, TNF-α, MAPK, NF-κB, and JAK/STAT that adversely affect the cardiovascular health in T2DM. The AGE–RAGE axis is also involved in modulating SMC properties and neointima expansion, where it mediates SMC proliferation, phenotype transformation of VSMCs into macrophages during cardiovascular pathology. Therefore, clinical and experimental research is now focused on AGEs as new biomarkers or therapeutic target to prevent the development and progression of diabetic vascular complications. Based on AGE-mediated effects in pathogenesis of T2DM and its complications, pharmacological approaches are exploring combination therapies targeting multiple pathways based on inhibitors of AGE formation, AGE cross-ink breakers, free radical scavengers, and anti-inflammatory therapies, detoxifying the dicarbonyl intermediates and AGE–RAGE signaling blockers that may attenuate AGE-mediated effects in diabetic cardiovasculature. The use of phytochemicals with antioxidant and anti-inflammatory properties is promising for arresting the detrimental effects of AGEs. Also, there is a need to develop more specific and sensitive methods for the assay of circulatory AGEs. An epidemic of diabetes over the past half century has also been associated with increased consumption of modern heat-processed and highly palatable AGE-rich diet. Therefore, lifestyle modifications including dietary AGE restriction, regular exercise and cessation of smoking are some of the important interventions and practical ways to attenuate the effects of the AGE–RAGE axis and AGE-associated pathways.

FOOTNOTES

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REVIEW

Dysglycemia and arrhythmias

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Abstract

Disorders in glucose metabolism can be divided into three separate but interrelated domains, namely hyperglycemia, hypoglycemia, and glycemic variability. Intensive glycemic control in patients with diabetes might increase the risk of hypoglycemic incidents and glucose fluctuations. These three dysglycemic states occur not only amongst patients with diabetes, but are frequently present in other clinical settings, such as during critically ill. A growing body of evidence has focused on the relationships between these dysglycemic domains with cardiac arrhythmias, including supraventricular arrhythmias (primarily atrial fibrillation), ventricular arrhythmias (malignant ventricular arrhythmias and QT interval prolongation), and bradyarrhythmias (bradycardia and heart block). Different mechanisms by which these dysglycemic states might provoke cardiac arrhythmias have been identified in experimental studies. A customized glycemic control strategy to minimize the risk of hyperglycemia, hypoglycemia and glucose variability is of the utmost importance in order to mitigate the risk of cardiac arrhythmias.

Key Words: Dysglycemia; Hyperglycemia; Hypoglycemia; Glucose variability; Cardiac arrhythmia

Core Tip: Different mechanisms by which these dysglycemic states might provoke cardiac arrhythmias have been identified in experimental studies. A customized glycemic control strategy to minimize the risk of hyperglycemia, hypoglycemia and glucose variability is of the utmost importance in order to mitigate the risk of cardiac arrhythmias.

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INTRODUCTION

Hyperglycemia, hypoglycemia, and glycemic variability (GV) represent three important domains of dysglycemia. Type 2 diabetes mellitus (T2DM) is a metabolic disease that is diagnosed mainly on the basis of sustained hyperglycemia, which has been associated with a number of adverse health outcomes, such as coronary artery disease, stroke and cardiac arrhythmias[1-3]. Epidemiologic studies have demonstrated that the incidence of many diabetic complications is directly associated with the degree of hyperglycemia[1]. However, overcorrection of hyperglycemia may lead to episodes of hypoglycemia, then increasing the risk of fatal adverse events, and that has been observed in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. The ACCORD study was terminated early due to the observation of significant increased mortality in the intensive glycemic control group, and the majority of excess deaths in this group has been attributed to either unexpected deaths or witnessed deaths due to arrhythmias[1]. Glycemic variability is an integral component of glucose homoeostasis, which can represent the presence of excess glycemic excursions, namely the hyperglycemic spikes and hypoglycemic incidents[4]. Increased GV has been linked to the development of cardiac arrhythmias, including atrial fibrillation (AF) and ventricular tachy-arrhythmias[5,6]. High GV appears to exert more detrimental effects than persistent hyperglycemia on the pathogenesis of diabetic complications[7,8], and has also been associated with an increased risk of cardiac arrhythmias compared to those with good glycemic control[9]. Overall, each of these three dysglycemic states has been associated with an increased risk of certain types of cardiac arrhythmias. Therefore, in this review, we explore the epidemiology of three dysglycemic states and arrhythmias, identify potential mechanisms, consider what additional research is required, and suggest how the issue might be approached in clinical practice (Figure 1).

LITERATURES REVIEW

Literature search and study selection

This review focused on the associations between hyperglycemia, hypoglycemia, and GV with cardiac arrhythmias, which was implemented within databases of PubMed and EMBASE, from April 1975 to November 2022. The literature search was conducted using the following keywords: "hyperglycemia", "hypoglycemia", "glycemic variability", "glucose variability", "glucose fluctuation", "dysglycemia", "diabetes", "type 2 diabetes", "type 1 diabetes", "arrhythmia", "tachycardia", "bradycardia", "premature beat", "ectopic", "flutter", "fibrillation", "atrioventricular block", "sudden cardiac death", and "QT prolongation". Studies that focused on the associations between three dysglycemia domains with cardiac arrhythmias were included in this review, without study design restriction. Duplicate records and studies without full-text access were excluded. Two reviewers (D.S. and N.Z.) independently conducted the literature search and study selection, and discrepancies were resolved by a third author (T.L.).

Definitions of dysglycemia domains

Hyperglycemia mainly includes impaired fasting blood glucose (IFG), impaired glucose tolerance (IGT), and overt diabetes[10]. IFG was defined as a fasting plasma glucose (FPG) level between 110 mg/dL and 125 mg/dL, according to the 2006 World Health Organization guidelines. IGT was defined as FPG < 126 mg/dL with 2-h plasma glucose after a 75-g oral glucose challenge of 140-199 mg/dL. Patients with DM were defined as those with a history of physician-confirmed diabetes or history of oral hypoglycemic agents or insulin use[10]. Hypoglycemia is defined as blood glucose concentration less than 70 mg/dL[11,12]. Glycemic variability refers to intraday or daily blood glucose fluctuation, and months or years of blood glucose fluctuation. At present, the definition of GV is very vague, and it is mainly measured by indicators such as mean blood glucose and standard deviation, J index and coefficient of variation, postprandial hyperglycemia and mean amplitude of glucose excursion[7].

LITERATURES RESULTS

A total of 1929 records were identified, after excluding duplicates (n = 509) and those irrelevant (n = 1296), 124 studies were included in this review. An overview of studies included in this review is showed in Supplementary Tables 1-3.

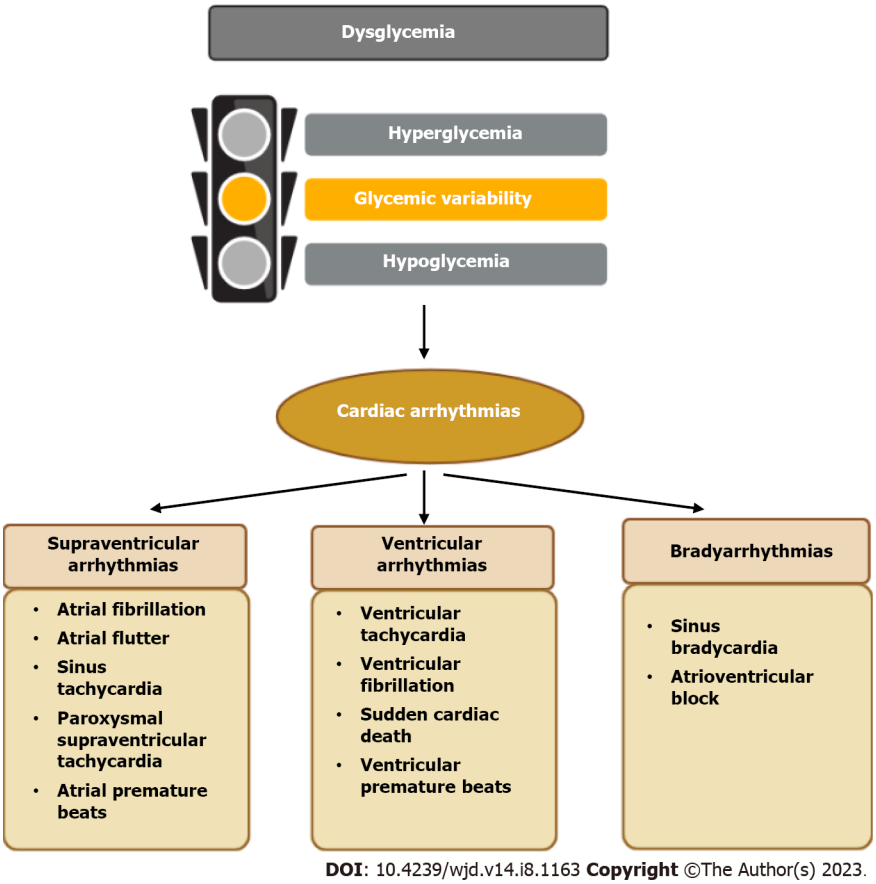

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Figure 1 Graphic abstract. The association between dysglycemia and cardiac arrhythmias.

HYPERGLYCEMIA AND CARDIAC ARRHYTHMIAS

Chronic hyperglycemia is a hallmark and remains one of the most important pathophysiologic features of DM. Previous studies have observed multiple types of cardiac arrhythmias in patients with diabetes, including supraventricular and ventricular arrhythmias[2]. An overview of studies evaluating the association between hyperglycemia and cardiac arrhythmias is provided in Supplementary Table 1.

Hyperglycemia and supraventricular arrhythmias

Studies have found that patients with diabetes are more likely to develop AF, atrial flutter, and paroxysmal supraventricular tachycardia than those without diabetes[13,14]. Current researches on hyperglycemia and supraventricular arrhythmias have mainly focused on the association between abnormal state of glucose metabolism, including IFG, IGT, and DM, with the risk of AF[13,15,16].

Hyperglycemia and AF: Epidemiology of hyperglycemia-related AF: A cross-sectional study found a two-fold increased risk of incident non-valvular AF amongst individuals with an elevated blood glucose levels compared to those with normal glucose levels[17]. IFG has also been identified as a risk factor for AF in healthy Asian populations[15]. In patients with IGT, FPG but not progression to diabetes is one of the predictors for AF, and a one mmol/L increase in baseline FPG has been associated with a 33% increased risk of AF[16]. As for the overt DM, numerous studies have shown that diabetes is associated with an increased risk of AF and has been considered a risk factor for AF in healthy individuals and hospitalized patients[13,18,19]. Diabetes is included in the CHA_2DS_2-VASc, CHARGE-AF, and MR DASH scores which have been established to predict the chances of developing AF[20,21]. A relevant meta-analysis showed that the risk of AF was 34% higher in patients with DM than non-DM patients[22]. In addition, hyperglycemia is also associated with the development of AF in some certain clinical settings. A retrospective cohort study with an average 11-year follow-up has identified that fasting hyperglycemia was independently correlated with new-onset AF in patients with acute myocardial infarction (AMI)[23]. Moreover, another retrospective analysis suggested that stress hyperglycemia is associated with an increased prevalence of AF in AMI[24]. A prospective study has demonstrated that tighter glycemic control in diabetic coronary artery bypass grafting (CABG) patients is associated with a lower incidence of perioperative AF[25].

Hyperglycemia or DM could not only increase the incidence of AF but also affect the prognosis of patients with AF. Studies have shown a significant correlation between admitted blood glucose levels and increased mortality of hospitalized patients with AF[26]. Moreover, diabetes has been considered a significant predictor of ischemic stroke, major bleeding, and heart failure in patients with non-valvular AF[27]. In AF patients with DM, a positive linear correlation has been identified between glycated hemoglobin (HbA1c) levels with all-cause and cardiovascular mortality[28]. However, a

previous study has reported that there was no significant association between diabetes and future hospitalization for AF [29]. The different results may be related to population differences and different study designs. Overall, hyperglycemia has a significant impact on the prognosis of AF, therefore, glycemic control should be paid more attention among patients with AF.

Mechanisms of hyperglycemia-related AF: Electropathology is identified as the underlying cause of AF. Abnormal electrical activity of pulmonary veins and non-pulmonary veins trigger foci is a significant mechanism of AF, which causes electrical, structural and neural remodeling. Patients with AF and abnormal glucose metabolism have significantly longer total activation times and lower atrial voltages in the left and right atrial than those without. Moreover, patients with abnormal glucose metabolism are more likely to have greater chances of AF relapse after catheter ablation[30]. Therefore, as the main character of abnormal glucose metabolism, hyperglycemia may change the atrial substrate to some extent, which increases the susceptibility to the occurrence and maintenance of AF[30].

Electrical remodeling: Accumulating evidence from basic studies has suggested that the effect of hyperglycemia on the atrium was related to electrical remodeling[31]. Prolonged action potential duration (APD) and increased APD dispersion (APDD) were observed in animal models of type 1 diabetes (T1DM), indicating increased susceptibility to AF and difference of refractoriness in atrium[32,33]. Furthermore, the densities of Na^+ current (I_{Na}) were reduced and the densities of L-type Ca^{2+} channel ($I_{Ca\text{-}L}$) were increased in the atrial of alloxan-induced diabetic rabbits[32]. In rat models of T2DM, similar prolongation of APD and increased susceptibility to AF were observed[34,35]. However, atrial myocytes isolated from Zucker diabetic fatty rats had decreased current densities of transient outward K^+ current (I_{to}), ultrafast delayed rectifier K^+ current (I_{Kur}) and $I_{Ca\text{-}L}$[34]. The different changes in densities of $I_{Ca\text{-}L}$ in these studies may be related to the type of model[32,34]. Additionally, the ion channel protein (Kv4.3, Kv1.5 and Cav1.2) expression in HL-1 cells treated with advanced glycation end products was significantly down-regulated, indicating that hyperglycemia can directly affect the electrical remodeling of cardiomyocytes through alterations in ion channels[34].

Structural remodeling: Fibrosis is a major feature of the atrial structural remodeling[31]. A large body of studies have demonstrated that hyperglycemia contributes to atrial interstitial fibrosis in animal models[32,34-36]. Transforming growth factor beta 1, the main profibrotic cytokine, presented with an increased expression in the atrium of diabetic rabbits[32]. It also has been shown that diabetic rats have significantly enlarged left atria[34,37]. Furthermore, Studies have shown that mast cells could contribute to the development of AF by enhancing inflammation and fibrosis in diabetic mice, and AF can be attenuated by the deletion of mast cells[38].

Neural remodeling: A prospective study has shown that there was a significant association between reduced heart rate recovery and new-onset AF in patients with T2DM, suggesting that autonomic dysfunction may play an important role in DM-related AF[39]. In a previous animal study, sympathetic nerve stimulation significantly increased the incidence of AF in streptozotocin (STZ)-induced DM rats, while parasympathetic nerve stimulation increased the risk of AF both in the DM rats and control rats[40]. Besides, both the stimulation of sympathetic nerve and parasympathetic nerve decreased the atrial effective refractory period, and the former also increased atrial effective refractory period heterogeneity in DM rats[40]. These alterations in the autonomic nervous system are likely to be associated with the increased incidence of AF in diabetes.

Other mechanisms: Cellular researches have showed that hyperglycemia could induce endoplasmic reticulum stress in atrial cardiomyocytes, in which mitofusin-2 (Mfn-2) plays a major role[41]. Mfn-2 downregulation was found to prevent mitochondrial Ca^{2+} overload-mediated mitochondrial dysfunction and subsequent cardiomyocyte death[41]. Furthermore, clinical studies have found that the maximum ability to oxidize fatty acids and glutamate of myocardial mitochondria is impaired, and mitochondrial H_2O_2 release is increased in patients with T2DM. Disruption of myocardial oxidative balance and mitochondrial metabolism may affect the normal function of the atrium[42], which may also contribute to the development of AF (Figure 2).

Based on these mechanisms, some upstream therapies have been proposed to prevent the development of AF in patients with diabetes. For example, the sodium glucose co-transporter-2 inhibitor (SGLT2i), empaglifozin, can ameliorate atrial structural and electrical remodeling as well as improve mitochondrial function in T2DM animal models[43]. In addition, Lee *et al*[44] have confirmed the benefit of SGLT2i in prevention of incident AF among T2DM patients, compared with dipeptidyl peptidase-4 inhibitor (DDP-4i). These findings consistently suggested that SGLT2i may play an important role in the prevention of T2DM-related AF. Apart from SGLT2i, thiazolidinedione[37,45] and allopurinol[36] have also been demonstrated to have protective effects on prevention of incident AF in patients with diabetes. However, a prior populationbased study has observed that sulphonylurea use was associated with a higher risk of incident AF compared to metformin in T2DM patients, especially in males and those older than 65 years[46]. Future large-scale studies are needed to optimize the prevention strategy of DM-related AF, especially in higher risk population.

Hyperglycemia and other supraventricular arrhythmias: Unlike AF, evidences regarding the association between hyperglycemia and other supraventricular arrhythmias are less frequently reported. Agarwal *et al*[2] have conducted a cross-sectional study including 100 patients of T2DM, and found that sinus tachycardia is one of the common arrhythmias in T2DM patients, with a prevalence of 32%. In addition, previous studies also suggested that the risk of symptomatic paroxysmal supraventricular tachycardia[14] and atrial flutter[13] was higher among DM patients, in relation to the non-DM population.

Hyperglycemia and ventricular arrhythmias: Hyperglycemia or diabetes has been associated with a higher risk of ventricular arrhythmias and sudden cardiac death (SCD) in some studies. Besides, as a well-established marker for ventricular arrhythmia, QT prolongation has also been observed in hyperglycemic settings[47-49].

Epidemiology of hyperglycemia-related ventricular arrhythmias

Ventricular tachycardia, ventricular fibrillation, and SCD: A retrospective study has shown that HbA1c levels are

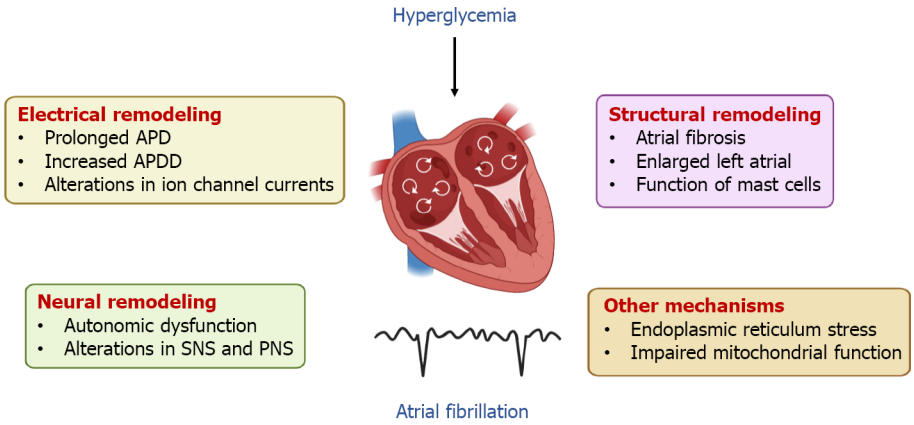

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Figure 2 Mechanisms underlying the association between hyperglycemia and atrial fibrillation. APD: Action potential duration; APDD: Action potential duration dispersion; PNS: Parasympathetic nerve stimulation; SNS: Sympathetic nerve stimulation.

associated with spontaneous ventricular tachycardia (VT) in high-risk male patients, independently of QT interval duration[50]. Moreover, another study also suggested that hyperglycemia on admission was significantly associated with early VT after myocardial infarction[51]. As for ventricular fibrillation (VF), Movahed *et al*. have observed that the prevalence of VF in patients with T2DM was significantly increased after adjusting for potential confounders[52]. Additionally, in a prior prospective study conducted among women in the United States, diabetes significantly increased the risk of SCD[53]. Another study also showed that the risk of sudden cardiac arrest was significantly reduced in DM patients taking antidiabetic medications than those without, indicating that hyperglycemia may play an important role in sudden cardiac arrest[54,55].

QT prolongation: Using The Third National Health and Nutrition Examination Surveys (NHANES III), Brown and colleagues have found that there was a 1.2-fold increased risk of developing QTc prolongation in patients with IFG than those with normal glucose tolerance (NGT)[56]. Meanwhile, patients with established diabetes experienced a 1.6-fold increased risk of QTc prolongation than those with NGT[56]. Another cross-sectional study also suggested that mean blood glucose level is an independent risk factor for QTc prolongation[57]. In addition to the observational studies mentioned above, there are many experimental studies investigating the relationship between hyperglycemia and QT interval. Through hyperglycemic clamp tests, studies have found that acute hyperglycemia increased the QTc interval in healthy individuals and patients with T1DM[58,59]. Besides, hyperglycemia has also been associated with increased QTc dispersion (QTd) among healthy individuals, which reflects the inhomogeneity of myocardial repolarization[58]. However, a prospective study (n = 26) failed to observe a significant change in QTc or QTd among patients with newly diagnosed T2DM[60], which may be due to the small sample size, short follow-up duration and unknown confounding factors.

Mechanisms of hyperglycemia-related ventricular arrhythmias: Alterations of ion channels: Studies have found that diabetes prolongs cardiomyocyte APD, and changes in APD are mainly due to alterations in ion channels[61,62]. Meo *et al* [61] have observed that hyperglycemia in STZ-treated mice was associated with prolongation of the QT interval, enhanced temporal dispersion of electrical recovery, and susceptibility to ventricular arrhythmias, compared with controls. According to Meo *et al*[61], the density of voltage-gated K^+ current (Kv) currents were decreased in STZ myocytes, in comparison to cells from normoglycemic mice. In another study using diabetic rabbits model, the inhibition of rapid delayed rectifier K^+ current (I_{Kr}) was found to be a major ionic factor in APD prolongation[62]. However, in diabetic rats model, researchers have suggested that the DM-related APD prolongation was mainly due to the reduction in I_{to}[63,64].

Compared with the control group, the density of Na^+ current in ventricular myocytes of diabetic rabbits and HEK-293 T cells exposed to high glucose was reduced[65,66]. Reduced I_{Na} amplitude also has been shown to be a key determinant of diabetic ventricular conduction impairment[65]. Furthermore, studies on posttranslational modification have found that hyperglycemia increases the O-GlcNAcylation of cardiac Nav1.5 expression, resulting in abnormal Nav1.5 expression and distribution, as well as alteration of QT interval[66]. Studies have shown conflicting results on the alterations of $I_{Ca\text{-}L}$ in DM animal models[61,62,67]. Further research is needed to investigate the association between hyperglycemia and alterations of cardiac calcium channels.

Connexins: As a component of gap junctions, play crucial roles in electrical coupling between cardiomyocytes and affect myocardial electrical propagation velocity and coordinated contraction[68]. The connexin 43 (Cx43) isoform is predomainantly expressed in ventricles. Researches in diabetic animal models have observed an association between enhanced Cx43 phosphorylation mediated by ε-PKC with a decrease in myocardial conduction velocity[69,70]. However, other studies also suggested that hyperglycemia promotes the nitrification of Cx43 tyrosine rather than phosphorylation [71]. Moreover, a study has shown that the content of total Cx43 increases in short-term diabetic rat hearts and does not significantly change in long-term diabetic rat hearts, while others showed the opposite result[69,70,72]. This may be related to the different modeling time and measurement methods.

Oxidative stress: Oxidative stress is involved in hyperglycemia-related ventricular arrhythmias through multiple pathways. The excess reactive oxygen species (ROS) induced by hyperglycemia in cardiomyocytes impaired the function of the ion channel[73,74]. Previous studies have shown that hyperglycemia induces sarcoplasmic reticulum Ca^{2+} release events and downregulates the functional expression of most K^+ channels through Calcium/calmodulin-dependent protein kinase II (CaMKII) activation[75,76]. The properties of I_{Na} are also found to be altered by oxidative stress[77]. Oxidative modification of tyrosine-mediated signaling may play an important role in the mechanism of Cx43 alteration in diabetes[71]. Additionally, glutathione oxidation enhances APD heterogeneity and increases the arrhythmia score index in diabetic animal models[78].

Hormones: Hyperglycemia causes alterations in the levels of hormones *in vivo*, which are involved in the pathogenesis of arrhythmias. A significant negative correlation was observed between serum-free thyroxine and glucose concentration [79]. Thyroid hormone reduced the expression of ε-PKC in non-diabetic rat hearts, resulting in the downregulation of Cx43, which is related to increased myocardial conduction and arrhythmia susceptibility[69]. Moreover, it has been found that reduction of the ventricular fibrillation threshold in diabetes is associated with altered sympathetic activity in myocardium, and there was a significantly greater decline of ventricular fibrillation threshold in response to epinephrine infusion in diabetic dogs[80].

Hyperglycemia and other arrhythmias

Studies have shown an increased incidence of cardiac conduction abnormalities in patients with diabetes[81]. Right bundle branch block, bifascicular block and high degree atrioventricular block (AVB) are more likely to occur in diabetic patients[81]. It has been found that T2DM is independently associated with third-degree AVB in multivariable model[82, 83]. In addition, the prevalence of diabetes in patients with pacemakers is six to ten times higher than the general population due to severe bradycardiac arrhythmias[84].

Hypoglycemia and cardiac arrhythmias: Hypoglycemia is a frequent and feared adverse effect among individuals treated with insulin and insulin secretagogue drugs. The average incidence of mild hypoglycemia is 1-2 episodes per patient per week in T1DM and 0.3-0.7 episodes per patient per week in insulin-treated T2DM[85]. It has been reported that the insulin-mediated hypoglycemic events account for approximately 100000 emergency department visits per year in the United States[86]. A pivotal report by Tattersall *et al*[87] first presented evidence that hypoglycemia was implicated in the sudden overnight death of young individuals with T1DM. This mode of death has been described as the dead-in-bed syndrome since then, and thought to be caused by fatal hypoglycemia-induced arrhythmias during sleep. Generally, hypoglycemia can affect cardiac repolarization and cardiac electrophysiology[88], inducing various types of arrhythmias, which has been considered as a proarrhythmic event. Information about the studies regarding the association between hypoglycemia and cardiac arrhythmias is presented in Supplementary Table 2.

Hypoglycemia and supraventricular arrhythmias: Several types of supraventricular arrhythmias have been observed during hypoglycemia, including sinus tachycardia[89], atrial premature beats[90,91], AF[92-94], and non-paroxysmal atrioventricular junctional tachycardia[95].

Hypoglycemia and AF: Hypoglycemia-induced AF was first reported in nondiabetic patients undergoing insulin shock therapy for some psychiatric illnesses[96]. Several other case reports have also observed the epidodes of AF during hypoglycemia in both diabetics and nondiabetics, which reverted to sinus rhythm after intravenous dextrose[93,97]. In a recent prospective study, 21 insulin-treated T2DM patients were monitored with continuous glucose monitoring (mean ± SD, 118 d ± 6 d) and an implantable cardiac monitor for a one-year follow-up. The researchers have found that the time spent in hypoglycemia was higher during nighttime than daytime, and the AF accounted for 22% of episodes of potentially clinically significant arrhythmias[92]. In another nationwide population-based Korean study, 1509280 participants with T2DM and free of baseline AF were included. After a mean follow-up of 8.5 years, the incidence of AF was significantly higher in patients with severe hypoglycemia than those without, where the severe hypoglycemia was defined as any hypoglycemic events requiring the assistance of another person to actively administer carbohydrates, other corrective actions, hospitalization, or medical care. This study also observed that previous severe hypoglycemia was a significant risk factor for the development of AF after adjusting for potential confounders[94]. The association between hypoglycemia and AF is not limited to DM patients. Humos *et al*[98] have assessed the impact of hypoglycemia in patients with ST-elevation myocardial infarction (STEMI) using the National Inpatient Sample database, and found that the risk of AF was significantly higher in STEMI patients with in-hospital hypoglycemia, compared to those without hypoglycemia.

These case reports and clinical studies suggest an association between hypoglycemia and AF. However, the animal study exploring the underlying mechanism of hypoglycemia-induced AF is still scarce. Vardas *et al*[99] observed that the incidence of induced AF, sustained AF (> 3 min), and the susceptibility to AF was significantly higher in the hypoglycemic group than the normoglycemic and hyperglycemic groups in *ex vivo* dog models. According to the Vardas *et al* [99], the refractory period of the atrium was significantly shorter under hypoglycemia, which might be due to the hypercatecholaminemia in hypoglycemic settings and then contribute to the profibrillatory electrophysiologic changes. Future basic studies are needed to elucidate the mechanisms of hypoglycemia-induced AF.

Hypoglycemia and other supraventricular arrhythmias: Increased heart rate is usually an initial electrocardiographic manifestation caused by hypoglycemia. In an interventional study where 119 individuals underwent experimentally-induced hypoglycemia, the mean heart rate increased from 62.2 bpm ± 9.6 bpm at baseline to 70.6 bpm ± 11.7 bpm during hypoglycemia, and recovered to baseline after oral ingestion of glucose[100]. Individuals may develop sinus tachycardia if the hypoglycemia is not corrected promptly, as seen in an animal study[89]. Atrial premature beats is also one of the common arrhythmias among patients with hypoglycemia, and has been reported to have a nearly fourfold higher risk

during nocturnal hypoglycemia, compared with euglycemia[90]. There have been sporadic case reports of other supraventricular arrhythmias. For example, Pezzarossa and colleagues have reported a case of a non-diabetic patient presented with non-paroxysmal atrioventricular junctional tachycardia during postprandial hypoglycemia, and the sinus rhythm was promptly restored with the correction of hypoglycemia[95].

Hypoglycemia and ventricular arrhythmias: Compared with supraventricular arrhythmias, much interest has been focused on the potential for hypoglycemia to cause dangerous and life-threatening ventricular arrhythmias. The hypoglycemia-induced ventricular arrhythmias and related electrophysiological events include ventricular premature beats (VPBs)[90,91,101], QT prolongation[89,100-102], VT[103,104], VF[98], and SCD[1].

Epidemiology of ventricular arrhythmias during hypoglycemia: Hypoglycemia-induced VPBs have been observed both in the spontaneous hypoglycemia[90] and experimentally-induced hypoglycemia settings[101], and among individuals with T1DM[91], T2DM and non-diabetes[101]. Although being a less dangerous arrhythmia, more attention should be paid to the occurrence of VBPs, especially in DM patients, which could facilitate the early identification of the onset of hypoglycemia. Moreover, the presence of VPBs has been shown to be associated with a significantly increased risk of SCD in middle-aged men[105].

QT prolongation: Consistent evidence from different types of studies have established that hypoglycemia could induce QT prolongation. Profound hypoglycemia has been observed to cause significant QT prolongation in animal models[89,102]. Corresponding to these basic experiments, hypoglycemia causes longer QT intervals in humans, irrespective of the diabetes status. In an experimentally-induced hypoglycemic study, the insulin-treated T2DM patients and matched controls underwent a sequential hyperglycemic and hypoglycemic clamp, both groups experienced progressively increased QTc interval (corrected by Fridericia's formula) prolongations during hypoglycemia[101]. In another interventional study enrolling 119 individuals underwent routine insulin-induced hypoglycemia testing for clinically suspected pituitary dysfunction, Kacheva *et al*[100]. observed that the QTc (Bazett's formula) increased from 415.1 ms ± 21.9 ms at baseline to 444.9 ms ± 26.5 ms during hypoglycemia, accompanied by a significant increase of QT dispersion (QTd). In addition, Fitzpatrick *et al*[106] also provided pooled evidence in their meta-analysis which supported the association between hypoglycemia and QTc prolongation among patients with T1DM and T2DM. Besides the severity of hypoglycemia, the time of onset also plays an important role in the development of QTc prolongation. Tsujimoto *et al*[107] retrospectively assessed the ECG characteristics among patients presenting to the emergency department with hypoglycemia, and found that the incidence of abnormal QT prolongation during severe hypoglycemia was significantly higher in the night-time, particularly in the early morning. In addition, both the depth and duration of hypoglycemia have been associated with the severity of QT prolongation[90,108].

It is well recognized that prolongation of the QT interval can lead to life-threatening arrhythmias such as torsades de pointes (TdP). Thus, monitoring of the QT interval is critical in patients with hypoglycemia. Duration of the QT interval naturally varies inversely with heart rate; hence, a corrected QT (QTc) that is adjusted for heart rate is most predictive of proarrhythmic potential and has been widely used in clinical practice. However, key aspects of QTc monitoring lack standardization in some clinical settings, including hypoglycemia[109]. In a previous study where 21 T1DM patients underwent continuous glucose and ECG monitoring for 72 h, the researchers have confirmed previous findings of prolonged QTc corrected by Bazett's formula during spontaneous hypoglycemia, but not by Fridericia's formula and the nomogram method, which suggested that Bazett's formula might result in overcorrection of QTc while both Fridericia's formula and the nomogram method might undercorrect the QTc during hypoglycemia[110]. Therefore, future studies are needed to standardize QTc monitoring in hypoglecemia settings.

VT, VF, and SCD: A causal relationship between hypoglycemia and fatal arrhythmias is usually difficult to demonstrate in clinical practice, since simultaneous monitoring of cardiac rhythm and blood glucose levels is seldom undertaken, even in intensive-care settings[85]. Chelliah *et al*[103] have reported a case of a frail old man who developed VT intraoperatively with a random blood glucose level of 2.9 mmol/L, which was aborted immediately on correction of hypoglycemia. In another cohort study, 94 patients with T2DM and established cardiovascular disease underwent concomitant continuous glucose monitoring and Holter monitoring for five days. It was found that patients experiencing episodes of hypoglycemia had a significantly higher number of VT than those without[104]. Using the National Inpatient Sample database, Humos *et al*[98] have observed a significantly higher risk of ventricular fibrillation (OR, 1.80; 95%CI, 1.41-2.30) and cardiogenic shock (OR, 1.72; 95%CI, 1.39-2.13) among patients hospitalized with STEMI and complicated with hypoglycemia, in relation to those without in-hospital hypoglycemia. In the ACCORD trial, the incidence of hypoglycemia requiring assistance was over three times higher in the intensive control group. Furthermore, the intensive glycemic control resulted in a significant increase in all-cause mortality, mainly driven by a 35% increase in cardiovascular mortality compared with the standard therapy, which led to an early termination of the trial. The majority of excess deaths in the intensive treatment group of ACCORD were caused by cardiac events, the most common of which was unexpected, that is, sudden death[1].

Mechanisms of hypoglycemia-related ventricular arrhythmias: The mechanism of hypoglycemia-induced ventricular arrhythmias is multifactorial, involving the inhibition of cardiac ion channel, altered levels of electrolytes (potassium) and hormones (epinephrine and norepinephrine), and also related to the underlying diseases of the patient. First, hypoglycemia itself inhibits the rapid component of the cardiac delayed rectifier K^+ current (IKr), which is one of the main repolarizing K^+ channels in human myocytes and encoded by human ether-a-go-go-related gene (HERG)[74]. Blockade of the IKr leads to a longer action potential, then causes QT interval prolongation, which is recognized as a marker of the propensity to develop early afterdepolarizations and VT[111]. Second, the development of hypokalemia during hypoglycemia has been observed both in the basic study and clinical study[89,100]. Hypokalemia could prolong the QT interval, and promote the development of calcium overload and associated electrical instability (early and delayed

afterdepolarizations). Third, the catecholamine surge induced by hypoglycemia plays an important role in the development of ventricular arrhythmias. Plasma epinephrine and norepinephrine significantly increased during severe hypoglycemia[89,100], which may lower serum potassium[112], cause QT prolongation, calcium overload, early and delayed afterdepolarizations[113]. Fourth, the underlying diseases, such as left ventricular hypertrophy, myocardial infarction, autonomic neuropathy and diabetes, may reduce the tolerance of myocardial tissue for the further proarrhythmic action of hypoglycemia, as described in a review by Nordin[113]. Fifth, both the clinical and experimental evidence suggests that hypoglycemia can cause ischemia of myocardial tissue, which is known to be highly proarrhythmic. Libby *et al*[114] have observed that the size of myocardial infarctions in dogs with hypoglycemia was larger than those with normoglycemia. Consistently, Desouza *et al*[115] also confirmed that hypoglycemia is more likely to be associated with cardiac ischemia and symptoms than normoglycemia and hyperglycemia in humans.

Hypoglycemia and other arrhythmias: Apart from tachyarrhythmias, bradyarrhythmias induced by hypoglycemia, such as bradycardia and AVB, also have been observed in preclinical and clinical studies. In a previous study where 25 insulin-treated T2DM patients underwent 5 d of simultaneous Holter and continuous interstitial glucose monitoring, the researchers found that bradycardia was eightfold higher during nocturnal hypoglycemia compared with euglycemia. However, during the daytime, no bradycardia was observed in this study[90]. Other case reports have also noted bradycardia during hypoglycemic episodes[116,117]. Bradycardia then could cause action potential and QT interval prolongation, and increase the risk of early afterdepolarizations. According to the Reno *et al*[89], different types of AVB, from first- to third- degree, have been observed during hypoglycemia in rat models.

Bradycardia is more likely to be induced by nocturnal hypoglycemia, which may be explained by sympathetic withdrawal followed by vagal overcompensation. Chow *et al*[90] have observed an initial vagal withdrawal during hypoglycemia resulting in an increase in heart rate, but with more prolonged hypoglycemia, vagal reactivation then resulted in relative bradycardia.

GLYCEMIC VARIABILITY AND CARDIAC ARRHYTHMIAS

GV includes short-term variability and long-term variability in blood glucose[118]. Short-term GV refers to intraday or daily blood glucose fluctuation, and long-term GV refers to months or years of blood glucose fluctuation, which is supposed to predict complications of diabetes[119,120]. Currently, only a few studies have investigated the relationship between GV and arrhythmias, which mainly focused on AF and QT prolongation. Information about the studies regarding the association between the GV and cardiac arrhythmias is presented in Supplementary Table 3.

Glycemic variability and supraventricular arrhythmias

Glycemic variability and AF: Epidemiology of GV-related AF: A retrospective cohort study with a median follow-up of 6.9 years has found that higher HbA1c variability was associated with an increased risk of new-onset AF in patients with T2DM, which indicated that long-term GV has the potential to be one of the early predictors of new-onset AF[9]. By measuring the HbA1c variability score, another retrospective cohort study including 27246 subjects in Taiwan also showed that high GV was independently associated with the occurrence of new-onset AF in patients with T2DM[121]. Both the HbA1c variability score and HbA1c variability are measures of long-term GV, and these two studies have suggested the predictive value of long-term blood glucose fluctuation in the development of incident AF[9,121]. However, the effect of short-term fluctuation in blood glucose on AF has rarely been studied. More research is needed to investigate the relationship between short-term GV and AF.

The relationship between GV and AF has also been observed in patients with underlying cardiovascular diseases and in those undergoing cardiac surgery. Xia *et al*[122] have conducted an observational study enrolling 864 patients with acute coronary syndrome, and found that higher GV during hospitalization was associated with a higher incidence of AF, compared to the lower GV group. Furthermore, a retrospective study on patients undergoing CABG showed that every 10% increased in GV in the first 24 h after surgery, the risk of postoperative AF (POAF) increased by 16%[123]. Another Singapore study also showed that wider perioperative glycemic fluctuations in patients undergoing CABG represented an independent risk factor of POAF[124].

In general, studies on the association between GV and AF, especially in healthy people and patients with T1DM, are relatively deficient. Different measures of blood glucose fluctuation have their own advantages. More research is needed to explore the relationship between GV and AF in different populations and evaluate the effect of different measures of GV on this relationship.

Mechanisms of GV-related AF: Cardiac fibrosis: In a prior study evaluating the association between glucose fluctuations and AF in diabetic rats, Saito *et al*[125] have induced the glucose fluctuations by fasting for 24 h and additional regular insulin injections, and observed that the degree of myocardial fibrosis in DM rats with glucose fluctuations was significantly increased compared with the uncontrolled or controlled DM group. Moreover, the interatrial conduction time in glucose fluctuation group was significantly longer than the other two groups, and the rate of AF induction was also the highest, which suggested that higher GV increased the incidence of AF by promoting cardiac fibrosis. In another similar study, where the glycemic fluctuations was induced by subcutaneous injection of insulin and intraperitoneal injection of glucose, the researchers found that glycemic fluctuations worsened myocardial fibrosis in diabetic rats[126].

Oxidative stress: A prior basic study has found that the level of ROS significantly increased in the myocardium of DM rats with glucose fluctuations, compared to the controls. Meanwhile, this study also suggested that elevated ROS levels caused by upregulation of thioredoxin-interacting protein (Txnip) may be a mechanism of glucose fluctuations-induced

fibrosis[125]. In another study, Ying *et al*[126] have demonstrated that blood glucose variability can aggravate heart tissue fibrosis, possibly involving oxidative stress by inhibiting protein kinase B (AKT) signaling path.

Consistent with these basic experiments, clinical studies also confirmed the role of oxidative stress in the development of GV-related AF. Chang and colleagues evaluated the relationship between GV and oxidative stress markers among 34 T2DM patients, and found that both the short-term GV measure (mean amplitude of glycemic excursions, MAGE) and long-term GV measure (standard deviation of HbA1c) were positively associated with the level of plasma 8-iso-prostaglandin F2α (8-iso-PGF2α), a marker of oxidative stress[127]. In another case-control study, a more accurate measurement of urinary 8-iso-PGF2α excretion was used to represent the oxidative stress level *in vivo*, which also confirmed the previous findings[128]. Similarly, another cross-sectional study has included 68 patients with T2DM, where the plasma oxidant capacity was measured with the diacron-reactive oxygen metabolites test, the researchers found that higher levels of daily and day-to-day GV was associated with an increased level of oxidative stress[129]. Oxidative stress plays a substantial role in the cardiac electrical and structural remodeling, increasing the susceptibility to AF, which might represent an important mechanism of GV-related AF.

Autonomic neuropathy: Abnormal autonomic activity is generally recognized to play an important role in the development and maintenance of AF[130]. A study has showed a significant correlation between MAGE and cardiac autonomic neuropathy in patients with newly diagnosed T2DM[131]. Other cross-sectional studies have also shown that GV in patients with T2DM is negatively correlated with baroreflex sensitivity and heart rate variability parameters[132, 133]. These studies suggested that GV-mediated abnormal autonomic activity might contribute to the development of AF.

Glycemic variability and other supraventricular arrhythmias: Zhang *et al*[134] evaluated the association between GV and arrhythmia in middle-aged and elderly T2DM patients (n = 107), and found that compared with the middle-aged group, elderly patients have greater GV and are more likely to develop atrial premature beat, couplets of atrial premature beat and atrial tachycardia.

Glycemic variability and ventricular arrhythmias

Epidemiology of GV-related ventricular arrhythmias: Studies reporting the asso-ciation between GV and ventricular arrhythmias are sparse. Zhang *et al*[134] they have observed that elderly patients with greater GV are more prone to arrhythmias, including ventricular premature beats. A retrospective study on patients with insulin-treated T2DM has showed that HbA1c variability significantly predicts the development of SCD[5]. As for QT interval, in a previous cross-sectional study that included 2904 T2DM patients, the researchers have found that increased long-term variability of postprandial plasma glucose is a strong independent risk factor for prolonged QTc interval[135]. In general, studies focusing on the relationship between GV and ventricular arrhythmias are scarce and mainly focus on patients with T2DM. Thus, future studies are needed to explore the association between GV and ventricular arrhythmias among different populations.

Mechanisms of GV-related ventricular arrhythmias: Overall, the effects of GV on ventricular arrhythmias are similar to those of AF, to some extent. Firstly, higher GV exacerbates left ventricular fibrosis in diabetic rats, which might increase the predisposition to ventricular arrhythmias[125]. Secondly, oxidative stress plays an important role in the GV-related ventricular fibrosis[126]. Oxidative stress associated with GV observed in clinical studies may also potentially cause ventricular remodeling[127-129]. Thirdly, cardiac autonomic neuropathy induced by higher GV may also contribute to the development of ventricular arrhythmias[136].

LIMITATIONS

In this study, although we have applied a comprehensive search strategy using relevant keywords regarding the associations between three dysglycemic states with cardiac arrhythmias, it is possible that we missed some data, because we did not search the grey literature or the google scholar, and the search was limited to papers published in English. Besides, some of the included studies were conducted with specific target populations that may not be generalizable to all populations and, thus, our results should be extrapolated with caution. In addition, the definitions of hyperglycemia, hypoglycemia, and GV are consistent in most of the included studies, whereas some minor difference existed in a few studies.

FUTURE DIRECTIONS

Chronic hyperglycemia and diabetes have been associated with a higher risk of AF and considered as important risk factors of AF. Therefore, study exploring novel predictors for new-onset AF among patients with diabetes is of the utmost importance. Besides, evidence regarding the associations between hyperglycemia and supraventricular arrhythmias are mainly focused on AF. Only a few studies have reported the association between hyperglycemia and other supraventricular arrhythmias, such as sinus tachycardia and atrial flutter[2,13]. More studies are needed to further evaluate the associations between hyperglycemia and other arrhythmias.

Although both case reports and clinical studies have suggested an association between hypoglycemia and increased risk of AF, little is known about the underlying mechanisms, which highlights the need for future basic studies to elucidate the mechanisms of hypoglycemia-induced AF. In addition, a causal relationship between hypoglycemia and

fatal arrhythmias is usually difficult to demonstrate in clinical practice, since long-term simultaneous monitoring of cardiac rhythm and blood glucose levels is seldom undertaken[85], which might result in underestimation of the incidence of hypoglycemia-induced fatal arrhythmias. Therefore, long-term, large-scale, prospective studies are needed to elucidate the real incidence of various types of arrhythmias during the episodes of hypoglycemia. Besides, susceptibility to cardiac arrhythmias during hypoglycemia seems to be confined to a few individuals[137], thus identifying individuals who are at increased risk of arrhythmias during hypoglycemia is important and possesses great clinical significance.

CONCLUSION

Hyperglycemia, hypoglycemia, and GV has been associated with various types of arrhythmias, through different mechanisms. It is important to establish a customized glycemic control strategy that takes individual characteristics into account, such as age and underlying diseases, in order to maintain a healthy glycemic homoeostasis and minimize the risk of cardiac arrhythmias.

FOOTNOTES

Author contributions: Sun DK and Zhang N wrote the paper and collected the data, had equal contribution to this paper; Sun DK, Zhang N, Liu Y, Qiu JC, Tse G, and Li GP have contributed to the conception, design, and review of the manuscript; and all authors have read and approve the final manuscript; Roever L and Liu T had equal contribution to this paper.

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REVIEW

Gestational diabetes mellitus and COVID-19: The epidemic during the pandemic

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Abstract

During the global coronavirus disease 2019 (COVID-19) pandemic, people worldwide have experienced an unprecedented rise in psychological distress and anxiety. In addition to this challenging situation, the prevalence of diabetes mellitus (DM), a hidden epidemic, has been steadily increasing in recent years. Lower-middle-income countries have faced significant barriers in providing accessible prenatal care and promoting a healthy diet for pregnant women, and the pandemic has made these challenges even more difficult to overcome. Pregnant women are at a higher risk of developing complications such as hypertension, preeclampsia, and gestational diabetes, all of which can have adverse implications for both maternal and fetal health. The occurrence of gestational diabetes has been on the rise, and it is possible that the pandemic has worsened its prevalence. Although data is limited, studies conducted in Italy and Canada suggest that the pandemic has had an impact on gestational diabetes rates, especially among women in their first trimester of pregnancy. The significant disruptions to daily routines caused by the pandemic, such as limited exercise options, indicate a possible link between COVID-19 and an increased likelihood of experiencing higher levels of weight gain during pregnancy. Notably, individuals in the United States with singleton pregnancies are at a significantly higher risk of excessive gestational weight gain, making this association particularly important to consider. Although comprehensive data is currently lacking, it is important for

clinical researchers to explore the possibility of establishing correlations between the stress experienced during the pandemic, its consequences such as gestational gain weight, and the increasing incidence of gestational DM. This knowledge would contribute to better preventive measures and support for pregnant individuals during challenging times.

Key Words: Pregnancy; Gestational diabetes; Stress; Social determinants; Pandemic; COVID-19; Diabetes type 1; Diabetes type 2; Insulin; Diabetes mellitus treatment

Core Tip: The coronavirus disease 2019 pandemic has caused a rise in psychological distress on a global scale, overlapping with an increase in cases of diabetes mellitus. Women, in particular those residing in lower-middle-income countries, stumble upon difficulties for a decent prenatal care and maintaining nutritious diets. Pregnant women who have a higher susceptibility to gestational diabetes may face long-term health consequences for both them and their unborn child. Recent studies suggest a potential link between the pandemic and elevated rates of gestational diabetes. Additional research is necessary to establish a conclusive correlation between the impact of pandemic-induced stress, gestational gain weight, and the outcomes of pregnancies affected by gestational diabetes.

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INTRODUCTION

When the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a pandemic on March 11, 2020, the global count surpassed 118000 confirmed cases across 114 countries, resulting in 4291 reported deaths[1]. This rapid escalation of cases caught many by surprise, as the virus displayed high transmissibility and lacked effective control measures[2]. As a result, societal norms underwent a paradigm shift, compelling individuals to isolate themselves indoors to mitigate the viral spread and prevent transmission to their loved ones. Adapting to this new reality presented significant challenges, particularly for those balancing remote work with caregiving responsibilities for their families, including children, elderly relatives, and individuals with special needs. Unfortunately, the mounting responsibilities and pressures had a detrimental impact on mental well-being. During the initial year of the COVID-19 pandemic, there was a substantial 25% increase in global anxiety and depression rates[3].

During the pandemic, the focus on the overwhelming stress and challenges has inadvertently overshadowed the ongoing threat of diabetes mellitus (DM). In 2019, diabetes contributed to a staggering 1.5 million deaths globally, with nearly half of those occurring before the age of 70. Alarmingly, lower-middle-income countries witnessed a concerning 13% increase in mortality rates related to diabetes. This highlights the urgent need for attention and action to combat this pervasive disease, especially in the context of the current global crisis[4].

Accessing prenatal care is crucial for ensuring a healthy pregnancy, but this can pose challenges in lower-middle-income countries. Additionally, the pandemic has added stress factors for women, such as limited access to a healthy diet and opportunities for regular exercise. A review conducted by Park *et al*[5] highlighted the adverse effects of COVID-19 on physical activity, with varying impacts observed among different sub-populations.

Furthermore, an internet-based cross-sectional survey demonstrated that Spanish pregnant women had reduced access to exercise, negatively affecting their well-being during the pandemic[6]. Consequently, the risk of developing complications such as hypertension, preeclampsia, and gestational DM (GDM) is elevated. If a woman has pre-existing diabetes (type 1 or type 2) prior to pregnancy, it further amplifies the likelihood of complications, including premature delivery, frequently associated with polyhydramnios[7]. Pregnant women diagnosed with gestational diabetes often encounter challenges in the diagnostic process, as it typically relies on prenatal screening rather than solely relying on signs and symptoms. While gestational diabetes is a frequent pregnancy complication, it can have detrimental effects on the health of both the mother and the newborn, potentially impacting the child's long-term health outcomes[8]. Hence, it is of utmost importance for mothers to receive ongoing postpartum follow-up, as demonstrated by a 23-year cohort study conducted by Auvinen *et al*[9]. The study unveiled a consistent association between gestational diabetes and the subsequent onset of type 2 DM, emphasizing the need for lifelong monitoring and care.

According to the National Vital Statistics Reports of the United States, the overall incidence rate of GDM in 2020 was 7.8 per 100 births, representing a 30% increase from 2016[10]. However, it is important to note that this report was based solely on birth certificate data, which may have resulted in underreporting, potentially leading to an even higher prevalence of GDM than reported. Considering the circumstances where women are unable to attend prenatal checkups due to various limitations such as transportation issues, isolation measures, heightened stress levels, anxiety, or simply the fear of going outdoors during the pandemic, the consequences can be significant for their overall health, particularly

when they are expecting a baby and lack access to prenatal care. Although limited data is available to support this, a case-controlled study conducted by Zanardo *et al*[11] focused on women who gave birth in the heavily impacted Northeast region of Italy, concluding that the COVID-19 pandemic had a negative impact on the prevalence of GDM in 2020 compared to 2019. This impact was especially notable among pregnant women during the initial stage of their pregnancy. Likewise, research conducted in Quebec, which was the focal point of the pandemic in Canada, indicates that a sudden alteration in lifestyle can have a significant effect on the prevalence of gestational diabetes within a population. The study observed elevated rates of GDM during the first and second waves of the pandemic in comparison to the period before the pandemic[12].

Understanding GDM

DM is a chronic metabolic disorder that affects more than 400 million people worldwide, with a rising prevalence in low- and middle-income countries[13]. During pregnancy, diabetes can lead to various complications for both the mother and the baby, including an increased risk of pre-eclampsia, preterm birth, macrosomia, and stillbirth (Figure 1).

GDM is a variant of diabetes that manifests during pregnancy, impacting approximately 10% of pregnancies globally. It is linked to a higher probability of unfavorable pregnancy outcomes and an elevated susceptibility to developing type 2 diabetes in the future[14,15] (Table 1).

Several risk factors have been identified that increase the likelihood of developing GDM. Nonmodifiable risk factors include age, with women over 25 years old having an increased risk, and a family history of diabetes[16]. Ethnicity is also a significant risk factor, with women of Hispanic[17], other than white European origin[18], Asian[19], and indigenous descent[20] being more likely to develop GDM. Other modifiable risk factors include being overweight or obese before pregnancy[21], excessive weight gain during pregnancy[22,23], and a sedentary lifestyle. Women with polycystic ovary syndrome[24] or a history of GDM in a previous pregnancy are also at higher risk. Early identification of these risk factors and appropriate management can help prevent or mitigate the effects of GDM (Table 2).

A study carried out by Teh *et al*[25] assessed the accuracy of various guidelines in diagnosing GDM. The study identified a history of previous GDM, maternal age of 40 years or older, and a body mass index (BMI) of 35 kg/m^2 or higher as the most influential independent risk factors for GDM. The Health and Care Excellence, American Diabetes Association (ADA), and Australasian Diabetes in Pregnancy Society (ADIPS) guidelines exhibited various levels of sensitivity and specificity in diagnosing GDM, with the ADA demonstrating the highest sensitivity and the ADIPS showing the highest specificity.

Furthermore, a systematic review conducted by Kim *et al*[26] encompassing 13 studies examined the rates of GDM recurrence following the initial pregnancy. Recurrence rates varied from 30% to 84%, with higher rates observed among minority populations in comparison to non-Hispanic white populations. The studies did not identify consistent risk factors for GDM recurrence. Factors such as preexisting diabetes in subsequent pregnancies, socioeconomic status, rates of postpartum diabetes screening, and interpregnancy intervals were not consistently reported in the studies.

Although the GDM recurrence rate is high, with a median rate of 47.6% observed in a study conducted at the Mayo Clinic, strategies to prevent GDM recurrence are not well established. It is imperative to do further research to evaluate the effect of interventions before, during, and after pregnancy[27].

There are two common approaches for screening GDM, including universal screening and selective screening. Universal screening is applied without restriction to high-risk pregnant women to identify all potential GDM cases. On the other hand, selective screening is based on certain risk factors and might miss over 40% of GDM cases. However, selective screening may be more cost-effective by considering that screening with glucose measurements may be less beneficial to low-risk women[28].

The diagnostic criteria for gestational diabetes have undergone revisions over time. The initial guideline was established in 1964 by O'Sullivan and Mahan[29], which was later modified by the National Diabetes Data Group in 1979 [30] and Carpenter in 1982[31]. These frequent updates of the criteria are necessary to effectively identify women with gestational diabetes and assess their risk of perinatal complications (Figure 2).

Clinicians currently utilize the diagnostic criteria provided by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) in 2010 as the most recent standard[32]. The ADA[33] and the WHO[34] updated their guidelines in 2013 and 2018 to have the same criteria as the IADPSG. The ADA suggests using the IADPSG to improve pregnancy outcomes and offspring birth defects, rather than the prediction of subsequent maternal diabetes, based on initial data from randomized clinical trials[35].

Although they primarily support the one-step diagnosis, the American College of Obstetrics and Gynecology prefers the two-step Carpenter-Coustan screening, especially in patients with known risk factors[36]. Subsequently, a randomized trial conducted by Landon *et al*[37] demonstrated that even the management of mild cases of GDM [characterized by abnormal oral glucose tolerance test (OGTT) results surpassing established thresholds: 1-h, 180 mg/dL (10.0 mmol/L); 2-h, 155 mg/dL (8.6 mmol/L); and 3-h, 140 mg/dL (7.8 mmol/L), along with a fasting glucose level below 95 mg/dL (5.3 mmol/L)], has the potential to reduce the risks associated with fetal overgrowth, shoulder dystocia, the necessity for cesarean section, and hypertensive disorders[37,38].

Due to the lack of consensus in monitoring recommendations for women with gestational diabetes in different regions, and the predominant reliance on laboratory criteria rather than clinical symptoms for diagnosis, prompt and accurate identification of the condition during the pandemic became challenging. Many women received telemedicine consultations as an urgent safety measure to mitigate the spread of the virus[39]. However, some of these women did not exhibit clinical symptoms, highlighting the insufficiency of telemedicine technology in diagnosing and managing gestational diabetes compared to standard care. Further research is needed to explore this area and determine its effectiveness[40].

Table 1 Variations between type 2 diabetes mellitus and gestational diabetes mellitus

	Type 2 diabetes mellitus	Gestational diabetes mellitus
Occurrence	Generally, develops after age 40, but can occur at any age	Develops during pregnancy, typically after the 20th wk of gestation
Prevalence	Affects approximately 90% of people with diabetes	Affects approximately 2%-10% of pregnancies
Risk factors	Family history, obesity, physical inactivity, high blood pressure, and ethnicity	Family history, previous history of gestational diabetes, obesity, older maternal age, and certain ethnicities
Symptoms	Fatigue, increased thirst, frequent urination, blurred vision, slow healing wounds	Often asymptomatic, but may cause increased thirst, frequent urination, and increased hunger
Diagnosis	Blood tests measuring fasting blood glucose and hemoglobin A1C levels	Oral glucose tolerance test usually performed between 24-28 wk of gestation
Treatment	Lifestyle changes, medication, and/or insulin therapy	Lifestyle changes, close monitoring of blood glucose levels, and medication/insulin therapy if necessary
Potential complications	Cardiovascular disease, neuropathy, retinopathy, kidney disease, and foot ulcers	Preeclampsia, premature delivery, macrosomia, and increased risk of developing type 2 diabetes later in life

The table summarizes key differences between type 2 diabetes mellitus and gestational diabetes mellitus, including occurrence, prevalence, risk factors, symptoms, diagnosis, treatment, and potential complications.

Table 2 Risk factors for gestational diabetes mellitus

Risk factors for GDM	Description
Increasing maternal age	Increases in gestational diabetes were seen in each maternal age group, and rates rose steadily with maternal age; in 2021, the rate for mothers aged ≥ 40 yr (15.6%) was nearly six times as high as the rate for mothers aged < 20 yr (2.7%)[16,25]
Past medical history of GDM in a previous pregnancy OR family history of type 2 DM	The strongest risk factor for gestational diabetes mellitus, with reported recurrence rates of up to 84%[26]
Race/ethnicities at increased risk for development of GDM	Women of Hispanic[17], other than white European origin[18], Asian[19], and indigenous descent[17-20]
Prevalence of GDM by ethnicity	The highest prevalence using the 2000 ADA diagnostic criteria among Filipinas (10.9%) and Asians (10.2%), followed by Hispanics (6.8%), non-Hispanic Whites (4.5%), and Black Americans (4.4%)[28]

The table presents risk factors associated with gestational diabetes mellitus (GDM) and the prevalence of GDM by ethnicity. Factors include increasing maternal age, past history of GDM, family history of type 2 diabetes, and specific ethnicities at higher risk for GDM development. These factors aid in identifying individuals at risk for GDM. GDM: Gestational diabetes mellitus; ADA: American Diabetes Association; DM: Diabetes mellitus; OR: Operating room.

EPIDEMIOLOGY OF GDM DURING THE PANDEMIC

The COVID-19 pandemic had a substantial impact on the general population[41], but it posed additional challenges for pregnant women, exacerbating risk factors for GDM. These risk factors include heightened psychological distress, such as increased levels of depression and anxiety resulting from fear of the virus and other concerns, which can negatively impact their mental health during the perinatal period[42,43]. Additionally, the implementation of quarantine measures as a response to the pandemic led to prolonged periods of isolation at home[44,45], limiting opportunities for exercise and promoting sedentary lifestyles among pregnant women[46].

The prevalence of GDM increased at 38.9% during the COVID-19 pandemic, in comparison to pre-pandemic numbers - as demonstrated in a retrospective study by Mirsky *et al*[47] from data retrieved from deliveries at a single academic institution. In this study, 12.5% of patients were diagnosed with GDM during COVID-19, compared to 9.0% pre-COVID-19 ($P < 0.001$). But when this data was stratified by pre-pregnancy weight, no significant weight gain was shown, even among those with pre-pregnancy obesity. It was suggested then that maternal stress could have been the underlying component of gestational hyperglycemia[48]. The National Vital Statistics Reports showed data on trends for GDM from women giving birth in the United States from 2016 to 2020. Surprisingly in 2020, the rate of GDM was 7.8 per 100 births, marking a significant 30% rise compared to 2016[49].

The largest increase was seen in the annual percentage change from 2019 to 2020 (13%), surpassing the average annual percent change from 2016 to 2019 (5%). Additionally, in 2020, variations in the rate of GDM were noted based on maternal race and Hispanic origin. Non-Hispanic Asian women had the highest rate (14.9%), while non-Hispanic Black women had the lowest rate (6.5%)[49,50] (Figure 3 and Table 3). Despite a decline in the overall number of births from 2016 to 2020, the prevalence and rate of GDM indicate a resting trend.

Table 3 Gestational diabetes mellitus trends and statistics from 2016 to 2020

Year	Total births	GDM cases	GDM rate (%)	Confidence interval	Not stated cases
2016	3945875	234847	6.0	5.9-6.0	3781
2017	3855500	244716	6.4	6.3-6.4	3711
2018	3791712	252522	6.7	6.6-6.7	2882
2019	3747540	258676	6.9	6.9-6.9	3284
2020	3613647	281789	7.8	7.8-7.8	4063
Change, %	-8.6	+19.8	+30.0	N/A	+7.5

GDM: Gestational diabetes mellitus; N/A: Not applicable.

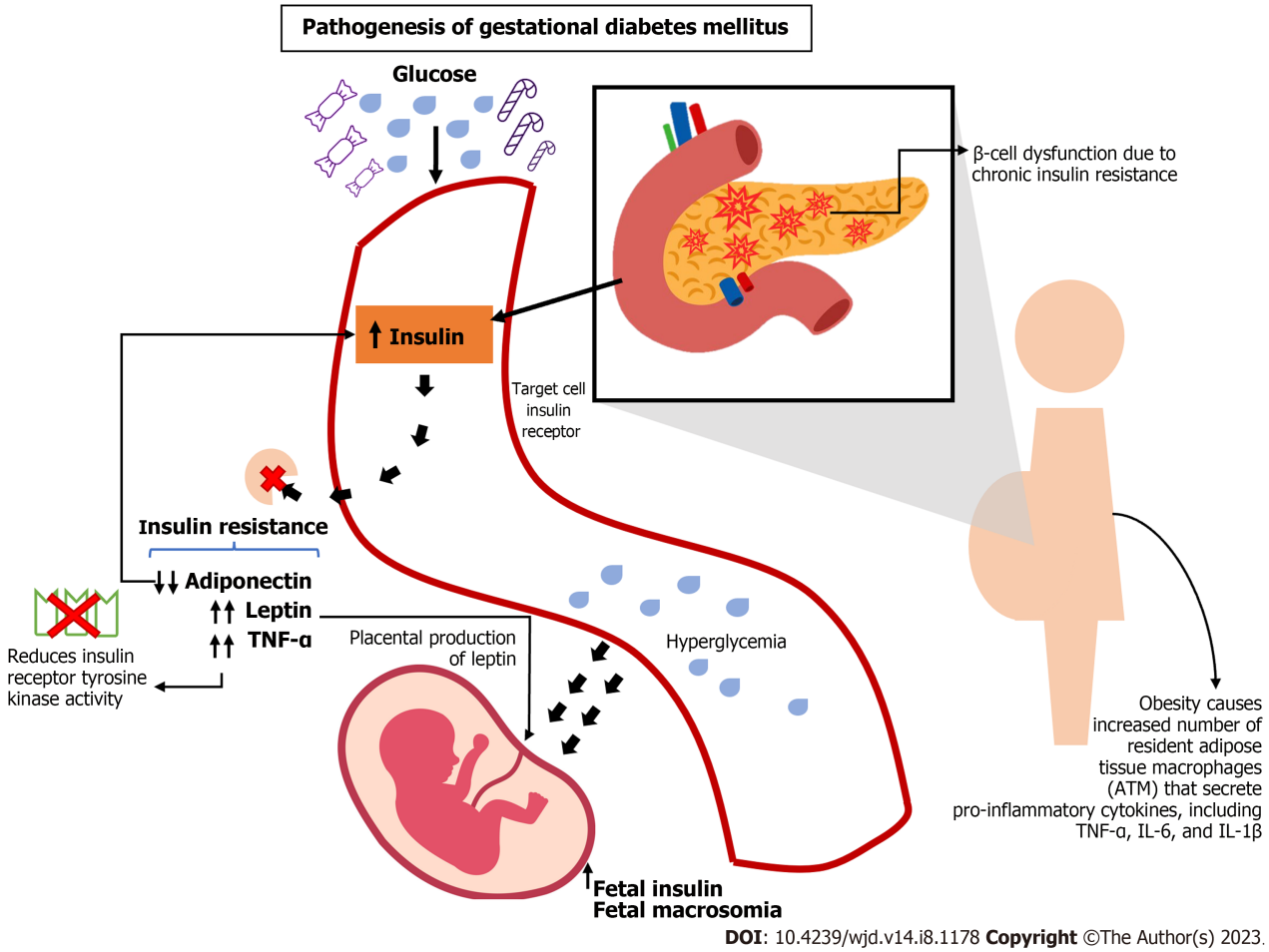


Figure 1 Pathogenesis of gestational diabetes mellitus. This image provides an overview of the underlying mechanisms and processes involved in the development of gestational diabetes mellitus[109]. TNF: Tumor necrosis factor; IL: Interleukin; ATM: Adipose tissue macrophages.

Taking a global perspective, a comprehensive report conducted in 2021 by Wang *et al*[51] examined the prevalence of GDM by analyzing data from 57 studies published in PubMed. Overall, the worldwide prevalence of GDM was found to be 14.9% [95% confidence interval (CI)]. The Middle East and North Africa exhibited the highest standardized prevalence at 27.6% (95%CI: 26.9%-28.4%), followed by South-East Asia with a prevalence of 20.8% (95%CI: 20.2%-21.4%).

IMPACT OF PANDEMIC-RELATED FACTORS ON GDM RATES

Gestational weight gain during COVID-19 pandemic

Due to the significant lifestyle changes during the pandemic, including reduced exercise opportunities, there is evidence to suggest that COVID-19 was linked to increased gestational weight gain (GWG) and a higher risk of excessive GWG

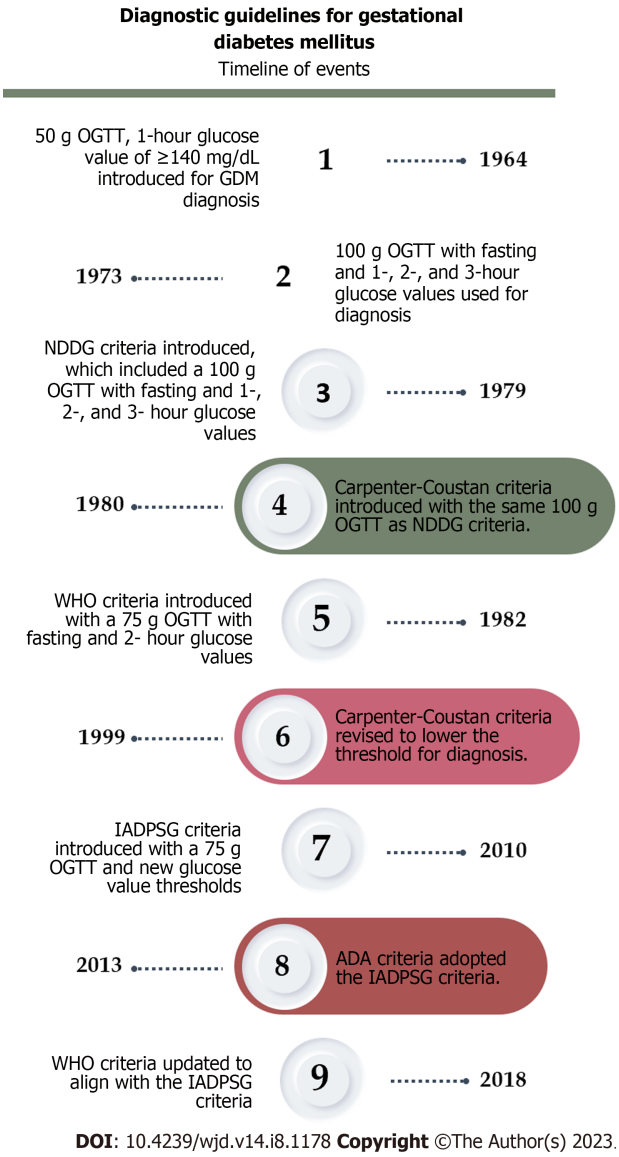


Figure 2 Timeline of events of diagnostic guidelines for gestational diabetes mellitus. The diagnostic criteria for gestational diabetes have evolved over time, with changes in fasting and post-challenge glucose thresholds. The criteria have become more standardized and sensitive in recent years, reflecting advancements in understanding the risks associated with elevated glucose levels during pregnancy. OGTT: Oral glucose tolerance test; GDM: Gestational diabetes mellitus; NDDG: National Diabetes Data Group; WHO: World Health Organization; IADPSG: International Association of the Diabetes and Pregnancy Study Groups; ADA: American Diabetes Association.

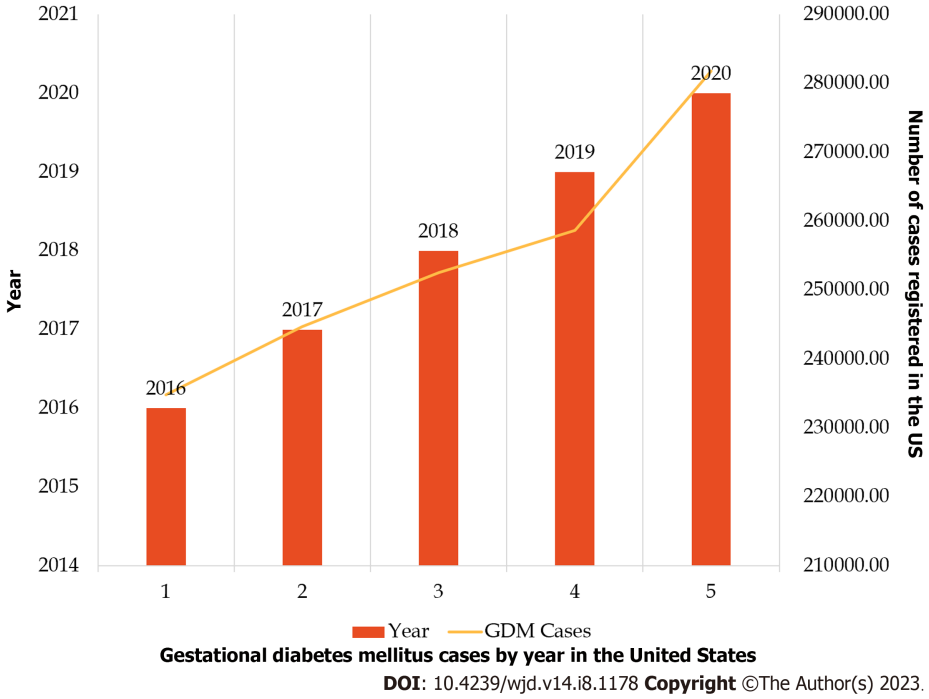
among individuals with singleton pregnancies in the United States.

In a cross-sectional study conducted by Cao *et al*[52], data from United States live births between January 1, 2018 to December 31, 2020 showed an increase in GWG by 0.06 kg (after adjusting for covariates and excluding pre-pandemic trends). This increase was particularly evident among pregnant women under the age of 25, non-Hispanic Black individuals, unmarried individuals, and those with pre-pregnancy obesity.

In Italy, a study conducted during the COVID-19 lockdown revealed that pregnant women had higher BMI and experienced increased weight gain during pregnancy. The incidence of GDM also showed a significant increase, with a rate of 9.3% during the pandemic lockdown period (from March 10, 2020 to December 04, 2020), compared to 3.4% before the pandemic (June 11, 2019 to March 09, 2020) ($P \leq 0.0001$)[53].

Also, a study made by Kołomańska-Bogucka *et al*[54], where the level of physical activity in the last trimester was evaluated, as well as the risk of postnatal depression and health habits in general, demonstrated that the COVID-19 pandemic lockdown negatively affected women even during the post-partum period, making these women be in an increased risk of developing GDM in their subsequent pregnancy. Nevertheless, some authors suggest that maternal stress is a potential factor for developing GDM[48] as some analyses of data have shown no significant weight gain in patients with gestational diabetes, even among individuals with obesity.

Conducting further investigations into the effects of lockdown measures on pregnant women, including changes in physical activity, dietary patterns, and their potential influence on maternal and neonatal outcomes, is imperative for advancing our understanding in this area. This research will contribute to a more comprehensive body of knowledge and inform evidence-based practices for optimal prenatal care.



DOI: 10.4239/wjd.v14.i8.1178

Figure 3 Linear trend of gestational diabetes mellitus trends and statistics from 2016 to 2020[49]. GDM: Gestational diabetes mellitus.

Lockdown blues: Escalated maternal stress and sedentary habits

The COVID-19 pandemic negatively impacted GDM prevalence, especially in pregnant women during their 1st trimester of gestation. An analysis made in Northeast Italy showed a 34% increase in the mean number of GDM diagnoses per month (logistic regression analysis). Hence, it was possible that exposure to stress-related factors due to the COVID-19 lockdown may have caused chronic inflammation in these pregnant women, which resulted in a higher risk of GDM[55].

It is also important to mention that maternal stress could have been exacerbated due to a lack of physical activity and sedentary behavior. Based on a survey conducted in the United Kingdom involving 553 eligible women, it was found that 79% of the participants reported an increase in sedentary behavior.

The primary reason for this decline in physical activity was a fear of leaving their homes[56]. As clinicians, it is important to encourage pregnant women to access online workout classes as an alternative to the gym or in-person classes[57]. This could potentially help them remain active and decrease their sedentary behavior. Although this could be a potential challenge, since not everyone has access to smart apps or online virtual classes, it is important to assess the patients' availability and offer them affordable options.

CLINICAL CHALLENGES

Current diagnostic criteria for GDM

GDM is a prevalent complication during pregnancy, and its misdiagnosis or inadequate control can result in substantial rates of adverse outcomes for both the neonate and the mother. The screening approaches utilized for GDM play a crucial role in its management and the prevention of future complications.

According to most health organizations, the initial prenatal visit is regarded as the optimal opportunity for screening GDM. The primary objectives of early screening are to detect patients with existing diabetes and to diagnose individuals at either low or elevated risk for GDM. The commonly employed methods for this diagnosis include measuring fasting plasma glucose (FPG), random plasma glucose (RPG), and glycosylated hemoglobin A1C (HbA1c)[58].

As per the guidelines set forth by the US Preventive Services Task Force, it is recommended to screen asymptomatic patients for GDM at 24 wk of gestational age[59]. As previously mentioned, the ADA provides two defined criteria for the diagnosis of gestational diabetes. The first approach, known as the "one-step" method, involves a 75-gram OGTT conducted between 24-28 wk of gestation, following an overnight fast of at least 8 h. The diagnosis of gestational diabetes is confirmed if any of the following values are observed: Fasting glucose: 92 mg/dL; 1-h glucose: 180 mg/dL; and 2-h glucose: 153 mg/dL.

The second approach, known as the "two-step" method[33,34], consists of a two-stage process. First, a 50-gram glucose load test (GLT) is performed (non-fasting) with plasma glucose measurement 1 h later, between 24-28 wk of gestation for women without a previous diabetes diagnosis.

If the plasma glucose level measured 1 h after the load is equal to or greater than 130, 135, or 140 mg/dL, the patient proceeds to the second stage: A 100-gram OGTT conducted after an overnight fast. In this step, the diagnosis of

gestational diabetes is confirmed if at least two of the following criteria are met or exceeded among the four plasma glucose levels measured: Fasting glucose: 95 mg/dL; 1-h glucose: 180 mg/dL; 2-h glucose: 155 mg/dL; and 3-h glucose: 140 mg/dL.

The ACOG[36] proposes a two-step approach for diagnosing gestational diabetes using an universal screening with a 50-g GLT followed by a target diagnostic test with 100-g OGTT. The diagnosis criteria for GDM based on these tests are as follows: GLT criteria: (1) GLT result > 130 mg/dL; (2) GLT result > 135 mg/dL; and (3) GLT result > 140 mg/dL; OGTT criteria: (1) Fasting glucose > 95 mg/dL; (2) 1-h glucose > 180 mg/dL; (3) 2-h glucose > 155 mg/dL; and (4) 3-h glucose > 140 mg/dL.

However, the WHO supports the use of the one-step approach using a 75-gram OGTT, similar to the recommendations of the ADA and the IADPSG. Diagnosis is made if the following thresholds are met or exceeded: Fasting glucose levels of ≥ 92-125 mg/dL, 1-h glucose levels of ≥ 180 mg/dL, and 2-h glucose levels of ≥ 153-199 mg/dL[60].

Consequently, there is a lack of consensus regarding the optimal approach for diagnosing GDM, as both the "one-step" and "two-step" methods have their advantages and limitations. The diagnosis of GDM presented significant challenges worldwide during the pandemic, requiring adaptations to screening tests in order to comply with social distancing recommendations and minimize the exposure of pregnant women to COVID-19[61].

The pandemic hindered routine prenatal care by disrupting the traditional face-to-face communication and reducing the access to laboratory testing[62]. In addition, women with diabetes may also be exposed to COVID-19 more often due to intensive monitoring. This includes additional education sessions, glucose monitoring, and fetal ultrasounds, all of which take place in healthcare settings where COVID-19 is more likely to be transmitted[63].

Although pregnant women are not more likely to contract severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, in comparison to the general population, they have been observed to experience a more severe course of the disease. Additionally, adverse effects on newborns have been reported. As a result, the classification of pregnant women as a high-risk group has led to temporary modifications in screening tests to minimize their extended hospital stays[64].

The completion of routine OGTTs has become challenging for healthcare providers due to factors such as self-isolation, limited public transport, social distancing measures, and specific laboratory requirements. The ability to care for a large number of pregnant women with mild hyperglycemia has been reduced due to understaffing in healthcare facilities caused by isolation, illness, or relocation[65].

During the pandemic, certain countries chose to adapt the algorithm used for diagnosing GDM. For instance, Canada adjusted their clinical guidelines with the aim of minimizing the amount of time that pregnant women spend in clinics, thus reducing their risk of prolonged exposure. They employed a non-fasting glucose screening approach, using criteria such as HbA1c ≥ 5.7% (39 mmol/mol) and/or random venous plasma glucose levels ≥ 11.1 mmol/L. As a result, they decided to avoid conducting OGTTs, reducing the frequency of GDM diagnosis to 1.7% according to Mcintyre *et al*[66].

In contrast, Australia and New Zealand revised their guidelines in 2020. The updated criteria for diagnosis included an HbA1c level of ≥ 5.9% or a fasting blood glucose level of ≥ 5.1 mmol/L. Nevertheless, the findings of a retrospective study by Zhu *et al*[67] indicated that the screening test performance for GDM, using the mentioned criteria, was suboptimal. Specifically, the study found that 25.3% of cases either remained undiagnosed or did not receive appropriate treatment.

When evaluating the diagnosis of GDM, it is important to note that the available evidence supporting the use of RPG, HbA1c, and FPG assessments is relatively limited compared to the gold standard OGTT. However, it is worth highlighting that RPG has shown promising outcomes as a predictive tool for GDM diagnosis during the first trimester. This suggests its potential usefulness in identifying women at risk of developing GDM later in pregnancy[68].

In various study cohorts, the measurement of HbA1c during the first trimester has demonstrated its potential in identifying patients at high risk of developing GDM and other adverse pregnancy outcomes. These studies have utilized HbA1c thresholds ranging from 39-41 mmol/mol. Specifically, pregnant individuals with HbA1c levels equal to or exceeding 39 mmol/mol (5.7%) in the first trimester have been found to have a significantly higher risk, approximately five times greater, of developing GDM compared to those below this threshold. While there may be clinical value in identifying such high-risk pregnancies, it is important to acknowledge that the routine use of HbA1c as a predictor of GDM is not widely supported due to its limited specificity.

There is considerable overlap in the distribution of HbA1c levels during the first trimester between pregnancies with gestational diabetes and those without[69]. This suggests that HbA1c has limited usefulness in pregnancy, mainly due to the increased turnover of red blood cells. This increased turnover can result in an underestimation of glucose intolerance, particularly in women with anemia[70].

A comprehensive analysis of published guidelines in May 2020 highlighted consensus on three key aspects concerning the screening and management of GDM during the COVID-19 crisis. First, it was recommended to explore alternative screening methods, such as fasting blood glucose, HbA1c, or RPG, for GDM screening between 24-28 wk of gestation instead of the OGTT. Second, it was advised to delay postpartum screening tests for a period of 4-12 wk until the conclusion of the COVID-19 crisis or reschedule them for 6-12 mo after childbirth. Lastly, the use of telemedicine and telecare was encouraged wherever possible, helping remote medical consultations and patient monitoring[71].

The global challenge lies in the inconsistent and controversial approaches to screening and diagnosing GDM. The decision to avoid OGTTs in order to reduce the risk of SARS-CoV-2 transmission can have significant consequences for maternal-fetal complications related to GDM.

Telemedicine use during pandemic

The COVID-19 pandemic raised substantial concerns regarding pregnant women at a considerable risk of experiencing adverse outcomes for themselves, as well as their neonates and fetuses. Measures such as social distancing, lockdowns, quarantines, and reduced in-person clinic visits were implemented to mitigate the risk of infection. However, these

changes also had an impact on the management and diagnosis of GDM. As a result, further reorganization and adjustment of the healthcare system were necessary to ensure appropriate care for pregnant women during this challenging time.

The exploration of innovative digital alternatives, including telemedicine, telephone calls, internet/web-based platforms, and smartphone/mobile app-based interventions, played a crucial role in facilitating the diagnosis, management, and control of GDM. These technologies offered promising solutions to overcome the challenges derived by the pandemic and ensured effective healthcare delivery for individuals with GDM[72].

The utilization of telehealth services displayed several advantages, including mitigating the risk of COVID-19 exposure, enhancing healthcare accessibility, and reducing expenses associated with travel and parking[73]. A study conducted by Munda *et al*[74] further revealed that transitioning clinic visits to telehealth did not compromise glycemic control or lead to adverse neonatal outcomes. This highlights the efficacy of telehealth in providing obstetric care. Nevertheless, it is crucial to recognize that there are challenges associated with the implementation of telehealth.

Kozica-Olenski *et al*[75] conducted a study to examine the experiences and acceptability of utilizing telehealth for diabetes management during pregnancy. The results indicated that women encountered various challenges, including issues with internet quality, connectivity problems, and audio and video clarity, which occasionally disrupted the continuity of care.

Further challenges included the occurrence of delays in acquiring insulin prescriptions and inadequate access to nutrition and lifestyle guidance. These barriers were especially prominent among individuals who did not primarily speak English. Addressing the needs of non-English speakers or those with limited health literacy became even more complex within the realm of telehealth. These challenges were associated with an augmented administrative workload for healthcare providers[76]. Besides, more than half of the women surveyed in the study conducted by Kozica-Olenski *et al* [75] expressed a lack of confidence or comfort in self-monitoring their weight, blood pressure, or fundal height. Some participants reported not having the necessary equipment to perform these measurements effectively.

During the early phases of the pandemic, healthcare professionals encountered challenges due to uncertainties surrounding the virus and limited familiarity with telehealth practices. The transition to telehealth presented various obstacles, including increased work demands, difficulties in reaching and communicating with patients (who were often distracted or engaged in multitasking), and a decline in patients' perceived importance and responsibility during telephone consultations[77,78]. In general, women expressed satisfaction with telephone consultations as it provided them with access to quality care during the pandemic. However, a considerable majority of women clearly preferred in-person maternity care and felt that telehealth compromised the overall quality of their healthcare experience[75,79].

TREATMENT

The management of GDM encompasses both non-pharmacological and pharmacological interventions. Research indicates that the majority of women (70%-90%) can effectively control GDM through lifestyle modifications, making medical and nutritional therapy the primary approach for treatment[80]. When lifestyle modifications alone do not effectively normalize blood glucose levels, pharmacological intervention becomes necessary. Insulin continues to be the primary treatment option, but oral medications have become increasingly popular. This is attributed to factors such as the cost of insulin, discomfort associated with multiple injections, and the requirement for frequent office visits for dose adjustments [81].

The primary objective in managing GDM is to ensure appropriate fetal growth while promoting steady weight gain and maintaining stable blood glucose levels. This requires maintaining euglycemia, defined as a fasting glucose level of ≤ 90-95 mg/dL and postprandial glucose levels of ≤ 140 mg/dL at 1 h or ≤ 120 mg/dL at 2 h[82].

NON-PHARMACOLOGICAL APPROACH FOR GESTATIONAL DIABETES

Carbohydrates

Carbohydrates (CHO) are vital for providing energy to pregnant women and their developing fetus. The ADA recommends a minimum daily carbohydrate intake of 175 g to prevent the harmful effects of ketosis on the fetus. Ensuring an adequate carbohydrate supply is crucial for maintaining optimal health during pregnancy[83]. However, the selection of CHO with a low glycemic index (LGI) holds greater significance in the management of GDM, as emphasized in a meta-analysis conducted by Xu and Ye[84]. Their study revealed that a LGI diet, while maintaining the same level of carbohydrate restriction, resulted in significant reductions in FPG and 2-h postprandial glucose levels compared to a high glycemic index (HGI) diet. These findings underscore the importance of considering the glycemic index when designing dietary interventions for GDM.

Additionally, in a randomized controlled trial conducted by Moses *et al*[85], it was observed that patients following a LGI diet had a notably lower percentage of individuals requiring hypoglycemic medications compared to those on a HGI diet. Importantly, patients in the HGI group were able to avoid insulin use by transitioning them to the LGI group. These findings highlight the potential benefits of implementing a LGI diet in the management of GDM[86].

Fats

Although the primary focus of medical nutritional therapy (MNT) in GDM is to ensure adequate caloric intake for fetal

development and maintain euglycemia in the mother, research from randomized controlled trials indicates that fetal growth is primarily influenced by fatty acids rather than glucose as an independent variable[87]. According to a prospective cohort study conducted by de Lima *et al*[88], a higher consumption of *n*-3 fatty acids was associated with a decreased likelihood of having a neonate with a large gestational age (LGA). Additionally, women with a higher intake of polyunsaturated fatty acids, including both *n*-3 and *n*-6, and a higher ratio of polyunsaturated fats to saturated fats (P/S), as well as a higher ratio of hypocholesterolemic to hypercholesterolemic fatty acids (h/H), had a significantly lower probability of giving birth to a neonate with macrosomia, with a potential reduction of up to 49%. These findings emphasize the importance of considering the impact of fatty acids on fetal growth and the potential influence of dietary factors on the outcomes of GDM.

Protein

During pregnancy, there is a reduction in protein breakdown, which is essential for supporting the growth of both the mother and the fetus. Interestingly, the difference in nitrogen loss between a normal pregnancy and one affected by GDM is minimal. However, this changes when advanced GDM necessitates intensive MNT and the use of hypoglycemic medications. Consequently, despite an increase in tissue synthesis, the ADA recommends a minimum daily protein requirement of only 71 g. The relationship between protein intake and LGA remains inconclusive, although one study found a correlation between leucine and birth weight in both GDM and normal pregnancies.

In the management of GDM, increasing protein intake is beneficial, regardless of the protein source, including plant-based options, lean meats, and fish. However, individuals following a vegetarian or vegan diet should be cautious and ensure adequate protein intake by supplementing with iron and cyanocobalamin and carefully planning their meals. This precaution is crucial to prevent the risk of inadequate protein intake among individuals adhering to a vegan diet[83,89].

PHARMACOLOGICAL APPROACH FOR GESTATIONAL DIABETES

While the majority of patients diagnosed with GDM can achieve normal blood glucose levels through MNT in the first week, there is a subset of approximately 20% of women who require treatment with hypoglycemic agents. Insulin is the preferred initial therapy due to its safety for the fetus, as it does not cross the placenta. It is important to note that the United States Food and Drug Administration has not approved oral agents for the treatment of GDM, further establishing insulin as the primary choice. The American College of Obstetricians and Gynecologists recommends considering the use of metformin only in specific scenarios, such as when the patient declines insulin therapy, faces financial constraints related to insulin costs, or expresses concerns about compliance[90].

Metformin

The Society of Maternal-Fetal Medicine has raised concerns about the use of metformin in managing GDM due to its potential impact on fetal development. This is attributed to metformin's ability to suppress mitochondrial respiration, inhibit growth, and affect gluconeogenic responses. However, there is currently no definitive evidence regarding the long-term fetal prognosis associated with metformin use. A study conducted by Landi *et al*[91] found that metformin treatment was associated with a reduced risk of planned cesarean section, hypoglycemia, and large-for-gestational-age infants compared to insulin treatment. In contrast, the Metformin in Gestational Diabetes Trial conducted by Rowan *et al* [92] involved 751 women with GDM and showed comparable glycemic control among the study groups. However, it also revealed a higher risk of preterm delivery in the metformin group. These conflicting results underscore the importance of conducting long-term studies to establish the comparative effectiveness of insulin and metformin. Despite these considerations, the ADA recommends the use of metformin in cases of GDM only when patients decline insulin treatment or face challenges with insulin compliance, such as financial constraints or language barriers[83].

The initial dosage of metformin is 500 mg taken once at night for the first week, followed by an increase to 500 mg taken twice daily. The maximum recommended dose of metformin is 2500 mg/d. For extended-release metformin, the maximum dose is 2000 mg[90].

Glyburide

Glyburide functions by binding to the ATP-sensitive potassium channel complex in pancreatic beta cells, leading to an increased secretion of insulin and subsequent reduction in blood glucose levels. Several studies have indicated that glyburide has similar safety profiles to insulin in terms of neonatal outcomes, as demonstrated by Langer *et al*[93] in their randomized clinical trial. The study found comparable glycemic control between glyburide and insulin, with no significant difference in neonatal adverse events. However, it is important to note that despite these findings, other studies have reported higher rates of neonatal intensive care unit admissions for fetal hypoglycemia and a higher incidence of failure to achieve optimal glycemic control in patients treated with glyburide[94].

Insulin

Regular insulin and neutral protamine Hagedorn are commonly utilized insulin types in pregnancy, and their safety has been established through numerous human studies. Attaining optimal glycemic control is crucial to mitigate the risk of hyperglycemia during pregnancy. When choosing an insulin regimen, it is important to replicate the physiological insulin secretion pattern and customize it based on the individual patient's condition. For example, some patients may only require a basal insulin dose if they have elevated fasting or postprandial plasma glucose levels, but not both. The selection of insulin type should be determined on a case-by-case basis to minimize the risk of hypoglycemia, particularly

when using rapid-acting and long-acting insulins[95]. For further details on the distinct types of insulin and oral agents, as well as additional information regarding glyburide, please refer to Table 4[96].

PHYSICAL ACTIVITY RECOMMENDATIONS FOR PATIENTS IN ISOLATION DUE TO COVID-19

Nutrition and physical activity are widely recognized as crucial components in managing blood glucose levels, especially in the treatment of GDM. However, when these lifestyle approaches prove insufficient in achieving normal blood glucose levels, pharmacological therapy may be required. Interestingly, during the COVID-19 pandemic, there has been an observed increase in GDM cases, both during the first wave (March 1, 2020 to August 22, 2020) and second wave (August 23, 2020 to March 31, 2021). This increase has been particularly notable among women who were previously considered to be at minimal risk for hyperglycemia. These women were between 25 to 34 years of age, with a high socioeconomic status and no existing comorbidities, and experienced significant health impacts during the initial year of the pandemic. The reasons for this increase may be attributed to changes in screening protocols or lifestyle factors[97].

Several authors have documented the impact of the COVID-19 pandemic on physical activity levels, noting a decrease in physical activity and an increase in sedentary behavior[5,54]. This observation was corroborated by a study conducted by Hillyard *et al*[56], which revealed a significant 79% rise in sedentary behavior among 553 pregnant women during the pandemic. The main reported factor contributing to this pronounced shift in behavior was the fear of venturing outside the home due to the COVID-19 pandemic.

As healthcare providers, it is our duty to educate the population on the prevention of GDM. A crucial aspect of prevention involves assessing women's lifestyles and providing comprehensive counseling to foster optimal conditions for pregnancy. According to a systematic review by Laredo-Aguilera *et al*[98], pregnant women diagnosed with GDM can derive advantages from participating in moderate-intensity exercise for a minimum of 20-50 min, at least twice a week. However, the review did not identify a specific exercise type due to the varied range of exercises mentioned in the studies analyzed.

MENTAL HEALTH CARE THERAPY FOR GDM PATIENTS

In recent years, there has been extensive research exploring the effects of the COVID-19 pandemic on mental health. Numerous authors have published reviews and case reports documenting an increase in anxiety, depression, stress, and psychosis attributed to several factors. These factors include work-related stress, the implementation of lockdown measures, the closure of public facilities, adherence to social distancing requirements, quarantine measures, the fear of contracting the virus, the disruption of traditional celebrations, and the promotion of safety behaviors, among other influences[99-102].

The literature review has provided valuable insights into the relationship between mental health disorders, particularly anxiety and depression, and GDM. Multiple articles have contributed to our understanding of this link, with the majority of the reviewed literature supporting the presence of an association. It suggests that pregnant women with a history of mental health disorders have an elevated risk of developing GDM, and likewise, women diagnosed with GDM are at a higher risk of experiencing symptoms of depression and anxiety[103-106].

In 2022, Trinh *et al*[107] conducted a study that revealed a decline in the utilization of mental healthcare services by women during pregnancy, followed by an increase in utilization during the postpartum period. This finding emphasizes the importance of implementing consistent psychological intervention measures to identify and address mental health disorders in pregnant women, regardless of whether they have GDM or not. By implementing such measures, women can ensure a safe pregnancy and enhance their overall pregnancy outcomes.

Having open and educational conversations with patients about the potential benefits of physical activity as a treatment for GDM and its role in managing mental health conditions is crucial. Equally important is discussing the potential risks and benefits of incorporating pharmacotherapy into the treatment plan. By engaging in these discussions, patients can make informed decisions about their healthcare journey[108].

CONCLUSION

The COVID-19 pandemic has had a profound impact on pregnant women, exacerbating the risk factors for GDM and complicating its management. Psychological factors, such as increased levels of depression and anxiety, have affected the mental health of pregnant women, potentially contributing to the development or worsening of GDM. Quarantine measures and reduced physical activity have also increased the risk for this condition.

A recent retrospective study by Mirsky *et al*[48] showed an increase in GDM diagnoses during the pandemic, but no significant rise in GWG, even among individuals with obesity. The study suggests that maternal stress may be a contributing factor, but further research is needed. Also, recent evidence suggests that the degree of SARS-Cov-2 and placental involvement could be crucial factors for adverse outcomes in pregnancy, including placental inflammation and vascular damage caused by the virus, hence putting the patient at risk for GDM[109]. However, further histology, immunohistochemistry, and molecular genetics analyses are needed to contribute to the understanding of the epidemiological changes[110].

Table 4 Dosing recommendations for insulin and oral agents in management of diabetes during pregnancy

Drug class	Drug	Dosing
	Insulin	
Rapid-acting insulin	Insulin lispro	First trimester 0.7 units/kg/d. 14-18 wk 0.8 units/kg/d. 26-27 wk 0.9 units/kg/d. 36-37 wk until delivery 1 unit/kg/d[95]
	Insulin aspart	
Short-acting insulin	Regular insulin	First trimester 0.7 units/kg/d. 14-18 wk 0.8 units/kg/d. 26-27 wk 0.9 units/kg/d. 36-37 wk until delivery 1 unit/kg/d[95]
Intermediate-acting insulin	NPH	Two thirds can be given prebreakfast and the remaining one third can be given during the pre-evening meal[95]
Long-acting insulin	Detemir	50% of total daily dose can be given in the pre-evening meal and the remaining 50% can be given as a basal insulin[95]
	Glargine	
	Oral agents	
Biguanide	Metformin	500 mg once or twice daily with an increase over 1 to 2 wk to a maximum daily dose of 2500 mg. 2000 mg if using metformin of extended release[90,92]
Sulfonylurea	Glyburide	Starting dose of 2.5 to 5 mg once daily with an increase to a maximum dose of 20 mg/d[96]

The table provides dosing information for various drugs in different drug classes used for the treatment of diabetes in pregnancy. The dosing recommendations include different trimesters and specific timeframes until delivery. NPH: Neutral protamine Hagedorn.

The COVID-19 pandemic has underscored the need for resilient healthcare systems in effectively managing and supporting pregnant women with GDM. Lessons learned from this crisis should inform future strategies for prevention, diagnosis, and management, while considering the impact of external factors on maternal and fetal health. By applying this knowledge, we can enhance the care provided to pregnant women and their infants, aiming for positive health outcomes.

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MINIREVIEWS

Ten-year review of trends in children with type 1 diabetes in England and Wales

Sze M Ng, Astha Soni

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Abstract

This review describes the prevalence, incidence, and demographics of children and young people (CYP) with type 1 diabetes in England and Wales using data from the United Kingdom National Paediatric Diabetes Audit (NPDA) and has almost 100% submission from all paediatric diabetes centres annually. It is a powerful benchmarking tool and is an essential part of a long-term quality improvement programme for CYP with diabetes. Clinical characteristics of this population by age, insulin regimen, complication rates, health inequalities, access to diabetes technology, socioeconomic deprivation and glycaemic outcomes over the past decade is described in the review. The NPDA for England and Wales is commissioned by the United Kingdom Healthcare Quality Improvement Partnership as part of the National Clinical Audit for the United Kingdom National Service Framework for Diabetes. The rising incidence of Type 1 diabetes is evidenced in the past decade. Reduction in national median glycated hemoglobin for CYP with diabetes is observed over the last 10 years and the improvement sustained by various initiatives and quality improvement programmes implemented with universal health coverage.

Key Words: Paediatric; Type 1; Trends; Outcomes; Glycated hemoglobin

Core Tip: This review describes the prevalence, incidence and demographics of children and young people (CYP) with type 1 diabetes in England and Wales using data from the United Kingdom National Paediatric Diabetes Audit. Reduction in national median glycated hemoglobin for CYP with diabetes is seen over the last 10 years and sustained by various initiatives and quality improvement programmes implemented with universal health coverage.

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INTRODUCTION

Type 1 diabetes is a chronic condition and represent the most common type of diabetes in children and young people (CYP). International epidemiology reported that there has been a significant rise in the diagnosis of type 1 diabetes in CYP in the past decade with an estimated incidence of approximately 1 in every 1000 children[1]. Globally, diabetes is reported to affect 1.5 million deaths due to short and long term complications. However, there is currently no accurate epidemiological data on the prevalence or incidence of Type 1 diabetes in many countries worldwide, particularly lacking in low-middle-income countries[2]. The United Kingdom has one of the highest prevalence of CYP with type 1 diabetes in Western Europe and it has an estimated incidence rate of 193.8 per 100000[3].

In the United Kingdom, there are approximately 400000 people diagnosed with type 1 diabetes, with 30000 CYP from 0 to of 18 years living with Type 1 diabetes[1]. The International Diabetes Federation Diabetes Atlas 9th edition reported that an estimated 600000 CYP with Type 1 diabetes are under 15 years of age worldwide[4-6]. A recent paper based on the discrete-time cohort-level Markov illness–death model, estimates that worldwide prevalence of type 1 diabetes is substantial and is growing[2].

Prevalence and incidence

The United Kingdom National Paediatric Diabetes Audit (NPDA) 2020/2021 in England and Wales reported approximately 30000 CYP with Type 1 diabetes and 600 CYP with type 2 Diabetes[7]. The reported prevalence rate of Type 1 diabetes in England and Wales was 204.5 per 100000 population in the United Kingdom. The NPDA 2019/2020 audit reported an incidence of 2900 CYP diagnosed with Type 1 diabetes, of whom almost 3000 CYP (95.3%) were aged between 0 and 15 years. In 2020/2021, there was an increase in number of both girls and boys diagnosed with Type 1 diabetes (27.4% and 12.6% increase in boys and girls respectively). The seasonal pattern of new diagnoses of type 1 diabetes mellitus (T1DM) was also disrupted in 2020/2021. Previously there had been a consistent pattern of new diagnoses of Type 1 amongst CYP with a spike in new diagnoses during winter months and fall in the summer. This is a well-known phenomenon in other countries with high incidence of diabetes[8]. The reason for this is unclear but it has been suggested that this could be due to increase in viral illnesses during winter months[7]. This pattern of new diagnoses was disrupted in 2020/2021 and reason for this is not known. One could attribute this to coronavirus disease 2019 (COVID-19) pandemic. Efforts to control COVID-19 such as lockdowns, social isolation led to reduction in common childhood viral illnesses[9-11].

Glycated hemoglobin outcomes and complication rates

Glycated hemoglobin (HbA1c) is a marker for glycaemic control over preceding 2-3 mo. The Diabetes and Complications Trial (DCCT) trial has shown that intensive diabetes management and good glycaemic control lower the risk of developing microvascular complications and early mortality in the future[12]. Data from NPDA have shown consistent year on year improvements in HbA1c[5]. Median HbA1c in England has fallen from 73 mmol/mol in 2009/2010 to 61 mmol/mol 2020/2021. Similar trend has been noticed in Wales where HbA1c fell from 72 mmol/mol to 62 mmol/mol over the same period (Figure 1).

In 2015, the National Institute for Health and Care Excellence (NICE) recommended a target HbA1c of 48 mmol/mol or less to improve the diabetes management[13]. This led to updated diabetes delivery plan in Wales[14]. Prior to that best practice tariff (BPT) was introduced in England in 2012. Peer review (Quality assurance) was introduced at the back of BPT to support the paediatric diabetes units in fulfilling the criteria as set out in BPT. Other national initiatives such as the Royal College of Paediatrics and Child Health Quality improvement programme have been introduced to help achieve the target HbA1c[15]. This QI collaborative supported diabetes teams with tools to identify and deliver their own initiatives that are relevant to the needs of the CYP and their families that they care for locally. Although the overall HbA1c trend has been downwards amongst the CYP with T1DM, there have been consistent differences in outcomes between different ethnic backgrounds. Those from white ethnicity achieve lower average HbA1c compared to those from black ethnicity and this trend is apparent year on year[7] (Figure 2). The NPDA showed a significant relationship between HbA1c and deprivation. Those living in deprived areas tend to have a higher HbA1c (Figure 3). However, this trend has not been noticed in CYP of black ethnicity. Average HbA1c for CYP from black ethnicity living in least deprived areas is similar to those from white ethnicity in the most deprived.

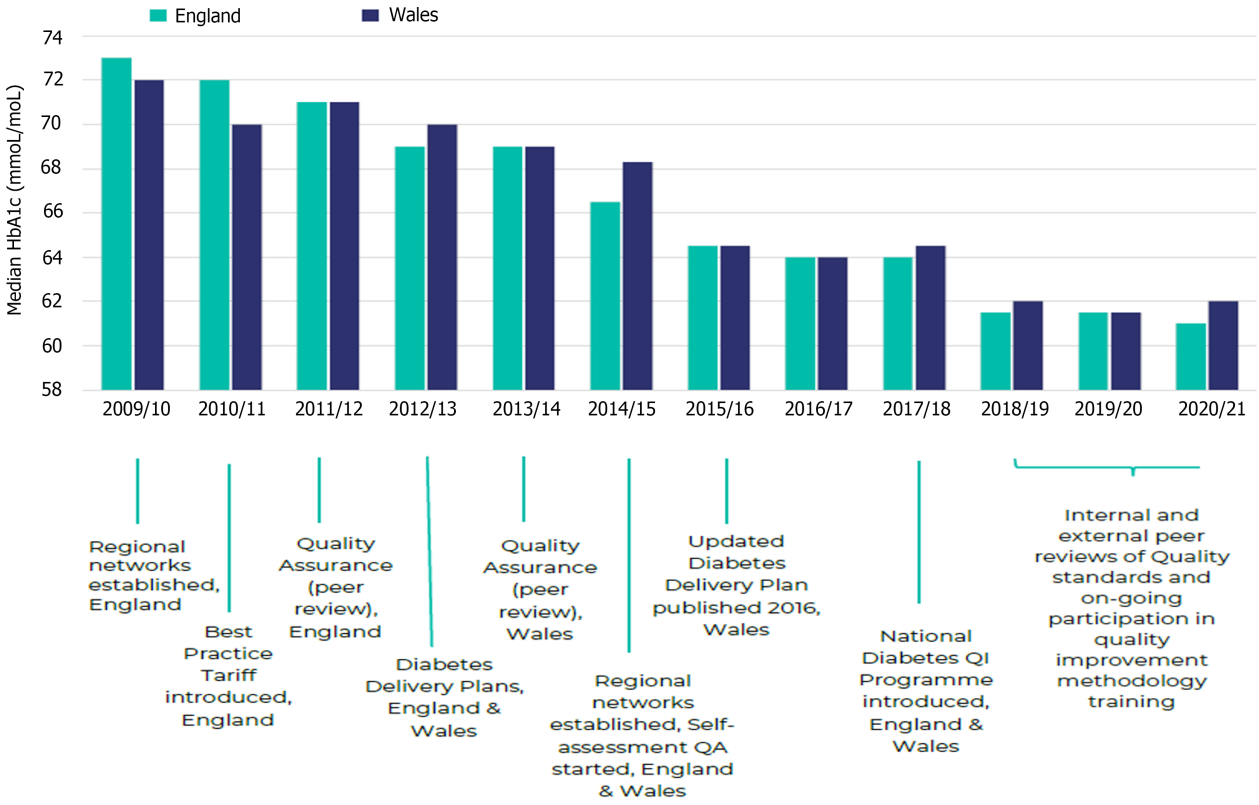
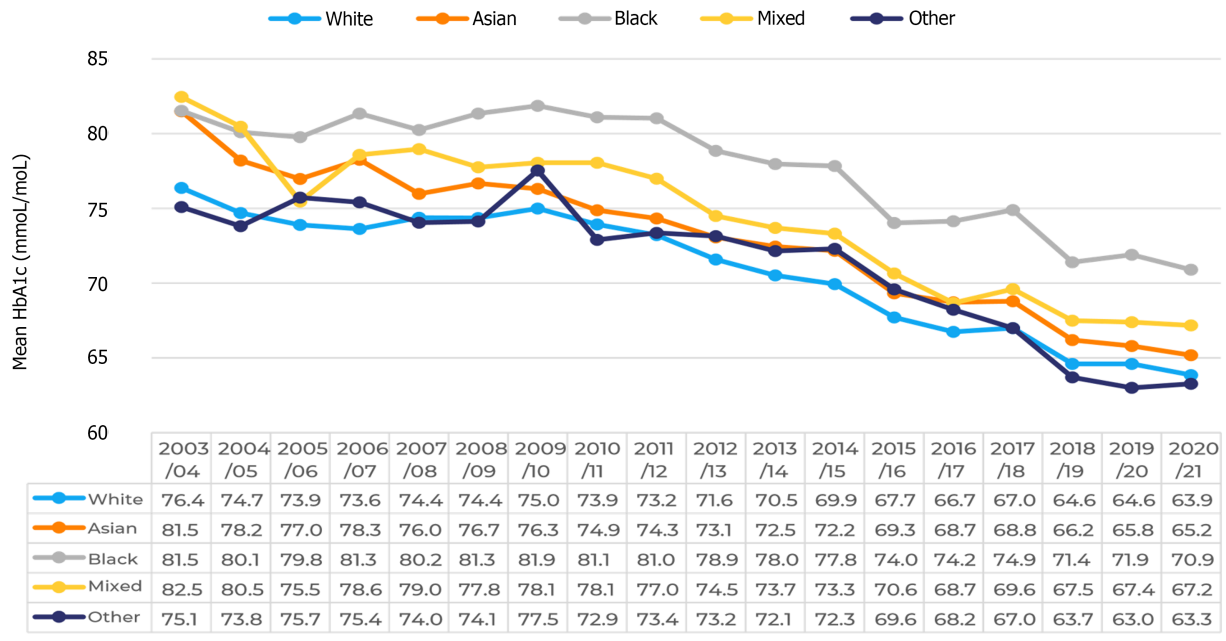
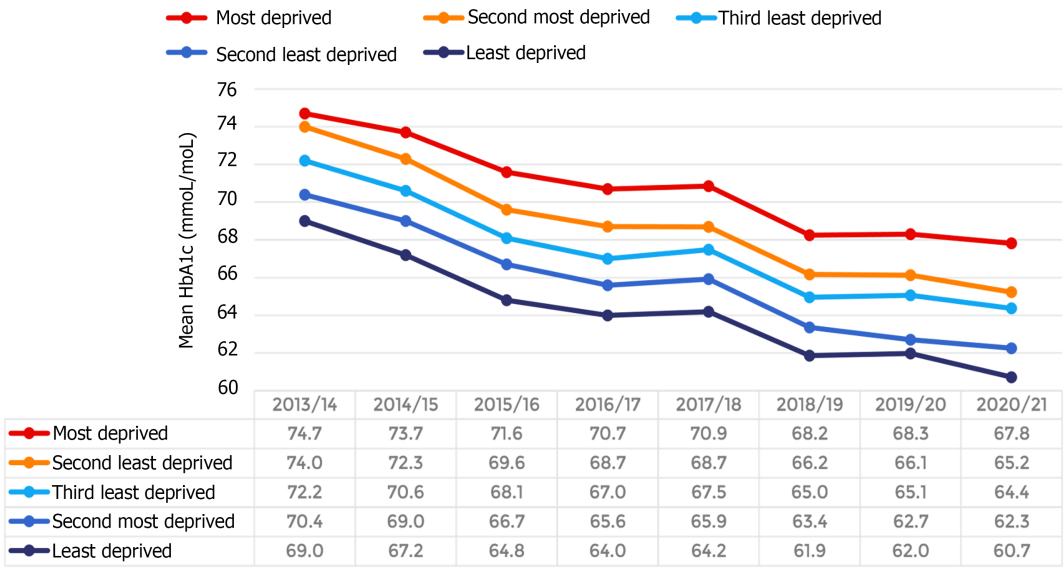


Figure 1 Median glycated hemoglobin of all types of diabetes in England and Wales from 2009/2010 to 2020/2021 for children and young people under the age of 18 years (permission to reproduce from National Paediatric Diabetes Audit Royal College of Paediatrics and Child Health and Healthcare Quality Improvement Partnership). Citation: National Paediatric Diabetes Audit Annual Report 2021-22: Care Processes and Outcomes. London: Royal College of Paediatrics and Child Health, 2023. Copyright © 2023 Healthcare Quality Improvement Partnership (Supplementary material).



	2003/04	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18	2018/19	2019/20	2020/21
White	76.4	74.7	73.9	73.6	74.4	74.4	75.0	73.9	73.2	71.6	70.5	69.9	67.7	66.7	67.0	64.6	64.6	63.9
Asian	81.5	78.2	77.0	78.3	76.0	76.7	76.3	74.9	74.3	73.1	72.5	72.2	69.3	68.7	68.8	66.2	65.8	65.2
Black	81.5	80.1	79.8	81.3	80.2	81.3	81.9	81.1	81.0	78.9	78.0	77.8	74.0	74.2	74.9	71.4	71.9	70.9
Mixed	82.5	80.5	75.5	78.6	79.0	77.8	78.1	78.1	77.0	74.5	73.7	73.3	70.6	68.7	69.6	67.5	67.4	67.2
Other	75.1	73.8	75.7	75.4	74.0	74.1	77.5	72.9	73.4	73.2	72.1	72.3	69.6	68.2	67.0	63.7	63.0	63.3

Figure 2 Mean glycated hemoglobin for children and young people with Type 1 diabetes in England and Wales by ethnic group from 2003/2004 to 2020/2021 (permission to reproduce from National Paediatric Diabetes Audit Royal College of Paediatrics and Child Health and Healthcare Quality Improvement Partnership). Citation: National Paediatric Diabetes Audit Annual Report 2021-22: Care Processes and Outcomes. London: Royal College of Paediatrics and Child Health, 2023. Copyright © 2023 Healthcare Quality Improvement Partnership (Supplementary material).



	2013/14	2014/15	2015/16	2016/17	2017/18	2018/19	2019/20	2020/21
Most deprived	74.7	73.7	71.6	70.7	70.9	68.2	68.3	67.8
Second least deprived	74.0	72.3	69.6	68.7	68.7	66.2	66.1	65.2
Third least deprived	72.2	70.6	68.1	67.0	67.5	65.0	65.1	64.4
Second most deprived	70.4	69.0	66.7	65.6	65.9	63.4	62.7	62.3
Least deprived	69.0	67.2	64.8	64.0	64.2	61.9	62.0	60.7

Figure 3 Mean glycated hemoglobin for children and young people with Type 1 diabetes by deprivation quintile, 2013/2014 to 2020/2021 (permission to reproduce from National Paediatric Diabetes Audit Royal College of Paediatrics and Child Health and Healthcare Quality Improvement Partnership). Citation: National Paediatric Diabetes Audit Annual Report 2021-22: Care Processes and Outcomes. London: Royal College of Paediatrics and Child Health, 2023. Copyright © 2023 Healthcare Quality Improvement Partnership (Supplementary material).

CYP with diabetes are at increased risk of diabetic nephropathy and retinopathy. All CYP with Type 1 diabetes are screened for albuminuria after 12 years of age since NICE made that recommendation in 2015[13]. 10.3% of CYP were recorded as having micro or macroalbuminuria. This number has been static since 2015/2016[7,14]. Across the audit year, there has been no significant changes in the presence of albuminuria associated with duration of diabetes. CYP above 12 years of age get retinopathy screening annually. But the interval for screening changed for many in 2020/2021. Many screening services were advised to screen biennially unless an abnormal result was identified previously. Almost 25% of CYP with T1DM who were eligible for eye screening were screened in 2020/2021 compared to 75% in 2019/2020. The NPDA records eye screening as abnormal or normal. It does not differentiate between the grade of retinopathy. In 2020/2021, 16.9% of those who were screened had an abnormal result, this number has varied between 12%-15% since 2015/2016. CYP with T1DM are more likely to develop other autoimmune conditions. They are annually screened for thyroid and coeliac disease. Two-point-seven percent of screened children had thyroid disease and 5.2% were positive for coeliac in 2020/2. Figure 4 shows the longitudinal trend of% of children with thyroid and coeliac disease from 2015/2016- 2020/2021.

Key care processes performed annually

NICE recommends 7 key health check that should be performed annually[13]. HbA1c (4 readings a year), height and weight for all CYP with T1DM. Thyroid function tests to be undertaken every year for all CYP. After 12 years of age, CYP with T1DM should get urinary albumin, blood pressure, retinopathy screen and foot examination. However, there were disruptions to retinopathy screening in 2020/2021[7]. Retinopathy screening was reduced from annually to biennially unless there was a previous abnormal result. There have been an improvement in completion of key health checks over the last 10 years. The completion rates for 2020/2021 reduced due to cessation of face to face clinic due the COVID-19 pandemic. Figure 5 shows the trend improvement in completion of all key processes over the years. There was a large difference amongst various diabetes units' ability in completing key health check in 2020/2021. Similar trends have been noticed in previous audit years.

Insulin regimens

In 2020/2021, 38.5% of CYP with T1DM in England and Wales were using an insulin pump to manage their diabetes[7]. This has increased from 28.1% in 2015/2016. In 2020/2021, 59.1% were on multiple daily injection and only 2.4% were on one-three injections a day. The number of CYP using pump therapy have steadily increased over the years. But this trend has reversed amongst 0-9 years old since 2018/2019 (Figure 6). CYP are more likely to be on insulin injections in the first year of their diagnosis compared to those who were 5-9 years in to diagnosis in 2020/2021. The percentage of those using insulin pumps in 1st year of their diagnosis reduced in 2020/2021 to 13.9% from 4.8% in the previous year. It could be a reflection of changes in care provision due to pandemic as this number has been steadily increasing since 2016/2017. There remains a larger gap in insulin pump usage and insulin injections amongst those CYP living in most deprived areas. In 2020/2021 the gap in number of CYP on insulin pump therapy in those living in the most and least deprived areas was 32.5% compared to 44.0%, respectively (a difference of 11.5 percentage points), which had widened from 2014/2015, when it was 18.4% *vs* 26.3% (a difference of 7.9 percentage points).

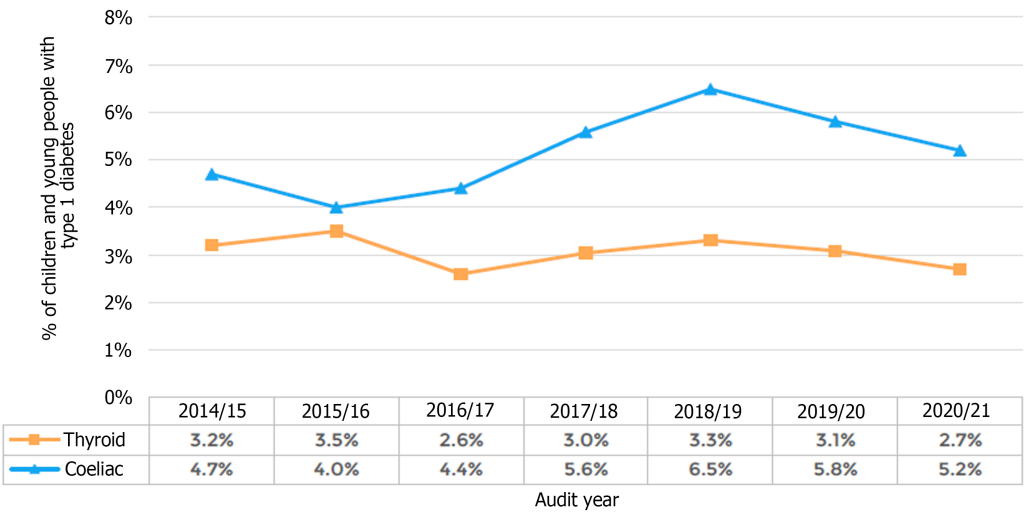


Figure 4 Percentage of children and young people with Type 1 diabetes with thyroid or coeliac disease in England and Wales, 2014/2015 to 2020/2021. Prevalence of coeliac disease was highest among the white children and young people (CYP) and thyroid disease was commonest among the Asian CYP in 2020/2021. Citation: National Paediatric Diabetes Audit Annual Report 2021-22: Care Processes and Outcomes. London: Royal College of Paediatrics and Child Health, 2023. Copyright © 2023 Healthcare Quality Improvement Partnership (Supplementary material).

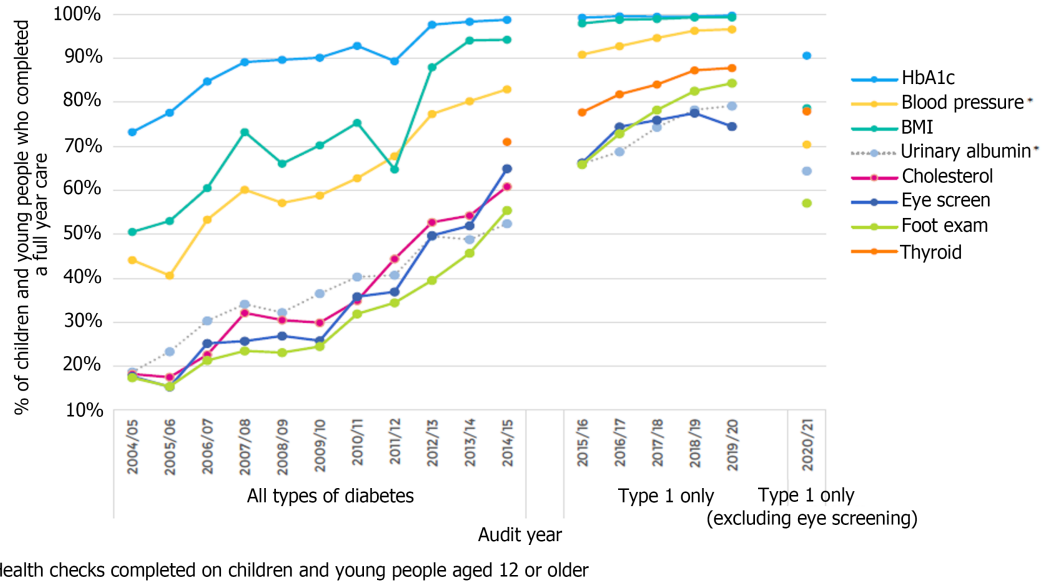


Figure 5 Percentage of children and young people who completed a full year of care recorded as receiving individual health checks, 2004/2005 to 2020/2021. Citation: National Paediatric Diabetes Audit Annual Report 2021-22: Care Processes and Outcomes. London: Royal College of Paediatrics and Child Health, 2023. Copyright © 2023 Healthcare Quality Improvement Partnership (Supplementary material).

Similar differences in the use of real time continuous glucose monitor (rtCGM) have been identified. Over last few years, increased use of rtCGM has been noticed but the gap in its usage for most and least deprived has widened with time. CYP from least deprived quintiles are more likely to use rtCGM. This is true across most ethnic groups but black CYP typically have lower use of rtCGM which was irrespective of their deprivation status[16]. NPDA data[7] has also reported that CYP who were using rtCGM technology were more likely to attain target HbA1c levels compared to those who were not on trCGM. Similarly, pump users were more likely to be using rtCGM compared to those on insulin injections.

Universal health coverage and national quality initiatives

In England and Wales, the existence of universal health coverage and national quality initiatives as well as the formation of 10 Diabetes Regional Networks geographically situated in former Strategic Regional Health Authorities has resulted in improved diabetes health outcomes and diabetes units' increasing participation in the NPDA[7]. As a result, the NPDA has allowed a country-wide data monitoring and benchmarking of diabetes outcomes and its services within and between regions. The ultimate aim of such national quality initiatives is to improve diabetes care and quality, and to

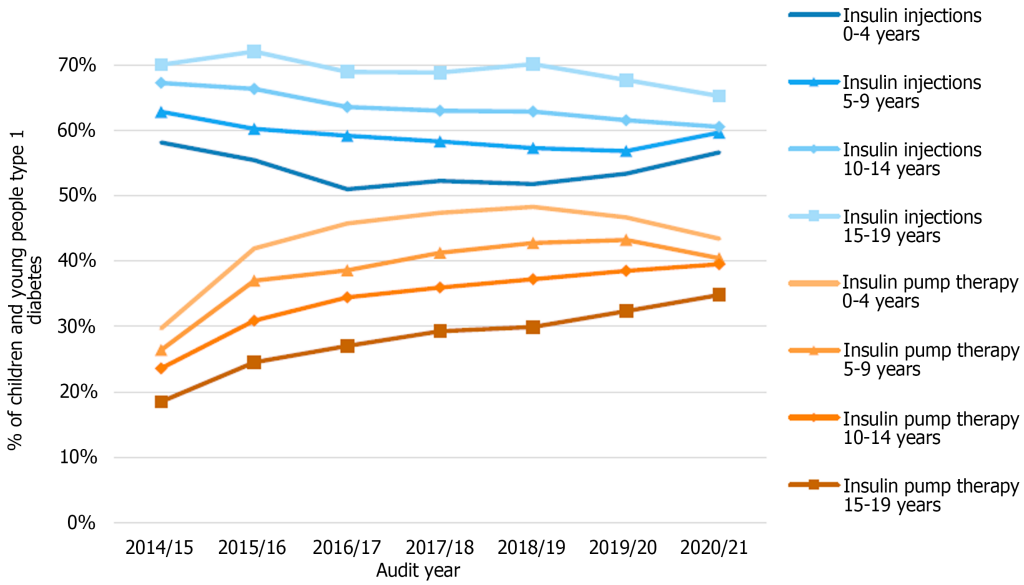


Figure 6 Percentage of children and young people either on daily insulin injections or pump therapy by age group, 2014/15 to 2020 /21.
Citation: National Paediatric Diabetes Audit Annual Report 2021-2022: Care Processes and Outcomes. London: Royal College of Paediatrics and Child Health, 2023. Copyright © 2023 Healthcare Quality Improvement Partnership (Supplementary material).

remove health inequalities of service provision within and between regions. The past decade have seen a move towards intensification of insulin therapy, and increasing use of diabetes technologies such as continuous subcutaneous insulin infusions and rtCGM. The BPT was introduced in England to increase the funding provisions per year of care for paediatric diabetes services, with the aim to enhance the quality of diabetes care and improve the health outcomes for CYP with diabetes[17]. Participation in the NPDA is one of the key requirements for obtaining the BPT and data for individual centres are further tracked and utilized as part of a 'peer review' quality assurance programme.

Health inequalities and social deprivation

The NPDA report[7] has shown that while there is an increasing trend in insulin pump usage compared to injections in all areas of deprivation, the gap between insulin pump usage and rtCGM usage amongst CYP living in the most and least deprived areas, and between CYP of White ethnicity and Black ethnicity has further widened year-on-year over the past 6 years. Table 1 shows the graphs of CYP with Type 1 diabetes by deprivation areas which are derived by postcode-matching to the English (IMD, 2016) and Welsh (WIMD, 2015) indices of multiple deprivation data. The proportion of CYP with Type 1 diabetes living in the most deprived quintile was slightly higher, and this has been a trend across the years.

There remains a persistent difference in HbA1c health outcomes achieved by Paediatric Diabetes centres across England and Wales even after patient characteristics have been accounted for in the last decade. In addition, there is clear evidence that there are inequalities on access to use of diabetes technologies such as insulin pump and rtCGM which has been shown to have the potential to impact positively on of glycaemic control, fear of hypoglycemia and quality of life [16].

CONCLUSION

Research has shown that healthcare professionals can hold strong and sometimes incorrect views about the kinds of individuals who will be the 'best candidates' for, and make the best use of, diabetes technologies. Such views may influence who healthcare professionals offer technologies to and/or how they present the benefits/burdens of the technology. Studies have also shown that other factors, such as lack of availability of funding and staff with relevant clinical training, can also influence who does/does not get given opportunities to use new diabetes technologies[18,19].

Similar trends of health inequalities and racial-ethnic disparities in diabetes outcomes and management are reported from the United States Type 1 Diabetes Exchange National Registry which reported that ethnic minority young people had significantly worse diabetes health outcomes and were also prescribed less advanced diabetes technologies, while carers' perceptions of cost and healthcare providers' perception bias of family competence cited as reasons to such variations[20-22].

Table 1 Percentage and number of children and young people with Type 1 diabetes by deprivation quintile, 2020/2021 permission to reproduce from National Paediatric Diabetes Audit Royal College of Paediatrics and Child Health and Healthcare Quality Improvement Partnership

Deprivation quintile	Total	% of cohort	% of total with known deprivation	% of children and young people aged 0-19 yr old (England and Wales)
Most deprived	6786	22.70%	22.70%	23.70%
Second most deprived	6069	20.30%	20.30%	20.70%
Third least deprived	5659	18.90%	19.00%	19.00%
Second least deprived	5682	19.00%	19.00%	18.10%
Least deprived	5665	19.00%	19.00%	18.50%
Missing	31	0.10%	-	-

Percentage of general population aged 0 to 19 years old in England and Wales. Calculations made using the "Lower layer Super Output Area population estimates" from the Office for National Statistics, mid-year 2020. Citation: National Paediatric Diabetes Audit Annual Report 2021-22: Care Processes and Outcomes. London: Royal College of Paediatrics and Child Health, 2023. Copyright © 2023 Healthcare Quality Improvement Partnership (Supplementary material).

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FOOTNOTES

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MINIREVIEWS

Impact of inhaled and intranasal corticosteroids on glucose metabolism and diabetes mellitus: A mini review

Kay Choong See

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Abstract

Inhaled corticosteroids (ICS) and intranasal corticosteroids (INS) are the mainstays of treatment for chronic respiratory diseases like asthma, chronic obstructive pulmonary disease, and allergic rhinosinusitis. In addition, these localized forms of steroid therapy are generally considered to have fewer systemic side effects compared to long-term oral corticosteroids. However, concern and controversy remain over the impact of ICS and INS on the incidence and control of diabetes mellitus (DM). Given the widespread use of ICS and INS, even small individual effects on DM could lead to large consequences for the global population. Multiple large observational studies suggest that high dose ICS is associated with increased incident DM and worsened DM control, though the contribution of other risk factors is less certain. In addition, only two studies were done to investigate the association of INS and DM, with both studies demonstrating a short-term association of INS use with hyperglycemia. While more research evaluating the risk of ICS/INS for DM-related adverse events is needed, high doses of ICS/INS should be avoided when possible. The following strategies for ICS/INS dose minimization can be considered: Use of non-pharmacological measures (trigger avoidance, smoking cessation, vaccination to avoid infection), control of comorbid conditions, use of non-ICS-containing medications, intermittent rather than regular ICS dosing, and appropriate de-escalation of high ICS doses.

Key Words: Beclomethasone; Budesonide; Fluticasone; Glucocorticoids; Glucose; Hyperglycemia

Core Tip: Inhaled corticosteroids (ICS) and intranasal corticosteroids (INS) are the mainstays of treatment for chronic respiratory diseases like asthma, chronic obstructive pulmonary disease, and allergic rhinosinusitis. Multiple large observational studies suggest that high dose ICS is associated with increased incident diabetes mellitus (DM) and worsened DM control, though the contribution of other risk factors is less certain. In addition, only two studies were done to investigate the association of INS and DM, with both studies demonstrating a short-term association of INS use with hyperglycemia.

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INTRODUCTION

Corticosteroids are important anti-inflammatory drugs that are widely used in respiratory disease. Inhaled corticosteroids (ICS) are the mainstay of treatment for patients with asthma[1]. ICS are also added to dual bronchodilators for patients with chronic obstructive pulmonary disease (COPD) who have frequent exacerbations and peripheral eosinophilia ≥ 300 cells/μL[2]. Like ICS for asthma and eosinophilic COPD, intranasal corticosteroids (INS) are the key medications to treat allergic rhinitis[3]. Given the high global prevalence of asthma, COPD, and allergic rhinitis, widespread use of ICS and INS is expected[4,5].

Diabetes mellitus (DM) is another disease with a high global burden[6]. Complications of uncontrolled DM include coronary artery disease, peripheral vascular disease, kidney failure, and eye disease, and can be a serious threat to both quality of life and survival[7]. As such, reducing both the development of DM, and the worsening of DM control, would be crucial in reducing the global burden of DM. Apart from antidiabetic drugs, prevention of chronic hyperglycemia would also be helpful. Therefore, long-term use of drugs that impair glucose metabolism, such as oral steroids, should be avoided[8]. However, it is uncertain if ICS and INS have systemic effects on glucose metabolism, and if ICS and INS increase the risk of incident DM (*i.e.,* development of new cases of DM) or worsen DM control. Therefore, this paper will use clinical data from human studies and review the impact of ICS and INS on DM incidence or control.

PHARMACOLOGY OF ICS AND INS

Corticosteroids are synthetic glucocorticoids, which differ in glucocorticoid receptor binding affinity and potency[9]. For ICS and INS, all corticosteroids are administered as active forms, except for beclomethasone dipropionate and ciclesonide, which are prodrugs requiring metabolism to active forms. The more potent agents used as ICS and INS are fluticasone furoate, mometasone furoate, fluticasone propionate, beclomethasone dipropionate (*via* its active metabolite beclomethasone monopropionate), and ciclesonide (*via* its active metabolite desisobutyryl ciclesonide). The less potent agents used as ICS and INS are budesonide, triamcinolone acetonide, and flunisolide. In general, the more potent glucocorticoids can be used in smaller doses to achieve the same anti-inflammatory effect as the less potent agents. In addition, given lower delivered doses, use of more potent glucocorticoids does not necessarily translate into more adverse effects.

For ICS, the delivered dose enters the systemic circulation *via* two routes[10]. The first route is *via* the gastrointestinal tract, where 60%-90% of the delivered dose is deposited in the oropharynx, swallowed into the stomach, absorbed through the intestines, and metabolized by the liver. Hepatic metabolism renders most of the systemically absorbed ICS inactive, even for corticosteroids with significant oral bioavailability (*e.g.,* beclomethasone dipropionate, budesonide, triamcinolone acetonide, and flunisolide). The second route by which ICS enters the systemic circulation is *via* the lungs, where the remaining 10%-40% of the delivered dose passes directly into the systemic circulation. ICS absorbed *via* the lung bypasses hepatic first-pass metabolism, and exerts greater systemic impact compared to ICS absorbed *via* the gastrointestinal tract.

For INS, the drug is sprayed as an aqueous suspension into the nose, with a relatively short dwell time of < 1 h[3]. Given rapid nasal ciliary clearance, much of the drug runs off after some absorption into the nasal mucosa. As such, systemic effects, if any, would arise from entry *via* the gastrointestinal tract. Like swallowed ICS, swallowed INS would also undergo first-pass metabolism in the liver with oral bioavailability depending on the type of corticosteroid.

EFFECT OF ICS AND INS ON GLUCOSE METABOLISM AND DM

Glucocorticoids drive hyperglycemia *via* increased hepatic gluconeogenesis and decreased hepatic/adipocyte glucose uptake, mediated by the glucocorticoid receptor in the cytoplasm of peripheral tissues (primarily liver, skeletal muscle, and adipose tissue)[11-13] (Figure 1) and possibly by hepatic activation of Krüppel-like factor 9[14]. Risk factors for hyperglycemia involve patient factors and drug factors. Patient factors include age and diseases that predispose to

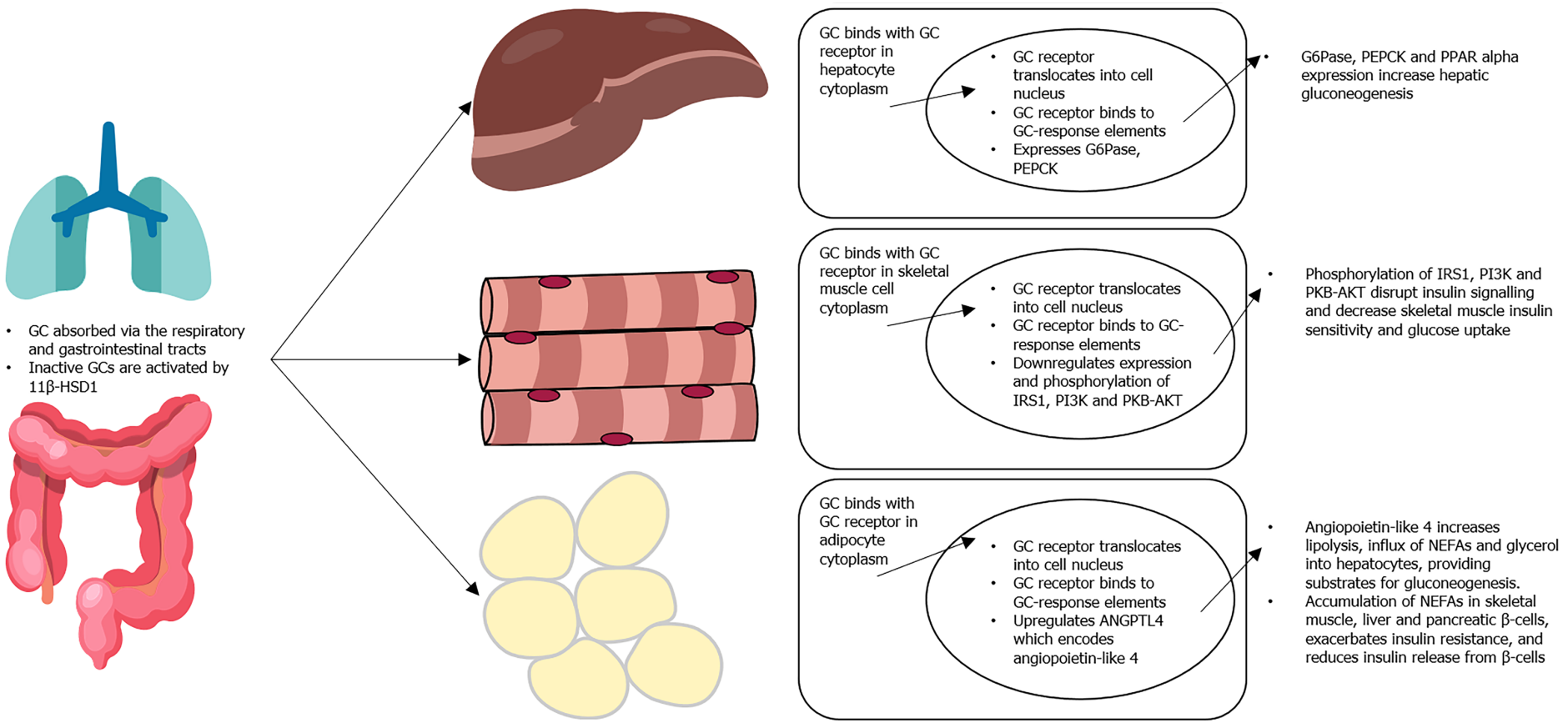

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Figure 1 Molecular signaling pathway of glucocorticoid-induced hyperglycaemia. GC: Glucocorticoid; G6Pase: Glucose-6-phosphatase, encoded by G6PC1; HSD1: Hydroxysteroid dehydrogenase type 1; IRS: Insulin receptor substrate; NEFA: Non-esterified fatty acid; PEPCK: Phosphoenolpyruvate carboxykinase, encoded by PCK1; PI3K: Phosphatidylinositol 3-kinase; PKB-AKT: Protein kinase B; PPAR: Peroxisome proliferator-activated receptor. Open-source clipart images from freesvg.org and scidraw.io.

hyperglycemia such as obesity. Drug factors include ICS/INS dose, corticosteroid formulation/potency, regular *vs* intermittent use of ICS/INS, and medications that inhibit cytochrome P450 3A4 and therefore hepatic metabolism of systemically absorbed ICS/INS. When hyperglycemia becomes chronic, DM and its complications may develop. Biochemically, chronic hyperglycemia can be reflected as elevations of fructosamine (indicates average serum glucose concentration over the preceding 2-3 wk)[15] and, more commonly, glycated hemoglobin (HbA1c).

Clinical studies investigating the association of ICS/INS have differing results. Some show no worsening of glucose metabolism or DM (Table 1), while others show worsening (Table 2). Multiple study designs from case reports to

Table 1 Studies showing no worsening of glucose metabolism/diabetes mellitus by inhaled corticosteroid/intranasal corticosteroid

Ref.	Study design	Patient population	ICS or INS exposure	Outcomes reported
Blackburn *et al* [18], 2002	Population-based cohort study	38441 elderly (≥ 66 years old) ICS users versus 53845 non-ICS users	Types and doses of ICS not stated	Over 3 yr, no association of ICS with incident DM
Borsi *et al*[36], 2018	Non-randomized trial	35 non-diabetic adults with mild to moderate asthma	BUD ICS 320 mcg every 12 h	Over 2 mo, ICS had no effect on HbA1c, insulin level and insulin sensitivity (HOMA-IR)
Canis *et al*[37], 2007	Non-randomized trial	Non-diabetic adults (12 asthma, 6 COPD)	BUD ICS 400 mcg twice daily	Over 8 wk, ICS had no effect on glucose, insulin level and insulin sensitivity (HOMA-IR)
Dendukuri *et al* [38], 2002	Nested case-control study	Adults aged ≥ 65 yr. 1494 cases of incident DM versus 14931 controls	Various types and doses of ICS	No increased risk of incident DM
Ebden *et al*[39], 1989	Prospective observational study	14 normal and 24 diet controlled DM subjects	BDP 2000 mcg/d for 2 wk	Over 2 wk, ICS did not worsen glucose tolerance test results or insulin levels
Faul *et al*[40], 2009	Crossover RCT	12 DM patients with asthma or COPD	FP ICS 440 mcg twice daily versus no ICS	Over 6 wk, no difference in HbA1c
Flynn *et al*[41], 2014	Record linkage study	4305 patients with COPD in Scotland	Various types and doses of ICS	Over at least 2 yr of follow-up, ICS did not increase incident DM or worsen pre-existing DM control
Giep *et al*[42], 1996	RCT	19 ventilator-dependent neonates < 1500 g birthweight	BDP ICS 1 mg/kg/d *via* ventilator circuit	No effect on blood glucose
Kiviranta and Turpeinen[20], 1993	Prospective observational study	15 adults with uncontrolled asthma; 15 healthy controls	Up to 2000 mcg/d of BDP ICS, and up to 1600 mcg/d of BUD ICS	Over 8 mo, no change of fasting glucose and insulin
Lee *et al*[33], 2016	Nested case-control study using South Korean claims database	Pregnant women who delivered between 1 January 2009 and 31 December 2011. 34190 GDM cases and 170934 control subjects	Various types and doses of ICS	ICS use was not associated with increase in the risk of GDM
Lempp *et al* [43], 2022	Electronic medical records study	127 patients aged 18 to 80 with COPD and type 2 DM on at least 2 oral anti-glycemic medications from 1 January 2000 to 31 December 2017	ICS (64 patients) versus no ICS (63 patients). Various types and doses of ICS	Over 5 yr, no difference in rate of DM worsening to HbA1c > 10% (threshold chosen as add-on insulin would be considered)
O'Byrne *et al* [21], 2012	Pooled analyses of RCTs	44528 patients with asthma (60 trials) or COPD (8 trials)	BUD and fluticasone ICS at various doses	Over a mean follow-up of 210 d in asthma trials and 268 d in COPD trials, no association between ICS use and hyperglycemia or incident DM
Pauwels *et al* [19], 1999	RCT	1277 adults with COPD and continued smoking	BUD ICS 400 mcg/d for 3 yr versus placebo	No increase in incident DM by BUD ICS 400 mcg/d
Pu *et al*[44], 2021	Systematic review of 17 RCTs which reported glucose/DM data	43430 adults with COPD	Various types and doses of ICS	No difference in glucose level, DM control or incident DM between the ICS group and the control group with follow-up ranging from 12-96 wk
Rogala *et al* [45], 2020	Cross-sectional study	6763 adult patients with asthma and/or diabetes	Various types and doses of ICS	No association with increased fasting glucose
Rogliani *et al* [46], 2014	Cross-sectional study	493 outpatients with COPD, seen between 2010-2012	Types and doses of ICS not stated	No association between ICS use and DM diagnosis
Rahman *et al* [47], 2021	RCT	70 patients with asthma, but no DM	Fluticasone ICS (at low to high doses) *versus* no ICS	Over 3 mo, no difference in fasting plasma glucose, 2 h after 75 g oral glucose intake, and in HbA1c
Slatore *et al* [48], 2009	Prospective cohort study	1698 adults with COPD	Various types and doses of ICS	No change of serum glucose in subjects without diabetes
Turpeinen *et al* [49], 1991	Prospective observational study	9 children with asthma	400-800 mcg/m^2/d of BUD ICS	Over 5 mo, no change of fasting glucose and insulin
Yucel *et al*[50], 2009	Case-control study	141 children with asthma (cases), 52 children without asthma (controls). All children did not have DM	75% of children were using on BUD ICS, and 25% of children were using FP ICS, at various doses	No significant association between cumulative dose of ICS and HbA1c

BDP: Beclomethasone dipropionate; BUD: Budesonide; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; FP: Fluticasone propionate; GDM: Gestational diabetes mellitus; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance;

ICS: Inhaled corticosteroid; INS: Intranasal corticosteroid; RCT: Randomized controlled trial.

randomized control trials have been employed, with the largest studies tapping on population registries. All the studies explored ICS as the exposure variable, while only two studies focused on INS[16,17].

Among the studies showing no worsening of glucose metabolism/DM by ICS/INS (Table 1), patients with both asthma and COPD were followed up for as long as three years[18,19]. The doses of ICS/INS range from intermediate to relatively high doses (up to 2000 mcg/d of beclomethasone dipropionate ICS, and up to 1600 mcg/d of budesonide ICS) [20]. Some studies, though large, did not collect DM-related adverse events purposefully, which can lead to false negative findings (*i.e.*, finding no association when a real association is present). For instance, in a pooled analysis of 68 randomized trials for ICS (60 for asthma; 8 for COPD), the number of DM-related adverse events relied on spontaneous adverse event reports only, without formal biochemical validation of DM[21].

Among the studies showing worsening of glucose metabolism/DM by ICS/INS, the smaller studies generally use relatively high doses of ICS (up to budesonide ICS 2000 mcg daily and fluticasone propionate ICS 2000 mcg/d) and demonstrated laboratory abnormalities related to hyperglycemia (*e.g.*, increased HbA1c, glycosuria). Both studies involving INS demonstrated hyperglycemia[16,17]. The case report involving INS suggests that dose matters, as off-label use of high-dose INS in an infant with type 1 DM resulted in hyperglycemia, which resolved when the INS was switched to a standard low-dose formulation[17].

Nonetheless, laboratory abnormalities do not necessarily translate into DM. Development of new DM has only been uncovered in large observational studies[22-27]. Within these large datasets, the risk factors for incident DM associated with ICS/INS use are not always obvious, though some studies have ascribed increased DM risk with higher ICS doses [25-29]. For example, using a Canadian health insurance database, Suissa *et al*[27] studied 388584 patients with respiratory disease, and found that current use of ICSs had a 34% increase in the incidence rate of DM [rate ratio (RR) = 1.34; 95% confidence interval (CI): 1.29-1.39] and a similar increase in the incidence rate of worsening DM control (RR = 1.34, 95%CI: 1.17-1.53). The RRs were greatest for the highest ICS doses, equivalent to at least 1000 mcg/d fluticasone: RR for incident DM 1.64, 95%CI: 1.52-1.76; RR for worsening DM control 1.54, 95%CI: 1.18-2.02. However, apart from ICS dose, and the possible role of increased bioavailability of triamcinolone INS contributing to hyperglycemia[16], other patient-specific or corticosteroid-specific risk factors have not been well-studied.

REDUCING THE IMPACT OF ICS AND INS ON GLUCOSE METABOLISM AND DM

From existing studies, the impact of ICS/INS on glucose metabolism and DM is inconsistent, though the reasons for inconsistency are not completely apparent. Nevertheless, ICS dose has been repeatedly identified as a risk factor in large observational studies, which would have adequate power to uncover significant associations between dose and incident DM. In addition, in the only 2 studies focused on INS, high INS doses were associated with hyperglycemia. Therefore, it is prudent that ICS/INS doses are minimized to obtain benefit while avoiding potential hyperglycemia and DM.

Strategies to minimize ICS and INS doses are outlined in Table 3. In general, non-pharmacological measures should be used to optimize disease control and reduce the reliance on high dose ICS/INS formulations. These non-pharmacological measures include trigger avoidance, smoking cessation, and vaccination to avoid infection. Holistic management of environmental triggers and comorbid conditions such as obesity, obstructive sleep apnea, cardiac dysfunction, anxiety, and depression can be considered as part of a "treatable traits" approach to improve the care of patients with chronic respiratory disease, further reducing the need for high dose ICS/INS. Using this approach, physiological, biochemical, psychosocial, microbiological, and comorbidity traits are targeted with both pharmacological and non-pharmacological interventions[30].

Additionally, non-ICS-containing medications may also be used to improve disease control, *e.g.*, use of long-acting bronchodilators in asthma and COPD[2]. If ICS/INS are needed, dosing strategies such as intermittent dosing can be employed. For asthma, compared to regular ICS use, intermittent dosing with ICS-formoterol has proven to be as effective for prevention of exacerbations in patients with mild asthma, with reduced cumulative exposure to ICS[31]. Finally, de-escalation of high ICS/INS doses should be considered when following up patients with well-controlled disease. Apart from clinically directed de-escalation, biomarkers such as blood eosinophil count can guide clinicians when reducing ICS exposure in COPD[2]. Similarly, exhaled nitric oxide may guide clinicians when reducing ICS exposure in asthma[32].

Although not supported by specific studies, given the pharmacology of ICS, avoidance of strong CYP450 3A4 inhibitors (*e.g.*, clarithromycin, itraconazole, ketoconazole, voriconazole) can preserve the high first-pass metabolism and hepatic inactivation of swallowed ICS and INS. Furthermore, it will be prudent to avoid other causes of hyperglycemia and DM, such as regular, high-dose oral corticosteroids.

FUTURE DIRECTION

Some systemic absorption of ICS/INS is inevitable, and systemic effects would be proportional to the dose of delivered. Apart from dose, other potential risk factors require further elucidation. Nevertheless, even if risk factors have for susceptibility to ICS/INS-related DM are identified, it is unknown how patients who receive ICS or INS should be

Table 2 Studies showing worsening of glucose metabolism/diabetes mellitus by inhaled corticosteroid/intranasal corticosteroid

Ref.	Study design	Patient population	ICS or INS exposure	Outcomes reported
Ajmera *et al* [22], 2017	Retrospective study of Medicaid claims (2005-2008)	15287 adults with newly diagnosed COPD, who were diabetes free at baseline	Types and doses of ICS not stated	Over 1 yr, ICS use associated with greater risk of new-onset diabetes (adjusted OR = 1.23, 95%CI: 1.07-1.47)
Ben-Dov *et al* [17], 2023	Case report	9-mo-old female with type 1 DM	Off-label use of otic ciprofloxacin 0.3%/dexamethasone 0.1% drops in the nasal passage for choanal obstruction with granulation tissue	Over 7 d, average daily blood glucose increased by 86 mg/dL. Hyper-glycemic spikes resolved within 2 d after switching to mometasone furoate 0.05% spray
Faul *et al* [51], 1998	Case report	67-year-old asthmatic man	FP ICS 2000 mcg/d	Over 40 wk, patient developed glycosuria with rise of HbA1c to 8.2%. Glycosuria resolved and HbA1c fell to 7.0% with reduction of FP ICS to 500 mcg/d
Faul *et al* [52], 1999	Case report	67-year-old asthmatic man	BUD ICS 2000 mcg/d	Over 20 wk, patient developed glycosuria with rise of HbA1c to 8.2%. Glycosuria resolved and HbA1c fell to 7.2% with reduction of BUD ICS to 800 mcg/d
Gayle *et al* [23], 2019	Nested case-control study	220971 adults with COPD and previous smoking registered at a United Kingdom Clinical Practice Research Datalink practice (January 2010-December 2016)	Types and doses of ICS not stated	Increased incident DM (OR = 1.73, 95%CI: 1.65-1.82), adjusted for smoking status, deprivation, BMI, hypertension, coronary heart disease and heart failure
Kruszynska *et al*[53], 1987	Prospective observational study	9 normal adults aged 21-44 yr	BDP ICS 500 mcg twice daily	Over 4 wk, ICS use associated with increased peak blood glucose (7.1 *versus* 6.7 mmol/L, $P < 0.01$) after 75 g oral glucose load. No effect on fasting blood glucose or HbA1c
Lelii *et al* [54], 2016	Case report	2-year-old boy with recurrent wheezing	FP ICS 100 mcg twice daily for 2 mo before presentation with whining, agitation, and diuresis	Transient symptomatic hyperglycemia (10 mmol/L). FP ICS then replaced with montelukast
Lund *et al* [24], 2023	Case-only symmetry analysis of Danish national registries	348996 individuals > 40 yr with a first-ever prescription for any antidiabetic drug 1996-2018	Inhaled β2-agonists combined with glucocorticoids	Increased risk of incident diabetes (SR = 1.35, 95%CI: 1.28-1.42 and SR = 1.14, 95%CI: 1.06-1.22 in replicate analyses)
Metsälä *et al* [25], 2020	Nationwide, register-based case-cohort study	Children who were born January 1, 1995, through December 31, 2008, in Finland and diagnosed with type 1 DM by 2010 (n = 3342), compared with 10% random sample from each birth-year cohort (n = 80909)	Beclomethasone, BUD, fluticasone. Dose not stated	Over a median of 7.9 yr, increased risk of type 1 DM after adjusting for other anti-asthmatic drugs, asthma, sex, and birth decade (HR = 1.29, 95%CI: 1.09-1.52), if patients received high-dose ICS (> 800 mcg budesonide equivalent dose)
Mizrachi *et al* [16], 2012	Retrospective observational study	1768 DM patients treated with INS, with 245 patients providing HbA1c data and 163 patients providing fasting glucose data	BUD, FP, triamcinolone acetonide INS. Dose not stated	Over 3 mo, triamcinolone acetonide associated with increased fasting glucose but not with HbA1c. Other INS had no association with either glucose or HbA1c changes
Price *et al* [28], 2016	Matched cohort study	682 adults (≥ 40 years old) with COPD prescribed ICS in two large United Kingdom databases (1983-2016)	Types and doses of ICS not stated	Over 12-18 mo of follow-up, ICS prescription associated with increased HbA1c, with adjusted difference 0.16% (95%CI: 0.05%-0.27%) in all COPD patients, and 0.25% (95%CI: 0.10%-0.40%) in mild-to-moderate COPD patients. ICS prescription also associated with more diabetes-related general practice visits and more frequent glucose strip prescriptions. Associations were stronger for higher cumulative ICS doses (> 250 mg FP equivalent), compared to ≤ 125 mg
Price *et al* [26], 2019	Matched cohort study	18774 adults (≥ 40 years old) with COPD initiating ICS or long-acting bronchodilator in two large United Kingdom databases (1983-2016)	Types and doses of ICS not stated	Over a median follow-up at least 3.5 yr, ICS use associated with increased risk of incident DM (HR = 1.27, 95%CI: 1.07-1.50). ICS use also worsened DM control for high-dose ICS (mean daily dose ≥ 500 mcg FP equivalent)
Saeed *et al* [55], 2020	Cohort study using Danish health databases	50148 adults with COPD	Predominantly BUD (about 50%) and fluticasone (about 45%) ICS, at various doses. Other ICS (< 5%) used included beclomethasone, ciclesonide and	Over 7 yr, ICS use was associated with an increased risk of DM (HR = 1.16, 95%CI: 1.01-1.32) for high-dose ICS use (≥ 970 mcg BUD equivalent) and BMI < 30 kg/m^2

			mometasone	
Schou and Wolthers [15], 2011	Crossover RCT	17 children with asthma	BUD ICS 400 mcg daily for 1 wk	Over 1 wk, ICS use increased serum fructosamine compared to no ICS use (228.1 μmol/L *versus* 223.1 μmol/L, $P = 0.02$)
Slatore *et al* [48], 2009	Prospective cohort study	1698 adults with COPD, among United States veterans enrolled in 7 primary care clinics between February 1997 and December 1999	Various types (*e.g.*, beclomethasone, flunisolide, fluticasone) and doses of ICS	Over 2-4 yr, among diabetics only, there was a 1.82 mg/dL (95%CI: 0.49-3.15) increase in serum glucose, for every 100-mcg triamcinolone equivalent/d increase in ICS dose
Ställberg *et al* [29], 2020	Cohort study	7078 Swedish patients with COPD using data from real-world, primary care settings	Types and doses of ICS not stated	Over at least 6 mo, ICS use, especially at high dose (≥ 640 mcg/d BUD equivalent), was associated with incident type 2 DM
Suissa *et al* [27], 2010	Nested case-controlled study using a Canadian health insurance database	388584 patients with respiratory disease	Various types of ICS (beclomethasone, BUD, triamcinolone, fluticasone, flunisolide), at various doses	Over 5.5 yr of follow-up, 34% increased rate of initiation of an anti-diabetic agent, especially in patients receiving high dose ICS (≥ 1000 mcg/d FP equivalent). In diabetics on oral hypoglycemic agents, ICS use increased risk of progression to insulin

BMI: Body-mass index; BUD: Budesonide; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; OR: Odds ratio; FP: Fluticasone propionate; HR: Hazard ratio; ICS: Inhaled corticosteroid; INS: Intranasal corticosteroid; RCT: Randomized controlled trial; SR: Sequence ratio.

Table 3 Methods to reduce the impact of inhaled corticosteroid and intranasal corticosteroid on glucose metabolism and diabetes mellitus

Strategy	Methods
Minimize ICS doses	Use non-pharmacological measures (*e.g.*, trigger avoidance, smoking cessation, vaccination to avoid respiratory infections) to optimize disease control and reduce the need for high dose ICS[2]
	Manage comorbid conditions to optimize disease control (*e.g.*, management of obesity, OSA, heart failure, anxiety, depression) and reduce the need for high dose ICS. Consider using the "treatable traits" approach for holistic management of chronic respiratory diseases[30]
	Use long-acting bronchodilators to reduce the need for high dose ICS[2]
	Ensure good inhaler technique (or use valved holding chamber) to improve lung delivery and effectiveness of ICS, reducing the need for high dose ICS[2]
	Consider intermittent formoterol-ICS therapy rather than regular ICS for asthma[31]
	Actively step-down regular ICS dosing, including changing regular to intermittent ICS use, by clinical assessment[31]
	Actively step-down regular ICS dosing by measuring FENO in asthma[32]
	Actively step-down or step-off ICS if peripheral eosinophil count < 300/μL in well-controlled COPD[2]
Minimize INS doses	Use non-pharmacological measures (*e.g.*, trigger avoidance, smoking cessation, vaccination to avoid respiratory infections) to optimize disease control and reduce the need for high dose INS[56]
	Use non-steroidal medications like intranasal antihistamines to reduce the need for high dose INS[56]
	Ensure good intranasal delivery technique to improve effectiveness of INS, reducing the need for high dose INS
	Actively step-down regular INS dosing, including changing regular to intermittent INS use, following clinical assessment, *e.g.*, as-needed intranasal corticosteroids for seasonal allergic rhinitis[57]
Maintain hepatic inactivation of ICS and INS	Avoid strong CYP450 3A4 inhibitors like clarithromycin, itraconazole, ketoconazole, and voriconazole[3,9]
Minimize risk of hyperglycemia	Avoid long-term oral corticosteroids[18]
	Weight management for overweight and obese patients[58]
	Ensure good glycemic control for diabetic patients[58]

COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; FENO: Fractional exhaled nitric oxide; ICS: Inhaled corticosteroid; INS: Intranasal corticosteroid; OSA: Obstructive sleep apnea.

screened or monitored. Therefore, future studies need to address both risk factors for DM-related complications of ICS/INS as well as mitigation of DM-related risk. In addition, special populations such as pregnant women require more study[33].

Also, only two studies involving INS have been done to investigate its relationship with hyperglycemia[16,17]. Although the studies demonstrate an adverse association of INS with fasting glucose levels, a more chronic effect is not apparent given the lack of association with HbA1c level. More research for INS is therefore required. These studies need to be large enough to uncover small but significant associations, and long enough to identify chronic hyperglycemia leading to incident DM.

Efforts to disentangle the desired anti-inflammatory effects and diabetogenic consequences of glucocorticoids have led to the discovery of several candidate pharmacological compounds[11]. Selective glucocorticoid receptor agonists and selective glucocorticoid receptor modulators can preserve anti-inflammatory function and minimize induction of hyperglycemia. For instance, caesaldekarine is a promising plant-derived compound that has selective glucocorticoid receptor modulator-like properties[34]. Another approach is to enhance insulin signaling and mitigate hyperglycemia *via* 11β-hydroxysteroid dehydrogenase type 1 inhibition[35].

CONCLUSION

Overall, the association of ICS/INS with DM cannot be ignored, especially given multiple large observational studies demonstrating a positive association and dose-response. As ICS/INS are widely used, even a small individual effect of ICS/INS on DM would be clinically significant on a population basis. To avoid under-recognition of DM-related adverse events, these events should be deliberately collected and validated in future observational cohorts and randomized trials involving ICS/INS. Meanwhile, although ICS/INS are critical agents for control of chronic respiratory diseases, harm minimization should be undertaken by patients and high doses avoided whenever possible.

FOOTNOTES

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MINIREVIEWS

Diabetes mellitus as a consequence of acute severe pancreatitis: Unraveling the mystery

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Abstract

The occurrence of diabetes mellitus (DM) in pancreatitis is being increasingly recognized lately. Diabetes can develop not only with chronic pancreatitis but even after the first episode of acute pancreatitis (AP). The incidence of diabetes after AP varies from 18% to 23% in 3 years and reaches up to 40% over 5 years. The exact pathogenesis of diabetes after AP is poorly understood and various mechanisms proposed include loss of islet cell mass, AP-induced autoimmunity, and alterations in the insulin incretin axis. Risk factors associated with increased risk of diabetes includes male sex, recurrent attacks of pancreatitis, presence of pancreatic exocrine insufficiency and level of pancreatitic necrosis. Diagnosis of post-pancreatitis DM (PPDM) is often excluded. Treatment includes a trial of oral antidiabetic drugs in mild diabetes. Often, insulin is required in uncontrolled diabetes. Given the lack of awareness of this metabolic disorder after AP, this review will evaluate current information on epidemiology, risk factors, diagnosis and management of PPDM and identify the knowledge gaps.

Key Words: Post-pancreatitis diabetes; Diabetes of exogenous pancreas; Endocrine insufficiency; Acute pancreatitis; Post-pancreatitis diabetes mellitus

Core Tip: Diabetes mellitus (DM) due to diseases of the exocrine pancreas, diabetes of exocrine pancreas (DEP), is a common but underrecognized clinical entity. Post-pancreatitis DM (PPDM), which develop after pancreatitis, is classified as a subtype of DEP. The PPDM can develop even after acute pancreatitis; it is termed as post-acute pancreatitis DM. It differs in pathogenesis and natural history from type 1 and type 2 DM. There is a loss of pancreatic endocrine tissue, fibrosis and a component of autoimmunity. Both insulin deficiency and resistance play a role in this process. There are a number of knowledge gaps in diagnostic criteria, natural history and treatment options of PPDM.

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INTRODUCTION

Metabolic abnormalities in, during and after an episode of acute pancreatitis (AP) are frequent. Diabetes mellitus (DM) due to pancreatic diseases is a commonly seen disorder. Earlier, terminologies like 'pancreatic diabetes' or 'pancreatogenic diabetes' were used to describe diabetes after pancreatic diseases[1,2]. Subsequently, American Diabetes Association (ADA) gave the term 'type 3c diabetes' in 2002 which later was abandoned[3,4]. Recently, ADA come up with a unified nomenclature of diabetes of exocrine pancreas which include 3 subtypes: (1) Post-pancreatitis DM (PPDM); (2) Pancreatic cancer-related diabetes; and (3) Cystic fibrosis-related diabetes[5].

Until recently, it was considered that PPDM is associated with chronic pancreatitis only. In 2014, Das *et al*[6] reported in a systematic review that PPDM can develop in pancreatitis patients even after a single episode of AP, identified as post-AP DM (PPDM-A). Subsequently a number of high-quality population-based studies confirmed these findings[7,8]. Despite a number of available studies, PPDM-A remains an under-recognized entity for most physicians, gastroenterologists, surgeons, and endocrinologists. This review consists of diagnostic criteria, epidemiology, pathophysiology, natural course of DM related to AP. We also discuss the predictors, screening recommendations and management of the same.

SPECTRUM OF DYSGLYCEMIA IN PANCREATITIS

Often, an episode of AP is not limited to a single episode in a number of patients. A systematic review in 2015 looked at this aspect and found that recurrent AP developed in 21% of the patients within 1 year of the initial episode of AP[9]. Also, chronic pancreatitis developed in 36% of patients after recurrent AP. Dysglycemia can develop in any of these subtypes of pancreatitis. It has been suggested that pathophysiological mechanisms of diabetes are different in these extreme forms of pancreatitis. Since there are two main types of pancreatitis *i.e.*, AP and chronic pancreatitis, PPDM is also subdivided into two types: (1) PPDM-A; and (2) post-chronic pancreatitis DM[10].

Irrespective of the type of pancreatitis, dysglycemia could be a manifestation of stress hyperglycemia, unrecognized diabetes or new-onset diabetes after pancreatitis[5] (Figure 1). Stress hyperglycemia is defined as an elevated level of blood glucose, without elevated glycated hemoglobin A1c (HbA1c ≥ 6.5%), during the course of pancreatitis and/or within 3 mo after hospital admission in patients without a previous diagnosis of diabetes. This stress hyperglycemia is usually transient, and the elevated levels of blood glucose normalize during the follow up period.

Unrecognized diabetes can be unveiled during an episode of pancreatitis and is defined as elevated glycated HbA1c ≥ 6.5% above the diabetes diagnostic threshold, first detected during the course of pancreatitis and/or within 3 mo after hospital admission[5]. New onset diabetes after pancreatitis (NODAP) acknowledges the metabolic effect of acute or chronic pancreatitis on previously normal glucose homeostasis[5]. The NODAP excludes the diabetic patients diagnosed during the episodes of pancreatitis or up to 3 mo after hospital discharge. PPDM includes patients with diabetes in the setting of pancreatitis irrespective of the timing of diabetes onset (Figure 1). In this review, the DM developing after AP *i.e.*, PPDM-A was focused as a point of discussion.

DIAGNOSTIC CRITERIA OF PPDM-A

The diagnosis of PPDM should be suspected in all patients with a history of pancreatitis and fulfilling the diagnostic criteria for diabetes by the ADA. The diagnosis of PPDM is more of a diagnosis of exclusion, after excluding the more common stress hyperglycemia, type 1 and type 2 diabetes. The diagnosis of PPDM-A is made in patients with first or recurrent episodes of pancreatitis without clinical or imaging features of chronic pancreatitis. Petrov and Yadav[10]

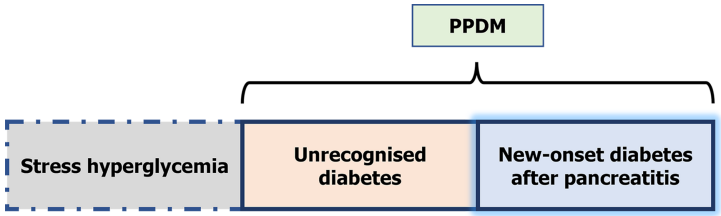

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Figure 1 Spectrum of dysglycemia in pancreatitis. PPDM: Post-pancreatitis diabetes mellitus.

proposed a stepwise and practical algorithm for diagnosing PPDM[10] (Figure 2).

EPIDEMIOLOGY

The global incidence of AP 34 cases/100000 of population based on pooled incidence[10,11]. Of these 6 cases/100000 will develop PPDM-A[10]. The course in AP can be mild, moderately severe, or severe which dictates duration of hospitalization and long-term sequelae. More than 80% of patients have a mild course with a hospitalization required for less than a week, while those with moderate to severe AP experience pancreatic necrosis and a protracted hospital course[12]. Long-term sequelae of AP include exocrine pancreatic insufficiency, complications related to pancreatic necrotic collections, and recurrent attacks of AP in up to 21% patients[13,14].

During hospitalization, hyperglycemia could be seen in up to 51% of patients during AP. Hyperglycemia in the early phase may arise from multiple mechanisms such as uncontrolled pre-existing DM, damage to endocrine pancreas or metabolic stress of critical illness[15]. Hyperglycemia is usually considered as a transient complication of AP. However, two recent meta-analyses have revealed the high incidence of AP related to DM observing that approximately 18%-23% patients of AP will develop DM within three years of discharge[6,16]. However, in longitudinal studies with more than five years of follow-up, the cumulative incidence rate of PPDM-A is up to 40%[16]. Moreover, the precise time of onset of pancreatic endocrine dysfunction cannot be determined. Some studies have demonstrated resolution while others have revealed persistence of endocrine dysfunction[7,17]. To summarize, post pancreatitis endocrine dysfunction is common, however it may be reversible in some cases.

PATHOPHYSIOLOGY

The exact mechanism of PPDM-A is poorly understood. However various mechanisms have been proposed which may lead to diabetes due to loss of islet cell mass, AP induced autoimmunity, alterations in insulin incretin axis and common risk factors. In patients with acute necrotizing pancreatitis, the loss of beta cell of islets of Langerhans leads to insulin deficiency resulting in DM. As a result of pancreatic necrosis, reduction or loss in the production and secretion of insulin as well as other islet hormones is expected. Since, a subset of patients with non-necrotizing AP also develop DM during short-term follow up, the pathophysiology of PPDM seems to be dependent on multiple factors other than immediate loss of islets secondary to necrosis of pancreatitis tissue[16]. It has been observed that the insulin requirements in PPDM-A are akin to type 1 diabetes. Hence, the role of autoimmunity is considered as an important factor in this process. In patients with type 1 diabetes, autoantibodies like glutamic acid decarboxylase (70%-80%), insulin associated antibodies, insulinoma associated autoantigen 2, zinc transporter, and/or tetraspanin 7 cause immune mediated beta cell destruction. There is a possibility that post-pancreatitis there could be immune activation, which though is less clearly defined, which destroys β-cells in pancreas. Some reports have also demonstrated generation of β-cell autoantibody in patients with PPDM-A[18]. However, no available study has evaluated the frequency of autoimmunity following an episode of AP.

The AP and type 2 DM share common risk factors like obesity and hypertriglyceridemia. These factors are independently associated with an increased risk for severe pancreatitis which may partly explain PPDM-A[19,20]. The prevalence of obesity is seen in 42% cases of PPDM-A while in type 2 diabetes obesity is seen in 48% cases supporting the evidence of obesity as a high risk for DM after an episode of AP[21]. Although similar data are not available for hypertriglyceridemia, these factors are likely to contribute towards the development of PPDM-A[22].

Pancreatic exocrine insufficiency may occur in up to 30% of the patients within three years of an episode of AP[23]. In such patients, the incretin-insulin axis is disrupted leading to insufficient incretin hormone production. This leads to reduce secretion of incretin hormones, glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1, and subsequently leads to PPDM-A[24].

NATURAL HISTORY

In the past, several studies ranging from single center studies to systematic reviews and meta-analyses, had looked at the

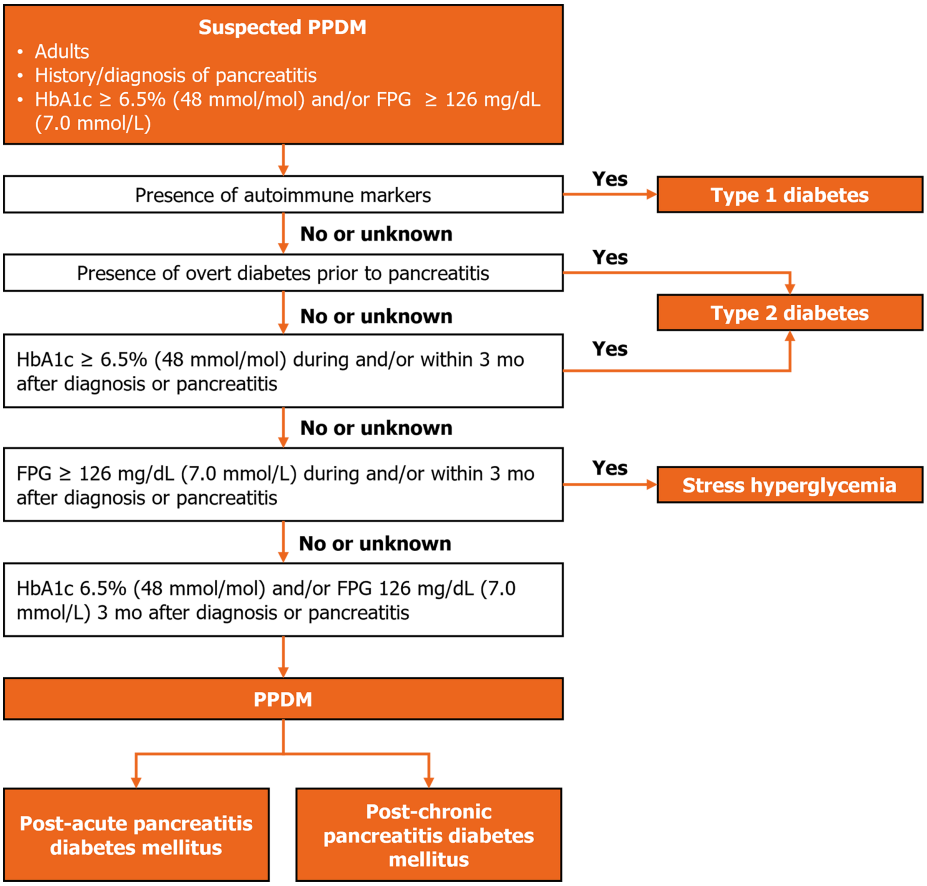

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Figure 2 Diagnostic algorithm to identify post-pancreatitis diabetes mellitus. PPDM: Post-pancreatitis diabetes mellitus; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c.

development of PPDM-A. A recent systematic review by Zhi *et al*[16] revealed that the incidence of new-onset DM post-AP on follow up was 23% overall. The authors also found that patients with severe pancreatitis had higher incidence of DM as compared to mild AP (39% *vs* 14%). In addition, they found that alcohol related pancreatitis had higher incidence of PPDM-A as compared to biliary pancreatitis (28% *vs* 12%). In a previous systematic review by Das *et al*[6] a similar incidence of PPDM-A was noted. It was also seen that the risk of diabetes increased two-fold at 5 years as compared to 12 mo, on follow up. A few studies have shown higher incidence ranging from 37% to 60.2%[7-10] while others have shown lower incidence, from 10.9% to 22.5%[7,17].

The etiology, severity and degree of pancreatic necrosis are considered important risk factors for development of PPDM-A[16]. In theory, it is believed that the extent of pancreatic necrosis determines the development of PPDM-A, even though some studies have found no association between post-pancreatitis diabetes and severity of pancreatitis[12,13,25-27]. These studies conjecture other mechanisms like autoimmunity and development of insulin resistance leading to PPDM-A. However, most studies have shown a strong association between severity of pancreatitis, extent of pancreatic necrosis and development of diabetes[16,25,27]. Vipperla *et al*[27] considered the risk of new-onset diabetes as determined by severity of AP. They derived the results from the general population and calculated the risk of new-onset diabetes after mild AP as 7%-15% and 30%-50% after severe or necrotizing pancreatitis over a period of 3 to 5 years[27]. The extent of necrosis and number of functionally active beta cells were considered major determinants for development of diabetes. Table 1 summarizes all the studies examined the endocrine insufficiency after AP episodes[8,17,25-60].

RISK FACTORS FOR DM AFTER AP

Sex difference

A population-based study from Taiwan confirmed higher risk of PPDM-A in both men and women. The risk was significantly more for males [adjusted hazard ratio (aHR) = 3.21; 95% confidence interval (CI): 2.59-3.98] compared to females (aHR = 1.58, 95%CI: 1.14-2.20)[8]. The COSMOS study also identified higher prevalence of PPDM-A in men (1.32 per 1000 general population) compared to women (0.93 per 1000 general population)[61]. Other population-based studies also demonstrated similar results with higher incidence of PPDM-A among men[62,63].

Table 1 Summaries all the studies examining endocrine insufficiency after episode of acute pancreatitis

Ref.	Study design	Number of patients evaluated for endocrine function	Severity of AP	Etiology of pancreatitis	Follow up period	Test to diagnose endocrine function	Pre-diabetic (%)	Diabetes (%)	Insulin treatment (%)	Comment
Ohlsén *et al*[28], 1968, Sweden	Prospective case control	23	-	-	Not stated	IV GTT, glucose infusion test	4 (17)	0 (0)	0 (0)	-
Johansen and Ornshlot[29], 1972, Denmark	Prospective cohort	22	-	Alcohol 4 (18%). Biliary 11 (50%). Others 3 (14%). Idiopathic 4 (18%)	24	OGTT	0 (0)	4 (18)	-	-
Olszewski *et al*[30], 1978, Poland	Prospective case control	25	-	-	12	OGTT, BI	-	7 (28)	-	-
Seligson *et al*[31], 1982, Sweden	Prospective cohort	9	All severe	-	63	OGTT	3 (33)	2 (22)	-	-
Angelini *et al*[32], 1984, Italy	Prospective cohort	19	All severe	-	25	OGTT	7 (36)	2 (10.5)	-	-
Eriksson *et al*[33], 1992, Finland	Prospective cohort	36	Mild: 16 (44%). Severe: 20 (56%)	Alcohol: 28 (78%). Biliary: 2 (6%). Post-ERCP: 2 (6%). Idiopathic: 4 (10%)	74	OGTT	4 (11)	19 (53)	9 (25)	Diabetes was more in surgical necrosectomy compared to conservative approach (100% *vs* 26%, $P = 0.0004$)
Doepel *et al*[34], 1993, Finland	Prospective cohort	37	All severe	Alcohol: 28 (76%). Biliary: 3 (8%). Post-ERCP: 2 (5%). Idiopathic: 4 (11%)	74	BG, C-peptide, HbA1, OGGT	-	20 (54)	9 (45)	Diabetes was more in surgical necrosectomy compared to no necrosectomy (100% *vs* 29.1%, $P < 0.005$). Diabetes was more common with alcohol related pancreatitis compared to other etiologies (64% *vs* 22%, $P < 0.05$)
Angelini *et al*[35], 1993, Italy	Prospective cohort	118	Mild: 35 (30%). Severe: 83 (70%)		53	OGTT	-	9 (8)	-	-
Appelros *et al*[36], 2001, Sweden	Prospective cohort	35	All severe	-	83	Questionnaire, BG, HbA1c	4 (11)	15 (43)	9 (26)	No difference in incidence of diabetes based on etiologies
Malecka-Panas *et al*[37], 2002, Poland	Prospective cohort	82	Mild: 54 (66%). Severe: 28 (34%)	-	56	OGTT, RIA insulin measurements	2 (2)	15 (16)	6 (7)	-
Ibars *et al*[17], 2002, Spain	Prospective cohort	55	Mild: 45 (71%). Severe AP 18 (24%)	-	1, 6 and 12	OGTT, arginine test	7 (13)	6 (11)	-	-
Halonen *et al*[38], 2003, Finland	Prospective cohort	145	All severe	Alcohol: 113 (78%). Others: 32 (22%)	66	Questionnaire	-	68 (47)	-	-
Boreham and	Prospective	23	Mild: 16 (70%).	-	3	FBG	-	4 (17)	1 (4)	-

Ammori[39], 2003, United Kingdom	cohort		Severe: 7 (30%)							
Szentkereszty *et al* [40], 2004, Hungary	Prospective cohort	22	All severe	-	38	Questionnaire	-	3 (14)	-	-
Sabater *et al*[41], 2004, Spain	Prospective cohort	27	All severe	-	12	Cardinal symptoms identification, 2 basal BG, OGTT in patients with lower BG	-	-	4 (15)	-
Hochman *et al*[42], 2006, Canada	Prospective cohort	25	All severe	Alcohol: 4 (16%). Biliary: 12 (48%). HTG: 2 (8%). Idiopathic: 7 (28%)	24 and 36	Questionnaire	-	8 (19)	5 (20)	-
Symersky *et al*[43], 2006, Netherland	Prospective cohort	34	Mild: 22 (65%). Severe: 12 (35%)	-	55	OGTT	-	-	3 (9)	Endocrine insufficiency develops independent of severity of AP
Kaya *et al*[44], 2007, Turkey	Prospective cohort	112	Mild: 136 (68%). Severe: 63 (32%)	-	12	OGTT	27 (24)	13 (21)	-	No association between endocrine insufficiency and necrosis or disease severity
Yasuda *et al*[45], 2008, Japan	Prospective cohort	41	All severe	-	56	FBG	-	16 (39)	4 (9)	No difference in etiology, presence of necrosis or alcohol intake among development of diabetes *vs* no diabetes
Pelli *et al*[46], 2009, Finland	Prospective cohort	46	Mild: 41 (76%). Severe: 13 (24%)	-	23 (median)	FBG, plasma HbA, OGTT	12 (20.1)	5 (10.8)	-	-
Gupta *et al*[47], 2009, India	Prospective cohort	30	All severe	Alcohol: 10 (33.3%). Biliary: 12 (40%). Alcohol + biliary 3 (10%). Idiopathic 5 (16.6%)	31	FBG, postprandial sugar level, OGTT, fasting serum C-peptide	6 (20)	6 (20)	6 (100)	No effect of etiology of pancreatitis on the incidence of endocrine insufficiency
Andersson *et al*[48], 2010, Sweden	Prospective cohort	39	Mild: 26 (65%). Severe: 14 (35%)	-	45	FBG, C-peptide, insulin, OGTT	13 (33)	9 (23)	-	-
Uomo *et al*[49], 2010, Italy	Prospective cohort	38	All severe	Alcohol 0 (0%). Others: 38 (100%)	179	FBG, OGTT	-	6 (16)	-	No relationship between extent of pancreatic necrosis and endocrine insufficiency
Wu *et al*[50], 2011 China	Prospective case control	59	Mild: 24 (41%). Severe: 35 (59%)	Gallstone 42 (71%). Hyperlipemia 7 (12%). Alcoholic 7 (12%). Idiopathic 3 (5%)	42	FBG, HbA1c, FBI, C-peptide. HOMA	14 (23.7)	5 (8)	-	Possible risk factors for endocrine dysfunction were pancreatic surgery, pancreatic necrosis, family history of diabetes, obesity, alcohol abuse, smoking and hyperlipidemia
Garip *et al*[51], 2013, Turkey	Retrospective cohort	96	-	-	32	OGTT	5 (5.2)	33 (43)	-	Severe disease and necrosis was associated with development of new onset diabetes
Vujasinovic *et al*[52], 2014, Slovenia	Retrospective cohort	100	Mild: 67 (67%). Moderate: 15 (15%). Severe: 18 (18%)	Alcohol: 42 (42%). Biliary: 36 (36%). Idiopathic: 12 (12%). Others: 10 (10%)	32	OGTT, HbA1c	-	14 (14)	-	Severe disease was associated with development of diabetes

Ho *et al*[53], 2015, Taiwan	Retrospective population-based database study	12284	Mild: 11519 (93.8%). Severe: 665 (6.2%)	Biliary: 6556 (53.3%). Alcohol 5728 (46.7%)	-	ICD-9-CM code for diabetes	-	618 (5)	-	Alcohol associated AP and ≥ 2 admissions for AP were predictors of new onset diabetes mellitus
Chandrasekaran *et al*[54], 2015, India	Prospective cohort study	35	All severe	Alcohol: 19. Gallstone: 11. Idiopathic: 5	26.6	OGTT	-	17 (48.5)	12 (34.3)	-
Winter Gasparoto *et al*[55], 2015	Retrospective cohort study	16	-	Biliary: 10 (62.5%). Alcohol: 4 (25.0%). HTG: 2 (12.5%)	34.8	OGTT, C-peptide, HOMA (homeostasis model assessment)	7 (43.7)	5 (31)	-	
Yuan *et al*[56], 2017, China	Retrospective cohort study	310	Mild: 261 (84.19). Moderate: 39 (12.58). Severe: 10 (3.23)	Biliary: 153 (49.35). Hyperlipidemia: 32 (10.32). Alcohol: 15 (4.84). Others: 110 (35.48)	-	FBG	34 (11)	35 (11.3)	-	Hyperlipidemia and fatty liver were predictors of abnormal FBG. Abnormal FBG was not different between alcohol and biliary pancreatitis
Lee *et al*[8], 2016, Taiwan	Retrospective population-based database study	3187	Mild: 2932 (92%). Severe: 255 (8%)	-	-	ICD-9-CM code for diabetes	-	324	-	-
Umapathy *et al*[57], 2016, United States	Retrospective cohort study	73	-	-	3 yr (median)			33 (45)		Risk of endocrine insufficiency was associated with extent of necrosis 2/3rd develop diabetes during index admission
Vipperla *et al*[27], 2016, United States	Retrospective cohort study	101	-	-	34.5	WHO criteria of OGTT	-	28 (28)	-	Risk of diabetes increased with severity of disease
Nikkola *et al*[58], 2017, Finland	Prospective cohort study	47	-	-	126	FBG, OGTT	13 (27.6)	7 (15)	7 (15)	Pancreatogenic diabetes develops in recurrent AP only
Tu *et al*[26], 2017, China	Prospective cohort study	113	Mild: 10 (8.8%). Moderate: 12 (10.6%). Severe: 91 (80.6%)	Alcohol: 3 (2.7%). Biliary: 65 (57.5%). Hyper TG: 39 (34.5%). Others 6 (5.3%)	42.9	FBG, OGTT	33 (29.2)	34 (30.1)	-	Extent of pancreatic necrosis > 50%, walled-off necrosis and insulin resistance were independent risk factors for new onset diabetes after AP
Tu *et al*[25], 2018, China	Prospective cohort study	256	Mild: 54 (21.1%). Moderate: 42 (16.4%). Severe: 160 (62.5%)	Alcohol: 7 (2.7%). Gallstone: 147 (57.5%). Hyperlipemia: 88 (34.5%). Others: 14 (5.3%)	42.9	FBG, OGTT	-	154 (60.2)	-	Incidence of pancreatic necrosis was higher in diabetics (64.7% and 53.0%, P = 0.06). Necrotic debridement (PCD or surgical necrosectomy) were higher in diabetes (66.3% *vs* 33.7%, P = 0.02)
Phillips *et al*[59], 2020, United States	Prospective cohort study	186	Mild: 120 (64.5%). Moderate: 40 (21.5%). Severe: 26 (14.0%)	Alcohol: 17 (9.1%). Biliary: 84 (45.2). Idiopathic 26 (16.1%). Post-ERCP 23 (12.4%). Other 17 (9.1%). Hyper TG 15 (8.1%)	12	Questionnaire	-	9 (4.8)	-	
Man *et al*[60], 2022, Romania	Prospective cohort study	329	Mild: 117 (35.6%). Moderate: 167 (50.8%). Severe: 45 (13.7%)	Alcohol: 87 (26.4%). Biliary: 217 (66.7%)	1, 3 and 12 mo	FBG, OGTT, HbA1c	-	29 (8.8)	-	Obesity and pancreatic necrosis > 50% were risk factors for new onset diabetes

AP: Acute pancreatitis; GTT: Gestational trophoblastic tumours; OGTT: Oral glucose tolerance test; BI: Blood insulin; ERCP: Endoscopic retrograde cholangiopancreatography; BG: Blood glucose; HbA1: Hemoglobin A1; HbA1c: Hemoglobin A1c; RIA: Radioimmunoassay; FBG: Fasting blood glucose; HTG: Hypertriglyceridemia; FBI: Fasting blood insulin; HOMA: Homeostatic model assessment; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; WHO: World Health Organization; TG: Triglycerides.

Age

The risk of PPDM-A is also age dependent, with increased risk of PPDM-A among younger population. A United Kingdom population-based study showed that individuals aged 30-39 [odds ratio (OR): 1.68; 95%CI: 1.20-2.35)] and 20-29 (OR = 4.25, 95%CI: 2.58-7.01) and a history of disease of exocrine pancreas had a higher risk of newly diagnosed diabetes compared with general population[62]. Individual with age group between 40-59 years has similar risk of developing PPDM and type 2 DM while those with age 60-79 years had increased risk of type 2 DM than PPDM. Bendor *et al*[61] in a population-based study also noted that individuals with age < 40 years and a history of AP had higher risk of developing DM [adjusted OR (aOR) = 4.65, 95%CI: 2.48-8.72) compared to the general population.

Recurrent attacks of AP

Evidence suggests that the probability of diabetes increases with the number of AP episodes. Lee *et al*[8] in a population-based study analyzed 12284 individuals with initial attack of AP. They found that two or more recurrent attacks of pancreatitis significantly increased the risk of PPDM-A (OR = 1.94, 95%CI: 1.48-2.40). Similarly, COSMOS study found that one recurrence of pancreatitis was not associated with the increased risk of PPDM-A (aHR = 0.93, 95%CI: 0.56-1.52) [61]. However, two (aHR = 1.9, 95%CI: 1.04-3.76) and more recurrences (aHR = 2.77, 95%CI: 1.34-5.72) were associated with significantly increased risk of PPDM-A.

Exocrine pancreatic dysfunction

A number of studies suggest that patients with DM have increased prevalence of exocrine pancreatic insufficiency. However, the reverse was not discovered until recently. Cho *et al*[64] in a national population-based study investigated patients of pancreatitis, both acute and chronic, without a history of both DM and exocrine pancreatic insufficiency. Study revealed that exocrine pancreatic dysfunction was associated with higher risk of PPDM-A (aHR = 2.51, 95%CI: 1.38-4.58). This association was independent of severity and etiology of AP.

Other factors

A number of other factors are shown to be associated with increased risk of PPDM-A. Deposition of intra-pancreatic fat after an episode of pancreatitis is a risk factor for PPDM, independent of obesity or visceral fat[65]. Yuan *et al*[56] identified the presence of hyperlipidemia and fatty liver as predictors of follow-up abnormal fasting blood sugar on Kaplan-Meier analysis with 2.52- and 1.87-fold increased risk, respectively, compared to absence of these conditions.

Etiology of pancreatitis as a risk factor for development of diabetes has been evaluated by a number of studies. Doepel *et al*[34] in a small study identified alcohol as the risk factor for the development of diabetes after severe pancreatitis. Subsequent population-based study by Ho *et al*[53] also found a similar association with alcohol oriented pancreatitis and risk of PPDM-A. Though a number of studies have not found such association with etiology of pancreatitis and risk of PPDM-A[56], a meta-analysis with meta-regression found no evidence to suggest a differential effect of alcohol or gallstone etiology on the risk of PPDM-A[6].

Severity of AP has long been considered as a risk factor of development of PPDM-A. Das *et al*[6] in a meta-analysis identified minimal effect of severity of pancreatitis on the development of PPDM-A. Subsequently, large population-based study by Lee *et al*[8] showed that risk of PPDM-A did not change significantly for mild (aHR = 2.10, 95%CI: 1.92-2.41) and severe disease (aHR = 2.22; 95%CI: 1.50-3.29). These findings were further confirmed in a large population-based study by Shen *et al*[7]. Though, severity of AP has no effect of PPDM-A, the amount of necrosis and requirement of surgical necrosectomy have been identified as predictors of PPDM-A in a number of studies[25-27].

CONCOMITANT ENDOCRINE AND EXOCRINE INSUFFICIENCY

Incidence of endocrine insufficiency varies from 4.8% to 60.2% after the initial episode of AP. Similarly, exocrine insufficiency develops in 0% to 35%[26,49]. Literature on the development of both exocrine and endocrine insufficiency after episodes of AP is limited. Ho *et al*[53] in a nationwide cohort study identified that 3% patients develop both exocrine and endocrine insufficiency after an initial episode of AP. The incidence of both exocrine and endocrine insufficiency was less than the individual endocrine (5%) or exocrine insufficiency (45.7%) after the first episode of AP. The study identified that alcohol-associated AP (OR = 1.804; 95%CI: 1.345-2.263; $P < 0.001$), and ≥ 2 readmissions for AP (OR = 3.190; 95%CI: 2.317-4.063; $P < 0.001$) were independent predictors for development of both exocrine and endocrine insufficiencies after AP. These risks were similar to the risk factors for development of individual endocrine or exocrine insufficiency[53].

Uomo *et al*[49] during long term follow up of AP patients managed non-surgically, found that exocrine insufficiency was temporary in patients with endocrine insufficiency. Huang *et al*[66] also found in the meta-analysis that exocrine insufficiency decreases from 62% to 35% during follow up after AP. These differences in incidences of exocrine insufficiency could be multifactorial and driven by the symptomatic nature, test used for screening, level of pancreatic necrosis during the episode of AP, pancreatic resection during necrosectomy *etc*.

Das *et al*[6] in a meta-analysis evaluated the concomitant development of exocrine and endocrine insufficiency after AP. The pooled prevalence of exocrine and endocrine insufficiency after AP was 29% and 43%, respectively. The prevalence of concomitant pancreatic exocrine insufficiency in newly developed prediabetes/DM was 40%. To summarize, the initial exocrine insufficiency after AP being transient recovers in a majority of patients and concomitant endocrine and exocrine insufficiency develops in 3%-17%.

BIDIRECTIONAL RELATIONSHIP BETWEEN AP AND DIABETES: DM AS A CAUSE OF AP

It is well established that AP can lead to DM, however the reverse is less well studied. Epidemiological studies have reported increased incidence of AP in patients with DM. A United States insurance claims database reported 2.83-fold increased risk of AP in diabetic cohort compared to non-diabetic counterpart[67]. In Taiwan, Lee *et al*[8] reported 1.95-fold higher incidence of AP in diabetics compared to non-diabetics. Same study also reported even higher HR in those who had a history of hyperglycemic episodes so there might be a severity-response relationship[8]. Another study from the United Kingdom reported 1.49-fold higher incidence of AP in patients with type 2 DM[68]. Proposed pathophysiology of increased incidence of AP in DM includes: (1) Chronic hyperglycemia leads to formation of reactive oxygen species, lipid peroxidation and may result in episodes of pancreatitis; (2) Association of comorbid risk factors like obesity, hypertriglyceridemia and gall stone disease which may independently precipitate pancreatitis; (3) Enhanced ryanodine receptor function leading to alteration in calcium metabolism; (4) Certain medications [dipeptidyl peptidase-4 (DPP-4) inhibitors] may enhance AP risk when used for the treatment[8].

Another study has reported structural changes in pancreas in patients with diabetes. Authors found reduced weight and volume of pancreas in patients with type 1 DM, when fibrosis without significant inflammation and ductal changes were observed in autopsy reports. Fecal elastase levels were low in these patients but there were no symptoms of pancreatitis. There were no significant changes in patients with type 2 DM. This study highlighted the complex interplay between exocrine and endocrine pancreas[69]. These studies suggest a bidirectional relationship between DM and AP. More studies are needed for a better understanding of this complex interplay between exocrine and endocrine pancreas.

MANAGEMENT OF PPDM-A

Screening for diabetes after AP

Currently there are no evidence-based guidelines for screening of diabetes after AP. Though diabetes can develop more frequently after necrotizing pancreatitis requiring necrosectomy, it can also develop even after an episode of mild pancreatitis. So, screening for diabetes should be done in every patient of AP even in the absence of robust risk factors for the development of the same.

One more dilemma is the timing and frequency of screening tests. A proposed approach is of frequent screening for the first year (HbA1c in 6 mo intervals) after hospital discharge. Subsequent, screening should be done on annual basis[70]. The rationale of frequent screening for the first year is based on the observation of new-onset of pre-diabetes or diabetes in 20% of the patient within 6 mo of an episode of AP[70]. However, further population-based studies regarding actual prevalence, time course of NODAP, cost and effectiveness of screening tests are needed for definite recommendation of screening in these patients.

Medical management

There are no evidence-based guidelines available regarding the treatment of PPDM-A in the absence of clinical trials. Current treatment is typically adapted using a similar paradigm as used in type 2 DM, however, PPDM-A is more difficult to control than type 2 DM. A large United Kingdom based study showed that mean HbA1c level was significantly higher at the time of diagnosis in patients with PPDM-A compared to type 2 DM (8.3% ± 2.4 % *vs* 7.9% ± 2%; $P = 0.002$)[62]. The difference of mean HbA1c level remained statistically significant at 1 year (7.1% ± 1.5 % *vs* 6.8% ± 1.2%, $P < 0.001$) and at 5 years (7.6 ± 1.7 *vs* 7.2 ± 1.4, $P < 0.001$) of follow-up. The proportion of patients with poor glycemic control (defined with HbA1c ≥ 7%) was higher at 1 year (aOR = 1.3) and at 5 years (aOR = 1.7) compared to type 2 DM. Same study also reported that a higher number of patients were on insulin therapy for glycemic control after 5 years of diagnosis in the PPDM-A group (20.1%) compared to type 2 DM (4.1%)[62]. In the absence of defined guidelines and prospective studies, metformin is most commonly used as a first line therapy in PPDM-A as in type 2 DM. Metformin is associated with reduced risk of hypoglycemia which is one of the main concerns in patients with PPDM-A[71].

Metformin is also associated with reduced risk of pancreatic neoplasia with anti-neoplastic properties. Even in patients with established pancreatic carcinoma, metformin is associated with better surgical and overall clinical outcomes[72-75]. As pancreatic carcinoma is also one of the dreaded long-term complications of chronic pancreatitis, these added benefits of metformin make its usually first line therapy in the management of PPDM. However, some gastro-intestinal side effects like nausea, diarrhea and weight loss might become more prominent in some patients with pancreatitis resulting in poor tolerability[71]. Incretins based therapy (glucagon like peptide 1 receptor agonists and DPP-4 inhibitors) have also been tried in PPDM-A, however, incretins can precipitate AP and they are more likely to be associated with gastro-intestinal side effects so preferably avoided in the treatment of PPDM-A[76,77]. Additional post-marketing surveillance studies are needed to confirm the safety of these medications in this setting.

Sulphonylureas are again not good choice because of poor beta cell reserve in PPDM-A. Thiazolidinediones are generally avoided given the risk of fluid overload, and risk of fracture, however this is an insulin sensitizing drug and can actually improve glycemic variability in patients on insulin injection[78]. Sodium-glucose cotransporter-2 inhibitors use in PPDM-A is limited due to the associated muscle/weight loss, which may be undesirable in already malnourished patients. In a nutshell, most oral antidiabetic drugs are recommended in mild PPDM-A with HbA1c < 8%. Despite the use of oral anti-diabetic agents, most patients require insulin at the onset or later, given the progressive nature of the disease. Insulin being an anabolic hormone, is associated with weight gain, a beneficial effect to combat malnutrition. Basal bolus regime, similar to being used in type 1 DM, are frequently used in PPDM-A according to pre-meal glucose levels and carbohydrate intake. Some patients require basal only, basal plus oral antidiabetic drugs or basal plus regimes. In the presence of associated alpha cell injury and blunted glucagon response to hypoglycemia, careful titration of insulin dose is required to prevent hypoglycemic episodes. Due to the complex issues in the management of hyper- and hypoglycemia in patients with PPDM-A, it is also called 'brittle diabetes'. Frequent blood glucose monitoring is the cornerstone of management.

Additionally, treatment of concurrent pancreatic exocrine dysfunction which can occur in up-to one third of patients as a sequel of AP, might also be associated with better glycemic control as shown in patients with chronic pancreatitis, by stimulating the incretin hormone response[79].

KNOWLEDGE GAPS AND FUTURE STUDIES

The pathophysiology of PPDM-A is incompletely understood. Currently the diagnosis of PPDM-A is mainly based on the chronological sequence of pancreatitis diagnosed before the onset of diabetes. Comparative studies of more common subtypes of diabetes like type 1 and type 2 diabetes are lacking. Large prospective epidemiological studies focusing on incidence, risk factors and natural history as well as studies focusing on tailored approaches for diagnosing, screening, preventive and treatment strategies are lacking. Studies with continuous glucose monitoring while using oral anti diabetic drugs and/or insulin can give insights into glycemic management in such patients. Randomized trials comparing insulin *vs* oral antidiabetic drugs in AP are warranted but may not be ethically viable.

To address these knowledge gaps, the National Institute of Diabetes and Digestive and Kidney Diseases of the United States recently formed a collaborative network referred as Type 1 Diabetes after Acute Pancreatitis Consortium. The objective of this consortium is to conduct large prospective observational studies to focus on pathophysiology, incidence, natural history and identification of risk factors. One such trial is Diabetes RElated to Acute Pancreatitis and its Mechanisms, NCT05197920. Animal models should also be developed to accurately replicate AP related diabetes, to better characterize the pathophysiology of the disease and provide a platform to investigate potential therapeutic interventions. Also, interdisciplinary and collaborative work is needed to address the screening, preventive and treatment approaches.

CONCLUSION

PPDM-A is increasingly being recognized as a long-term sequel of diseases of exocrine pancreas after the episodes of AP. This is a distinct clinical entity as mechanisms and natural history are different from type 1 and type 2 DM. As there is necrosis and fibrosis involving both the exocrine and endocrine pancreas; concomitant exocrine dysfunction is common. There is involvement of all the subtypes of islet cells of Langerhans which explains the brittle nature of diabetes. The

pathophysiology is poorly understood, large prospective cohort and animal studies are needed for better understanding. Also, interdisciplinary and collaborative work is needed to address screening, preventive and treatment approaches.

FOOTNOTES

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MINIREVIEWS

Advances in cardiovascular-related biomarkers to predict diabetic peripheral neuropathy

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Abstract

Diabetic peripheral neuropathy (DPN) is a common chronic complication of diabetes mellitus. One of the most common types is distal symmetric polyneuropathy, which begins as bilateral symmetry pain and hyperesthesia and gradually progresses into hypoesthesia with nerve fibre disorder and is frequently accompanied by depression and anxiety. Notably, more than half of patients with DPN can be asymptomatic, which tends to delay early detection. Furthermore, the study of adverse outcomes showed that DPN is a prominent risk factor for foot ulceration, gangrene and nontraumatic amputation, which decreases quality of life. Thus, it is essential to develop convenient diagnostic biomarkers with high sensitivity for screening and early intervention. It has been reported that there may be common pathways for microvascular and macrovascular complications of diabetes. The pathogenesis of both disorders involves vascular endothelial dysfunction. Emerging evidence indicates that traditional and novel cardiovascular-related biomarkers have the potential to characterize patients by subclinical disease status and improve risk prediction. Additionally, beyond traditional cardiovascular-related biomarkers, novel cardiovascular-related biomarkers have been linked to diabetes and its complications. In this review, we evaluate the association between major traditional and nontraditional car-diovascular-related biomarkers of DPN, such as cardiac troponin T, B-type natriuretic peptide, C-reactive protein, myeloperoxidase, and homocysteine, and assess the evidence for early risk factor-based management strategies to reduce the incidence and slow the progression of DPN.

Key Words: Diabetes; Diabetic peripheral neuropathy; Cardiovascular; Microangiopathy; Prediction; Biomarkers

Core Tip: Emerging evidence indicates that traditional and novel cardiovascular-related biomarkers have the potential to characterize patients by subclinical disease status and improve risk prediction. Additionally, beyond traditional cardiovascular-related biomarkers, novel cardiovascular-related biomarkers have been linked to diabetes and its complications. In this paper, we review the association between major traditional and nontraditional cardiovascular-related biomarkers and diabetic peripheral neuropathy (DPN) and assess the evidence for early risk factor-based management strategies to reduce the incidence and slow the progression of DPN.

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INTRODUCTION

Diabetes is one of the most severe and prevalent chronic diseases worldwide. The International Diabetes Federation estimates that approximately 536.6 million adults worldwide will have diabetes in 2021, and the number is predicted to increase to 783.2 million by 2045[1]. Diabetic neuropathy is a common chronic complication of diabetes mellitus. More than 50% of patients with diabetes will develop diabetic neuropathy during their disease course, 30%-40% of whom experience neuropathic pain symptoms, and the major neuropathy is diabetic peripheral neuropathy (DPN)[2]. A survey of patients with type 2 diabetes in 14 countries showed that the overall prevalence of DPN was 26.71%, indicating that more than a quarter of patients with type 2 diabetes in these 14 countries had DPN as a complication[3]. DPN can produce many symptoms, predominantly sensory impairment, which begins as bilateral symmetry pain and hyperesthesia and gradually progresses into hypoesthesia with nerve fibre disorder and is frequently accompanied by depression and anxiety. These symptoms typically start in the toes and feet and spread to the upper limbs. Studies of adverse outcomes show that DPN is the prominent risk factor for foot ulceration, gangrene and nontraumatic amputation, which diminishes quality of life[4]. Importantly, more than half of patients with DPN are asymptomatic[5]. Therefore, the early symptoms of the insidious disease are not easily detectable. Fortunately, early screening and intervention can effectively reduce the probability of amputation[6]. On the other hand, DPN imposes a physical and mental burden on patients and increases societal expenditure. According to statistics, the annual cost of treating DPN and its complications in the United States is estimated to be between 4.6 and 13.7 billion United States dollars, and DPN treatment accounts for 27% of total diabetes treatment expenditures each year[7]. DPN can suppress the immune function of the body[8], and this damage can also affect the neurological development of the next generation during pregnancy and induce congenital autism[9]. Therefore, it is essential to develop convenient diagnostic methods with high sensitivity.

Currently, the clinical diagnosis of DPN is based on the existence of signs and indications of peripheral nerve damage after excluding other causes of neuropathy[10]. Medical history, symptoms and physical examination can help doctors diagnose patients. When patients have atypical symptoms, electrophysiological examination can be used to assist in the diagnosis. Nerve conduction studies are the gold standard for the diagnosis of diabetic neuropathy. By measuring tactile and vibration sensations and proprioception, abnormally myelinated nerve fibres can be evaluated. Typically, this method is not suitable for small-fibre neuropathy[11]. A diagnosis of small-fibre neuropathy is made by measuring the intraepidermal nerve fibre density, but this test is invasive and is usually used for research purposes[12]. The other method used to diagnose small-fibre neuropathy is corneal confocal microscopy (CCM). CCM is used to diagnose DPN by observing corneal nerve fibres. Research has found that CCM data are related to a change in the severity of neuropathic pain and quality of life[13]. However, this method will also diagnose patients with other retinopathies. Moreover, this detection method requires professional personnel and equipment.

As an emerging diagnostic method, studies on biological markers of DPN have developed rapidly. Serum biomarkers can not only objectively reflect the pathological changes and pathogenesis of tissue cells but are also easy to detect, and have the capability of early prediction and high reproducibility[14]. Therefore, identifying serological markers for the early diagnosis of DPN is of great clinical significance. Although both the precise aetiology and pathogenesis of DPN are complex and not fully understood, DPN is mainly known to be associated with chronic hyperglycaemia, metabolic disorders (oxidative stress, lipid metabolism, increased end-products of advanced glycation, enhanced polyol and hexosamine pathways), the inflammatory response, and axonal degeneration[15]. The microvascular and macrovascular complications of diabetes may share common pathways. The increase in late glycosylation end products is a pathogenic mechanism of diabetes, which can damage endothelial cells and lead to endothelial dysfunction. Excessive production of reactive oxygen species (ROS) and NO can exacerbate oxidative stress and endothelial injury. Insulin resistance is a common phenomenon in diabetic patients that not only reduces the body's sensitivity to insulin but also inhibits the anti-inflammatory and antioxidant effects of insulin. All of these factors can induce microangiopathy and cardiovascular disease[16]. Studies have demonstrated that patients with microvascular disease (MVD) have a higher risk of developing cardiovascular-related disease than patients without MVD[17], such as those with diabetic polyneuropathy[18]. This suggests that the development of macrovascular and microvascular lesions in diabetes are closely related. In recent years, domestic and foreign scholars have explored whether cardiovascular-related biomarkers can predict diabetic microangiopathy.

Finding the delicate and precise biomarkers has been a top priority in order to reduce the negative effects and financial burden of DPN. Other excellent reviews have summarized markers of DPN. There are numerous biomarkers that can be utilized to diagnose DPN, such as inflammatory markers[19], nerve tissue damage factors[20], and oxidative stress markers[21]. Some researchers have used machine learning techniques combined with novel biomarkers to diagnose DPN, which can effectively improve the efficiency of physicians[22]. However, there is still no single marker that can be widely used for clinical diagnosis. Therefore, this is the first summary of cardiovascular-related markers that can be used to diagnose DPN (Table 1), such as cardiac troponin C and B-type natriuretic peptide (BNP)[23], and the underlying pathological mechanisms are briefly described in the review (Figure 1). We hope to provide a new direction for the clinical diagnosis of DPN to protect against this common and cruel disease.

MARKERS OF MYOCARDIAL INJURY

Troponin is a contractile protein present in the fine myofilaments of cardiac cells. It is composed of three subunits: cardiac troponin C, cardiac troponin I, and cardiac troponin T (cTnT). cTnT is found mainly in fine myofilaments. Troponin is a marker of myocardial injury. In general, patients with myocardial injury may have elevated troponin levels in their bodies[24]. It has been shown that increased troponin I levels can occur in obese mice with myocardial injury[25]. DPN is a microangiopathy, and a decrease in neural blood supply can result in the deterioration of axons and Schwann cells in DPN. Simultaneously, microvascular circulation disorders may partly affect the blood supply to the myocardium, leading to myocardial damage, and changes in coronary microcirculation can lead to coronary microvascular disfunction, affecting the levels of troponin in the body[26]. Jende *et al*[27] indirectly confirmed that microangiopathy contributes to nerve damage in type 2 diabetes and demonstrated the potential value of troponin as a marker of nerve damage in diabetic patients. A recent cross-sectional study showed that high-sensitivity cardiac troponin (hs-cTnT) is independently associated with peripheral neuropathy, regardless of diabetes mellitus diagnosis, and is a biomarker of end-organ injury, including peripheral neuropathy[28]. Therefore, when using hs-cTnT to screen DPN patients, other diseases that may cause peripheral neuropathy should be ruled out in advance. In conclusion, these studies showed that troponin could be a useful indicator for predicting the incidence of DPN, which needs to be confirmed in large-sample studies.

CARDIAC FUNCTION MARKERS

BNP is a natural hormone with biological activity synthesized by myocardial cells that is mainly secreted by the ventricle but also exists in brain tissue. BNP alters sodium excretion and vasodilation and inhibits sympathetic nerve activity. When left ventricular diastolic function is impaired, the myocardium rapidly synthesizes BNP and releases it into the blood to help regulate heart function. It is an essential indicator in the diagnosis of heart failure, patient management, and risk assessment of clinical events. Low BNP values can exclude the diagnosis of left ventricular heart failure. Multiple studies have shown that changes in BNP levels are associated with diabetic microvascular complications[29-31]. A cross-sectional study of patients with type 2 diabetes in China showed that circulating BNP levels were significantly increased in patients with neuropathy. Researchers found that BNP levels were positively correlated with vibration perception threshold values, suggesting that high BNP levels are a risk factor for DPN and that monitoring BNP levels can predict the risk of DPN. The best cut-off value for predicting DPN was a circulating BNP level of 15.18 pg/mL (sensitivity 78.7%, specificity 48.2%)[32].

N-terminal BNP (NT-proBNP) is the inactive N-terminal fragment of the BNP prohormone (proBNP) and is secreted mainly when the load of ventricular cells increases before and after division. BNP and NT-proBNP are essential markers in diagnosing acute and chronic heart failure. Studies have shown that the combination of NT-proBNP and its receptor can regulate blood pressure, blood volume, sodium balance, and glucose and fat metabolism. Natriuretic peptides bind to receptors located in adipose tissue to induce lipolysis in adipocytes, regulate fat distribution, and promote the absorption of more oxygen and glucose by adipose tissue[33,34]. Therefore, NT-proBNP can affect insulin and glucose metabolism in the body. A German study showed that the level of NT-proBNP is negatively correlated with the risk of type 2 diabetes. The correlation is more significant in female patients, and the higher the concentration of NT-proBNP is, the higher the risk of diabetes patients having large vessel and MVD. Therefore, NT-proBNP can be used as a biomarker to predict the risk of microvascular and macrovascular complications of diabetes[35].

CARDIOVASCULAR INFLAMMATORY MARKERS

C-reactive protein (CRP) is a nonspecific inflammatory marker produced by liver cells when the body is exposed to inflammatory stimulation, such as microbial infection or tissue damage. It can be used to identify bacterial and viral infections and assess the severity of infection. In addition, CRP is a marker of early myocardial injury that can be elevated within hours of the onset of myocardial damage. High-sensitivity CRP (hs-CRP) predicts the risk of cardiac events in asymptomatic populations and can assess the outcome of patients with acute coronary syndromes[36,37]. Chronic hyperglycaemia can induce vascular endothelial cell injury and an inflammatory response leading to DPN, while the inflammatory cytokines tumor necrosis factor-alpha and interleukin-6 can stimulate CRP synthesis *in vivo*[38]. Studies by Tang *et al*[39] showed that hs-CRP levels were significantly positively correlated with the occurrence of diabetic

Table 1 Biomarkers for diabetic neuropathy mentioned in this review

Biomarker candidate	Sample source	Quantitative method	Role in human body	Change	Ref.
hs-cTnT	Human serum/plasma	ECLI	A marker of myocardial injury	Increased	[27,28]
BNP/NT-proBNP	Human serum/plasma	CLIA	Exclude the diagnosis of left ventricular heart failure	Increased	[29-32,35]
hs-CRP	Human serum	ELISA/LEITA	A nonspecific inflammatory marker that can predict the early myocardial damage	Increased	[39-42]
MPO	Human serum	ELISA	An inflammatory factor in coronary artery disease	Increased	[47]
Hcy	Human plasma	FPIA/CLIA	Induction of vascular oxidative stress and endothelial cell damage	Increased	[51-53]

hs-cTnT: High-sensitivity cardiac troponin; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal B-type natriuretic peptide; hs-CRP: High-sensitivity C-reactive protein; MPO: Myeloperoxidase; Hcy: Homocysteine; ECLI: Electrochemiluminescence immunoassay; CLIA: Chemiluminescence analysis; ELISA: Enzyme-linked immunosorbent assay; LEITA: Latex-enhanced immunonephelometric assay; HPLC: High-performance liquid chromatography; FPIA: Fluorescence polarization immunoassay.

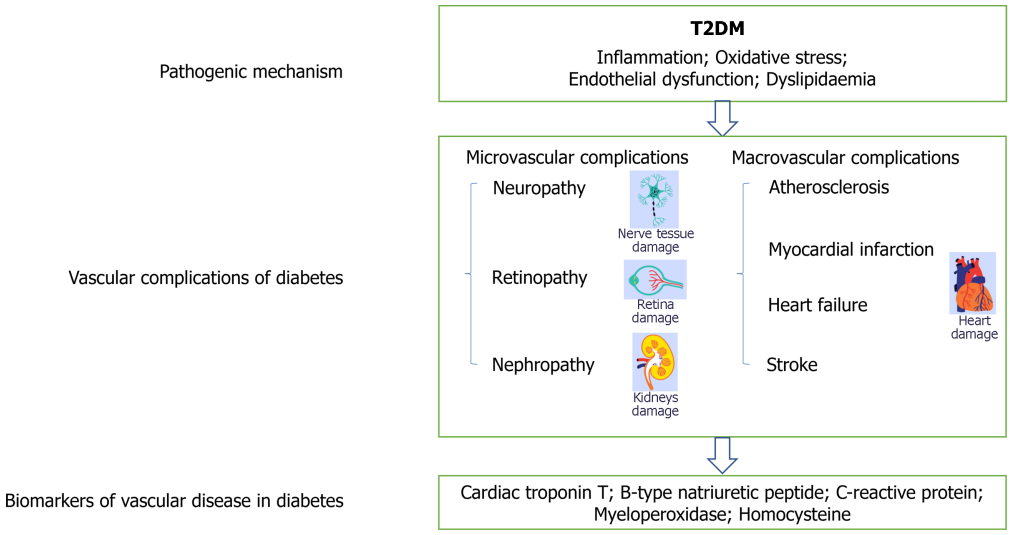

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Figure 1 A brief introduction to vascular-related complications of diabetes and their common diagnostic markers. Common pathogenic mechanisms for macrovascular and microvascular complications include inflammation, oxidative stress, abnormal lipid metabolism and endothelial dysfunction. Cardiac troponin T is a marker of impaired microvascular circulation, which can affect myocardial blood supply and vascular endothelial cell function, resulting in the release of large amounts of troponin in the blood. B-type natriuretic peptide regulates blood pressure, blood volume, sodium balance, and glucose and fat metabolism. C-reactive protein is a marker of early myocardial injury and nonspecific inflammation. Myeloperoxidase is involved in the regulation of inflammatory response and oxidative stress *in vivo* and can induce acute coronary syndrome. Homocysteine is a marker of impaired neurons and vascular endothelial cells that induces oxidative stress and excessive proliferation of vascular endothelial cells. T2DM: Type 2 diabetes mellitus. Image from FreePik.

nephropathy and can be used to predict and diagnose diabetic nephropathy in the clinic. Chuengsamarn *et al*[40] found that hs-CRP levels are correlated with the occurrence of chronic vascular complications of diabetes and can be used to predict the occurrence of diabetic microangiopathy. Another study found a positive correlation between hs-CRP levels and urinary albumin excretion, an indicator of diabetic nephropathy[41]. A prospective study has shown that baseline hs-CRP levels can predict the occurrence and improve the predictive efficacy of microvascular complications in type 2 diabetes[42]. In summary, these studies suggest that hs-CRP levels are associated with diabetic microvascular complications. In addition, hs-CRP levels have only been shown to be related to the development of diabetic nephropathy and diabetic retinopathy. However, the mechanisms of microvascular damage in the three diseases are similar, so it is reasonable to speculate that CRP is associated with the development of DPN. In the future, it is necessary to further explore the relationship between hs-CRP and DPN and determine whether hs-CRP can be used as a biomarker for diagnosing DPN.

Myeloperoxidase (MPO) is a haem protease secreted mainly by activated neutrophils and macrophages. Changes in MPO levels *in vivo* can reflect the activity and functional status of neutrophils. MPO not only kills microorganisms that

are phagocytosed by cells but also participates in regulating inflammatory responses. It is also an inflammatory factor in coronary artery disease, and a study showed that elevated plasma MPO levels are associated with inflammatory status in patients who suffer from acute heart attacks[43]. MPO can promote the formation of lesions in acute coronary syndrome and affect the stability of atherosclerotic plaques[44]. Additionally, it can be used to predict the risk of recent myocardial infarction in patients with coronary heart disease[45]. Moreover, MPO can catalyse hydrogen peroxide to produce ROS. When the balance of oxidants and antioxidants in the body is disrupted, oxidative stress can occur. Inflammation and oxidative stress are involved in the occurrence and development of DPN. Long-term hyperglycaemia can lead to increased nonenzymatic glycosylation end products and produce a large number of oxygen free radicals, thus aggravating oxidative stress and inflammation[46]. A prospective cohort study in Germany showed that a higher level of MPO was independently associated with DPN, suggesting that MPO may be involved in the occurrence of DPN and can be used as a biomarker[47]. However, the mechanism underlying MPO and its role in the development of DPN still needs further study. In addition, the specificity and sensitivity of MPO to diagnose DPN needs to be verified in more extensive cohort studies.

MARKERS OF CARDIOVASCULAR ENDOTHELIAL INJURY

Homocysteine (Hcy) is a sulfur-containing amino acid in the human body and an essential intermediate product in methionine and cysteine metabolism. Hcy content increases when metabolic disorders occur in the body, which makes it an important indicator to measure the health status of patients. Hcy has toxic effects on neurons and vascular endothelial cells. The underlying mechanism may be that Hcy can produce a large amount of oxygen free radicals, thus causing endothelial cell damage. Studies have shown that increased Hcy can induce vascular oxidative stress and mediate arterial inflammation and atherosclerosis[48]. Hcy can also interfere with glutathione synthesis by inhibiting the activity of glutathione peroxidase, disrupting the redox balance in the body and leading to excessive proliferation of vascular endothelial cells. In recent years, people have begun to explore the relationship between increased homocysteinemia and diabetic microangiopathy. The potential mechanism involved increased Hcy-induced oxidative stress and vascular endothelial growth factor (VEGF)[49,50]. Hcy can inhibit VEGF-induced vascular endothelial cell proliferation and migration. A Canadian study showed that diabetic patients with higher Hcy levels were more likely to develop diabetic neuropathy than those with lower Hcy levels. However, the potential influence of diet and lifestyle needs to be further clarified[51]. A cross-sectional study of patients with type 2 diabetes in China showed that plasma Hcy concentration was independently associated with the development of DPN and found that the threshold for distinguishing neuropathies by Hcy was lower than average[52]. González *et al*[53] found that plasma Hcy content was significantly correlated with the presence and degree of DPN and that the risk of DPN increased by 23% for every 1 μmol increase in plasma Hcy. In conclusion, several studies have shown that Hcy may be a promising biomarker for DPN. However, the elevation of Hcy can also occur in older adults with poor nutrition. Therefore, future studies need to verify the predictive value of Hcy and explore the best diagnostic thresholds in different age groups.

CONCLUSION

DPN can not only reduce the quality of life of patients but also cause disability and death in severe cases. Therefore, more sensitive diagnostic methods are needed. In recent years, many studies on DPN markers have emerged, and many DPN-related molecules have been found. In this review, biomarkers of cardiovascular-related DPN have been summarized, including cTnT, BNP, CRP, MPO, and Hcy. These results encourage further studies to identify the value of these biomarkers, thus improving the diagnostic efficacy of markers, achieving the goal of early diagnosis and early treatment, and improving patient prognosis. At present, although no single marker can be used for the accurate diagnosis and disease assessment of DPN, abnormalities in known markers in combination with traditional diagnostic methods for DPN can still direct clinicians to pay attention to high-risk groups as early as possible to achieve early diagnosis and early intervention. Computer simulation technology is widely used in medical research[54], not only to improve the efficiency of researchers but also to reduce costs. In recent years, many researchers have conducted preliminary studies using computer simulation techniques before conducting *in vivo* investigations[55]. Future studies will use machine learning technology to screen biomarkers in combination with artificial intelligence[56]. Currently, the treatment of DPN is limited to symptomatic treatment, and there is a lack of effective prevention and treatment measures. Exploring DPN-related markers can not only be used for the accurate diagnosis of DPN but also provide new ideas for treating DPN. Studying the pathogenesis of DPN and discovering related biomarkers will provide a new direction for diagnosing and treating DPN in the future.

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ORIGINAL ARTICLE

Basic Study

Potential role of microRNA-503 in Icariin-mediated prevention of high glucose-induced endoplasmic reticulum stress

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Abstract

BACKGROUND

Dysregulated microRNA (miRNA) is crucial in the progression of diabetic nephropathy (DN).

AIM

To investigate the potential molecular mechanism of Icariin (ICA) in regulating endoplasmic reticulum (ER) stress-mediated apoptosis in high glucose (HG)-induced primary rat kidney cells (PRKs), with emphasis on the role of miR-503 and sirtuin 4 (SIRT4) in this process.

METHODS

Single intraperitoneal injection of streptozotocin (65 mg/kg) in Sprague-Dawley rats induce DN in the *in vivo* hyperglycemic model. Glucose-treated PRKs were used as an *in vitro* HG model. An immunofluorescence assay identified isolated PRKs. Cell Counting Kit-8 and flow cytometry analyzed the effect of ICA treatment on cell viability and apoptosis, respectively. Real-time quantitative polymerase chain reaction and western blot analyzed the levels of ER stress-related proteins. Dual luciferase analysis of miR-503 binding to downstream SIRT4 was performed.

RESULTS

ICA treatment alleviated the upregulated miR-503 expression *in vivo* (DN) and *in vitro* (HG). Mechanistically, ICA reduced HG-induced miR-503 overexpression, thereby counteracting its function in downregulating SIRT4 levels. ICA regulated the miR-503/SIRT4 axis and subsequent ER stress to alleviate HG-induced PRKs injury.

CONCLUSION

ICA reduced HG-mediated inhibition of cell viability, promotion of apoptosis,

and ER stress in PRKs. These effects involved regulation of the miR-503/SIRT4 axis. These findings indicate the potential of ICA to treat DN, and implicate miR-503 as a viable target for therapeutic interventions in DN.

Key Words: Icariin; MicroRNA-503; Sirtuin 4; Endoplasmic reticulum stress; Diabetic nephropathy; Kidney damage

Core Tip: Icariin (ICA) has shown promise as a potential therapeutic agent for diabetes mellitus (DM) by regulating the miR-503-5p/sirtuin 4 (SIRT4) axis and subsequent endoplasmic reticulum (ER) stress. This study found that ICA treatment reduced high glucose-induced inhibition of cell viability, promotion of apoptosis, and ER stress in primary rat kidney cells. Mechanistically, ICA inhibited the upregulation of miR-503-5p and subsequently restored SIRT4 levels, thereby alleviating high glucose-induced injury in cells. These findings implicate ICA as a candidate drug for the treatment of DM and miR-503-5p as a potential therapeutic target for this disease.

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INTRODUCTION

Elevated blood glucose levels are a defining feature of diabetes mellitus (DM), one of the most prevalent chronic illnesses [1]. Over the last few decades, the incidence of diabetic nephropathy (DN) due to DM has risen in tandem with the growing number of individuals diagnosed with diabetes[2,3]. DN has become a threat to public health security[4,5]. However, the pathogenesis of DN is still unclear. Some studies have reported that endoplasmic reticulum (ER) stress may be a major factor in the development of DN[6]. The reason is that many properties of DN, such as hyperglycemia, proteinuria, advanced glycosylation end products, and increased free fatty acids, can trigger unfolded protein responses in kidney cells[7].

Traditional Chinese medicine (TCM) and its bioactive ingredients have been used in cancer treatment, with multi-target pharmacological effects and few side effects[8]. As a traditional TCM, Icariin (ICA) has been proven by many recent studies to have a good therapeutic effect on DN. For example, Ding *et al*[9] showed that ICA can protect podocytes from streptozotocin (STZ)-induced damage by inhibiting the inflammasome[9]. Zang *et al*[10] described that ICA mitigates the adverse impact of hyperglycemia on renal tubular epithelial cells by regulating the miR-122-5p/forkhead box P2 axis[10].

As an important member of the non-coding RNA family, microRNAs (miRNAs) play important roles in various biological processes, and their multiple regulatory mechanisms in DN have attracted increasing attention[11,12]. As two examples, the enhanced expression of miR-133b can attenuate the degree of renal fibrosis, thereby inhibiting the development of DN[13], and the inhibition of miR-503 expression can improve the renal tissue injury caused by DN[14]. By binding to the 3′ untranslated region (UTR) of downstream targets and suppressing their transcriptional activity and translation, miRNAs contribute to the regulation of cellular functions and can disrupt the onset and progression of DN [15,16]. Studies have shown that miR-503 targeting E2F transcription factor 3 causes podocyte injury[17], and miR-195 targeting Toll-like receptor 4 alleviates symptoms in DN rats[18].

The current investigation established a DM cell model induced by elevated glucose [high glucose (HG)] to investigate the mechanism and impact of ICA on DM, with a focus on regulating the miR-503/sirtuin 4 (SIRT4) axis.

MATERIALS AND METHODS

Animals

Twelve specific pathogen-free, 10-week-old, female Sprague-Dawley rats weighing 180-200 g were procured from the Laboratory Animal Center at Guangzhou University of Chinese Medicine (Guangzhou, China). The rats were randomly divided into two groups: Control (n = 6) and DM (n = 6). The DM group of rats were fasted for 12 h and then each received a single intraperitoneal injection of STZ (55 mg/kg). Blood samples were collected from the tail vein 72 h later, and a fasting blood glucose level of > 16.7 mmol/L for 3 consecutive days confirmed the establishment of DM. The STZ-induced hyperglycemic rats were observed for an additional 4 wk to allow the development of DN-related changes. All rats were kept in a polystyrene cage with ad libitum access to standard rat food and water, in a room with a 12-h light/dark cycle and humidity maintained at 50% ± 5%. At the end of the experiment, the rats were euthanized with an intraperitoneal injection of sodium pentobarbital (200 mg/kg body weight). The animal experiments were approved by the Animal Care and Use Committee of Guangzhou University of TCM (approval No. GZTCMF1-2022053) and were

Table 1 Sequences of miR-503 mimic/inhibitor

miRNA	Sequence (5'-3')
miR-503 mimic	TAGCAGCGGGAACAGTACTGCAG
miR-503 mimic NC	GACAGAGACACGAGCGGCTGTAT
miR-503 inhibitor	CTGCAGTACTGTTCCCGCTGCTA
miR-503 inhibitor NC	TAGTAACCGTCTTTCCCCTGGGC

miRNA/miR: microRNA.

performed in accordance with the National Institutes of Health guidelines.

High-throughput sequencing

Rat kidney tissue was harvested under aseptic conditions, ground into powder under liquid nitrogen and dissolved in TRIZOL reagent (Invitrogen, Thermo Fisher Scientific, Inc., Waltham, MA, United States). The initial total RNA was quantified with Qubit RNA Assay Kit (Invitrogen). The Epicentre Ribo-Zero™ Magnetic Kit (Illumina, San Diego, CA, United States) was used to separate and remove ribosomal RNA from total RNA, to ensure extraction with an RNA integrity number ≥ 7 and a ratio of 28 s to 18 s RNA ≥ 1.5:1. First and second strand cDNAs were synthesized, and 45 μL AMPure XP Beads were used for polymerase chain reaction (PCR) amplification. The final complete transcriptome library was prepared and computer-tested by Beijing Boao JingDian Biotechnology Co., Ltd. (Beijing, China). The sequencing results were analyzed, and differentially expressed genes were identified based on a $|\log_2(\text{fold-change, FC})| \geq 1.0$ and a P value ≤ 0.05.

Isolation and culture of primary rat kidney cells

The isolation and culture of primary rat kidney cells (PRKs) were performed carried out following an established protocol [19]. Kidneys were obtained from additional 10-week-old healthy Sprague-Dawley rats (n = 3). The renal cortex of the extracted tissue was sectioned into tissue fragments of approximately 1 mm^3 and digested with collagenase type I (Gibco, Thermo Fisher Scientific, Inc., Waltham, MA, United States). Cells were isolated by density gradient centrifugation using Ficoll (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) and incubated in 37 °C. The collected PRKs were cultured in DMEM/F-12 supplemented with 10% fetal bovine serum, antibiotics, and growth factors in a humidified incubator at 37 °C in an atmosphere of 5% CO_2. The culture medium was changed every other day, and the cells were passaged when they reached approximately 80% confluence. The PRKs used in this study were not used beyond the third passage to maintain their primary cell characteristics.

Immunofluorescence identification of PRKs

As previously described[20], PRKs were incubated with antibodies to α-smooth muscle actin (α-SMA; 1:250 dilution; ab124964, Abcam, Cambridge United Kingdom) and vimentin (1:300 dilution; ab45939, Abcam) for 12 h at 4 °C, followed by a 1 h treatment at 37 °C with antibodies labeled with Alexa Fluor® 488 (1:250 dilution; ab150077, Abcam) or 647 (1:150 dilution; 150075, Abcam). Finally, PRKs were stained for 5 min at 20 °C with 4',6-diamidino-2-phenylindole (0.5 μg/mL; Beyotime, Shanghai, China). Images were captured (magnification × 400) using a model BX53 fluorescence microscope (Olympus, Tokyo, Japan).

Cell transfection and HG and ICA treatments

MiR-503 mimics/inhibitors and overexpression (ov) SIRT4 plasmids were transfected into PRKs for 4 h using Lipofectamine® 3000 (Invitrogen). GenePharma Biotechnology Co., Ltd. (Shanghai, China) synthesized the aforementioned RNAs. The sequences of miR-503 mimics/inhibitors are listed in Table 1. For HG treatment, PRKs were exposed to 5.5 mmol/L glucose (Sigma-Aldrich) as the control or 25 mmol/L glucose (HG) for 24 h to simulate cell growth in either normal or DM conditions, respectively, as previously described[21,22]. According to previous studies, ICA was used in HG treatment at doses of 10 μM (low, L), 25 μM (medium, M), and 50 μM (high, H)[23,24]. Treatment of PRKs with HG or ICA was performed 48 h after cell transfection.

Cell viability assay

PRKs were cultured for 24 h at a density of 5 × 10^3 cells/well in 96 well plates. The cell viability rate was evaluated using Cell Counting Kit-8 reagent (Beyotime, Shanghai, China) at 37 °C for 1 h. The reagent was added at 0 and 24 h as per the manufacturer's instructions. The determinations were done by measuring absorbance at 450 nm.

Real-time quantitative PCR assay

Total RNA was extracted from kidney tissues or PRKs using TRIzol reagent. After centrifugation at 12000 ×g at 4 °C for 10 min in a model JIDI-17RS high speed refrigerated centrifuge (Guangzhou JiDi Instrument Co., Ltd., Guangzhou, China), RNA were reverse-transcribed to cDNA and analysis using One Step SYBR Green real-time quantitative PCR (RT-qPCR) Kit (Biomarker, Beijing, China). The conditions used were 95 °C for 1 min followed by 40 cycles of 95 °C for 5 s and

Table 2 Reverse transcription-quantitative polymerase chain reaction primers

Primer	Sequence (5'-3')
miR-151-3p-F	ACACTCCAGCTGGGCUAGACUGAGGCUCC
miR-151-3p-R	CTCAACTGGTGTCGTGGA
miR-19b-3p-F	ACACTCCAGCTGGGUGUGCAAAUCCAUGCAA
miR-19b-3p-R	CTCAACTGGTGTCGTGGA
miR-106b-5p-F	ACACTCCAGCTGGGUAAAGUGCUGACAGU
miR-106b-5p-R	CTCAACTGGTGTCGTGGA
miR-30e-5p-F	ACACTCCAGCTGGGUGUAAACAUCCUUGAC
miR-30e-5p-R	CTCAACTGGTGTCGTGGA
miR-122-5p-F	ACACTCCAGCTGGGUGGAGUGUGACAAUGG
miR-122-5p-R	CTCAACTGGTGTCGTGGA
miR-29a-3p-F	ACACTCCAGCTGGGUAGCACCAUCUGAAAU
miR-29a-3p-R	CTCAACTGGTGTCGTGGA
miR-29c-3p-F	ACACTCCAGCTGGGUAGCACCAUUUGAAAU
miR-29c-3p-R	CTCAACTGGTGTCGTGGA
miR-497-5p-F	ACACTCCAGCTGGGCAGCAGCACACUGUGG
miR-497-5p-R	CTCAACTGGTGTCGTGGA
miR-101a-3p-F	ACACTCCAGCTGGGUACAGUACUGUGAUA
miR-101a-3p-R	CTCAACTGGTGTCGTGGA
miR-741-3p-F	ACACTCCAGCTGGGAAAGAUGCCACGCUAU
miR-741-3p-R	CTCAACTGGTGTCGTGGA
miR-503-F	ACACTCCAGCTGGGTAGCAGCGGGAACAGTA
miR-503-R	CTCAACTGGTGTCGTGGA
miR-671-F	ACACTCCAGCTGGGUCCGGUUCUCAGGGC
miR-671-R	CTCAACTGGTGTCGTGGA
U6-F	CTCGCTTCGGCAGCACA
U6-R	AACGCTTCACGAATTTGCGT
SIRT4-F	TCCTGGGAGTGGACAGAATGA
SIRT4-R	CTGTGGATCCATGGGAACGC
Caspase 12-F	TGCCAATTCCGACAAACAGC
Caspase 12-R	CTGGATTCCCTGAGGAACTGT
GRP78-F	AACCCAGATGAGGCTGTAGCA
GRP78-R	ACATCAAGCAGAACCAGGTCAC
CHOP-F	CCAGCAGAGGTCACAAGCAC
CHOP-R	CGCACTGACCACTCTGTTTC
β-actin-F	CACCCGCGAGTACAACCTTC
β-actin-R	CCCATACCCACCATCACACC

F: Forward; R: Reverse; miRNA/miR: microRNA; SIRT4: Sirtuin 4; CHOP: C/EBP-homologous protein; GRP78: Glucose regulated protein 78.

62 °C for 30 s. Sequences of the primer pairs used for amplification are shown in Table 2. SIRT4 or miR-503 levels were normalized to *β-actin* or U6, and determined using the $2^{-\Delta\Delta Ct}$ method[25].

Table 3 Detection of 12 differentially expressed miRNAs between diabetes mellitus rats and normal rats by miRNA sequencing

miRNA_id	Log_2 FC	*P* value
rno-miR-151-3p	> 1.0	< 0.001
rno-miR-19b-3p	< -1.0	< 0.001
rno-miR-106b-5p	< -1.0	< 0.001
rno-miR-30e-5p	< -1.0	< 0.001
rno-miR-122-5p	> 1.0	< 0.001
rno-miR-29a-3p	< -1.0	< 0.001
rno-miR-29c-3p	< -1.0	< 0.001
rno-miR-497-5p	< -1.0	< 0.001
rno-miR-101a-3p	< -1.0	< 0.001
rno-miR-741-3p	> 1.0	< 0.001
rno-miR-503	< -1.0	< 0.001
rno-miR-671	> 1.0	< 0.001

miRNA/miR: microRNA; FC: Fold-change.

Flow cytometry analysis of apoptosis

Annexin V-fluorescein isothiocyanate (BD Biosciences, Santa Clara, CA, United States) and propidium iodide (BD) were incubated with PRKs (5×10^4 cells/mL) in the dark for 12 min at 25 °C, then analyzed with FACSAria™ Fusion using FACSDiva software (BD).

Western blotting

Denatured proteins extracted from PRKs were resolved by 10% SDS-PAGE (Beyotime). The resolved protein bands were subsequently transferred onto PVDF membranes. The membranes were incubated for 12 h at 4 °C with primary antibodies to SIRT4 (1:800 dilution; ab231137, Abcam), caspase 12 (1:800 dilution; ab62484, Abcam), C/EBP-homologous protein (CHOP; 1:1200 dilution, #5554; Cell Signaling Technology, Beverly, MA, United States), glucose regulated protein 78 (GRP78; 1:1000 dilution; ab108615, Abcam), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH, 1:2000 dilution; ab8245, Abcam). The membranes were then incubated with goat anti-rabbit antibody (1:12000 dilution; ab205718, Abcam) for 2 h at 25 °C. Immunoreactive bands were detected using an ECL system (Millipore, Temecula, CA, United States).

Dual luciferase assay

The 3′-UTR fragments of SIRT4 were amplified and cloned into the psi-CHECK-2 Luciferase reporter vector (Promega Corporation, Madison, WI, United States). PRKs were then transfected with miR-503 mimic/mimic NC and the psi-CHECK-2 containing either the wild type or mutant (Mut) of SIRT4 using Lipofectamine® 2000 (Invitrogen) as per the manufacturer's instructions. After 48 h, luciferase activity was measured using the Dual-Luciferase Reporter Assay System (Promega Corporation).

Statistical analyses

The data are expressed as mean ± SD of triplicate measurements. Statistical analysis was conducted by one-way analysis of variance followed by Bonferroni post hoc tests. Independent two-group comparisons were analyzed using the Student's t-test. The significance level was set at $P < 0.05$.

RESULTS

Differentially expressed miRNAs that affect DM progression

Sequencing of kidney tissues from normal and DM model rats revealed that 754 miRNAs were expressed. Among them, 12 miRNAs were differentially expressed (Figure 1A and Table 3). RT-qPCR results revealed that compared with normal rats, miR-106b-5p, miR-122-5p and miR-503 were significantly upregulated, miR-151-3p, miR-19b-3p, miR-30e-5p, miR-29a/c-3p, miR-497-5p and miR-671 were significantly downregulated, and miR-101a-3p and miR-741-3p was not significantly different in DM rats (Figure 1B-M).

Effect of ICA treatment on HG treatment

Isolated PRKs were subjected to immunofluorescence (IF) staining for vimentin and α-SMA. Fluorescence microscopy of

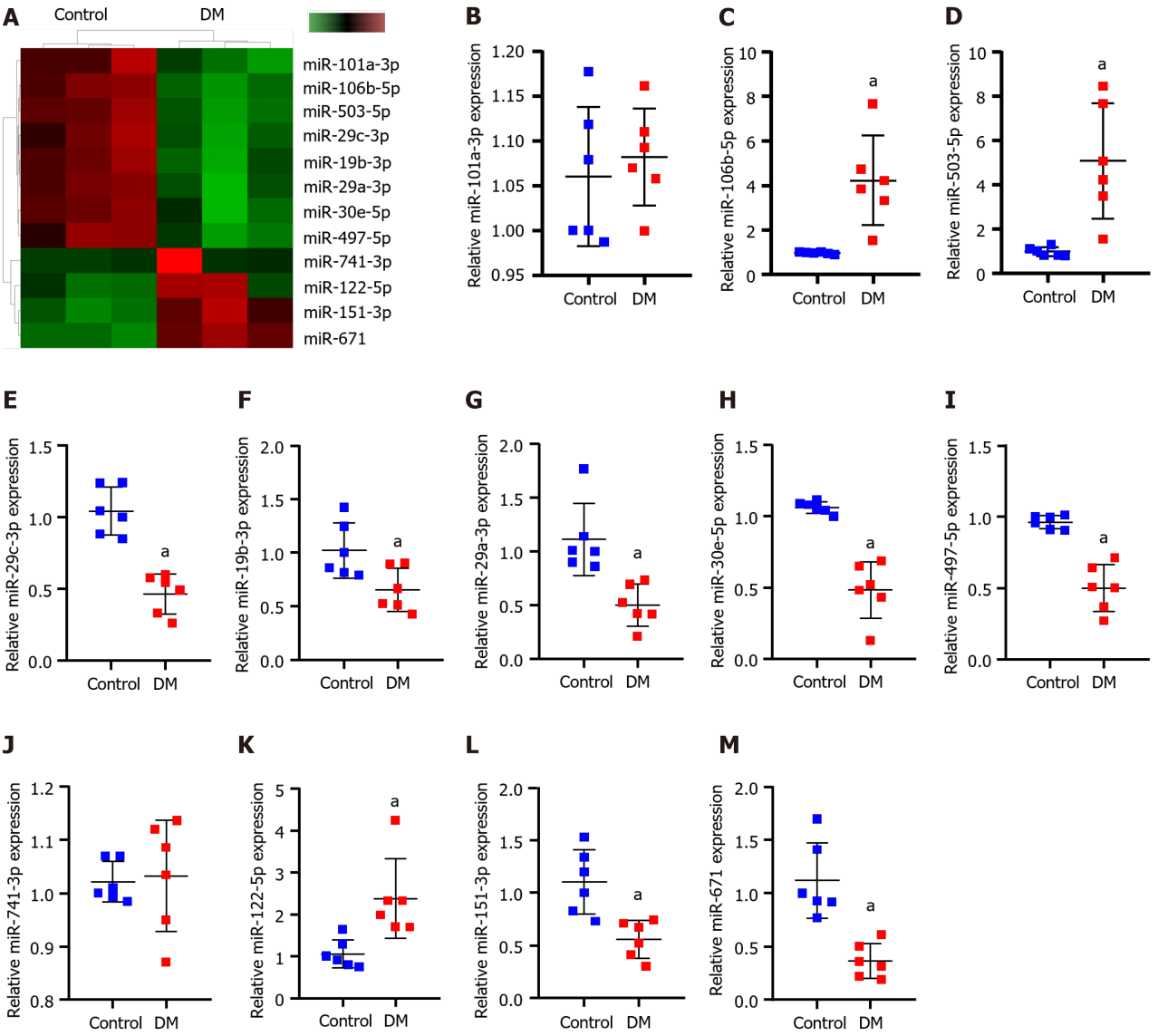

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Figure 1 Differentially expressed miRNAs that affect diabetic nephropathy progression. A: High-throughput sequencing analysis of the differences between the diabetes mellitus rats and normal rats concerning expressed miRNAs. In the heatmap, green squares indicate low expression and red squares indicate high expression; B-M: Real-time quantitative polymerase chain reaction verification of differentially expressed miR-151-3p, miR-19b-3p (B), miR-106b-5p (C), miR-30e-5p (D), miR-122-5p (E), miR-29a-3p (F), miR-29c-3p (G), miR-497-5p (H), miR-101a-3p (I), miR-741-3p (J), miR-503 (K), miR-671 (L), obtained by high-throughput sequencing (M). $^{a}P < 0.05$ *vs* the control group. DM: Diabetes mellitus; miR: microRNA; RT-qPCR: Real-time quantitative polymerase chain reaction.

these samples revealed the high expression of both vimentin and α-SMA in the PRKs (Figure 2A), indicating that the PRKs used in this study were effective. In vitro, the expression of miRNAs in the HG-induced cell model was consistent with the *in vivo* results (Figure 2B). Among the miRNAs, miR-503 had the highest expression *in vivo* and in vitro, and was explored as a potential therapeutic target for DM. Furthermore, the expression (Figure 2C) and protein levels (Figure 2D) of ER stress associated factors caspase 12, CHOP, and GRP78 were significantly upregulated in HG-induced PRKs. The expression of miR-503 upregulated by HG was decreased in PRKs after the addition of ICA; the effect of high doses of ICA was most obvious (Figure 2E). In addition, the high expression and protein levels of HG-induced caspase 12, CHOP, and GRP78 progressively decreased in the low, medium, and high doses of ICA (Figure 2F and G). Thus, miR-503 may be a therapeutic target for DM. The effects of HG-induced reduction in PRKs cell viability (Figure 2H) and increased apoptosis (Figure 2I) were reversed by ICA. Notably, low, medium, and high doses of ICA did not significantly change the activity of normal PRKs (Figure 2J). Therefore, ICA at a dose of 50 μM was used as the therapeutic dose in subsequent molecular mechanism experiments.

ICA ameliorates HG-induced cell injury by reducing miR-503

The synthesized miR-503 mimic/inhibitor was transfected into PRKs. The results showed that miR-503 was upregulated in the miR-503 mimic transfection group and downregulated in the miR-503 inhibitor transfection group (Figure 3A). These results confirmed the efficacy of the synthesized miR-503 mimic/inhibitor. The effect of HG-induced promotion of miR-503 expression was enhanced by mimic and reversed by inhibitor. However, ICA treatment inhibited the effect of

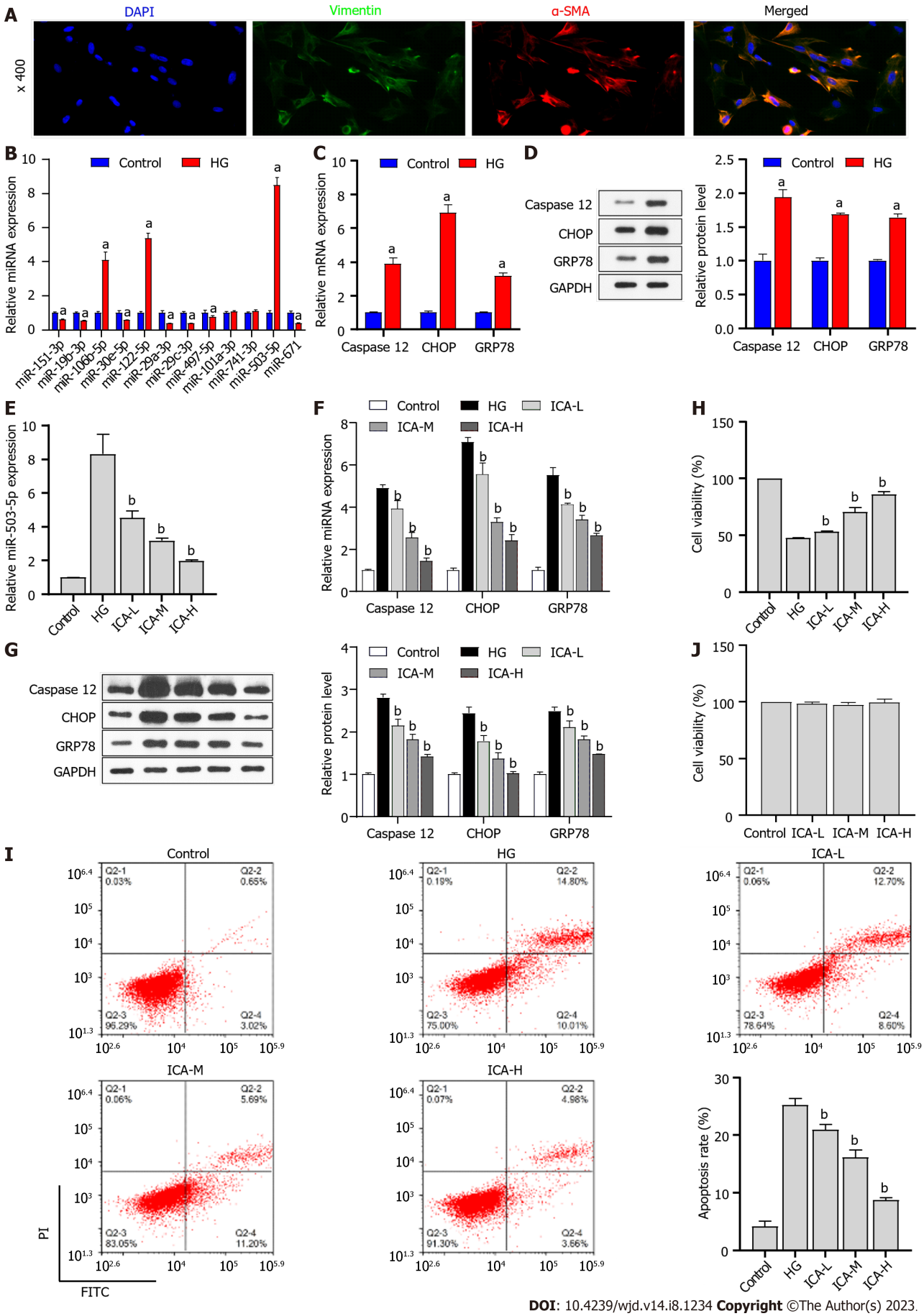

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Figure 2 Effect of Icariin on high glucose treatment. A: Immunofluorescence analysis of vimentin/α-smooth muscle actin (α-SMA) expression in primary rat

kidney (PRKs). Blue denotes 4',6-diamidino-2-phenylindole staining, green denotes vimentin expression, and red denotes α-SMA expression; B: Real-time quantitative polymerase chain reaction (RT-qPCR) analysis of the effect of high glucose (HG) treatment on the expression of miR-151-3p, miR-19b-3p, miR-106b-5p, miR-30e-5p, miR-122-5p, miR-29a-3p, miR-29c-3p, miR-497-5p, miR-101a-3p, miR-741-3p, miR-503, and miR-671; C: RT-qPCR analysis of the effect of HG treatment on the expression of Caspase 12, C/EBP-homologous protein (CHOP), and glucose regulated protein 78 (GRP78); D: Western blot analysis of the effect of HG treatment on the protein levels of Caspase 12, CHOP, and GRP78; E: RT-qPCR analysis of the effect of Icariin (ICA) treatment on HG treatment of miR-503 expression; F: RT-qPCR analysis of the effect of ICA treatment on HG-induced expression of endoplasmic reticulum stress-related factors Caspase 12, CHOP, and GRP78 expression; G: Western blot analysis of the effect of ICA treatment on HG-induced protein levels of Caspase 12, CHOP, and GRP78; H: Cell Counting Kit 8 (CCK8) analysis of the effect of ICA treatment on HG-induced cell viability of PRKs; I: flow cytometry analysis of the effect of ICA treatment on HG-induced apoptosis of PRKs; J: CCK8 analysis of the effect of low, medium, and high doses of ICA on cell viability of PRKs. $^{a}P < 0.05$ *vs* the control group; $^{b}P < 0.05$ *vs* the HG group. DAPI: 4',6-diamidino-2-phenylindole; α-SMA: α-smooth muscle actin; HG: High glucose; miR: MicroRNA; CHOP: C/EBP-homologous protein; GRP78: Glucose regulated protein 78; ICA: Icariin; L: Low; M: Medium; H: High; FITC: Fluorescein isothiocyanate; PI: Propidium iodide.

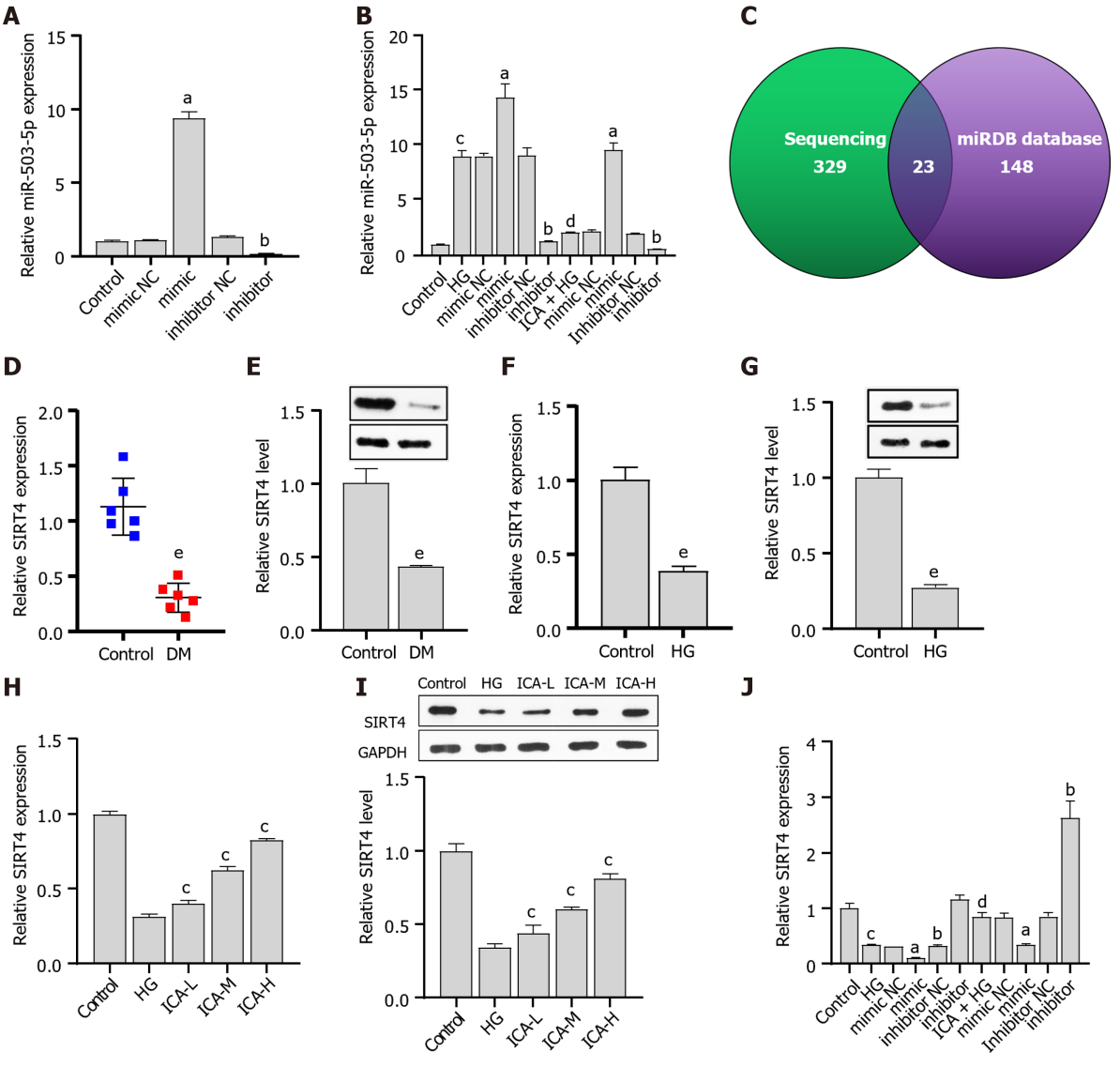

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Figure 3 miR-503 negatively regulates sirtuin 4. A: Real-time quantitative polymerase chain reaction (RT-qPCR) verification of the effectiveness of miR-503 mimic/inhibitor; B: RT-qPCR analysis of the effect of Icariin (ICA) treatment on high glucose (HG)-induced miR-503 expression; C: High-throughput sequencing results combined with the miRDB database to screen for the putative target gene of miR-503; D: RT-qPCR analysis of sirtuin 4 (SIRT4) expression in normal and diabetic nephropathy (DN) rat kidney tissue; E: Western blot analysis of SIRT4 protein level in normal and DN rat kidney tissue; F: RT-qPCR analysis of the effect of HG on SIRT4 expression; G: Western blot analysis of the effect of HG on SIRT4 protein level; H: RT-qPCR analysis of the effects of low, medium, and high doses of ICA in the treatment of HG-induced SIRT4 expression; I: Western blot analysis of the effects of low, medium, and high doses of ICA in the treatment of HG-induced SIRT4 protein level; J: RT-qPCR analysis of the effect of ICA treatment on HG-induced SIRT4 expression. $^{a}P < 0.05$ *vs* the mimic negative control (NC) group; $^{b}P < 0.05$ *vs* the inhibitor NC group; $^{c}P < 0.05$ *vs* the control group; $^{d}P < 0.05$ *vs* the HG group; $^{e}P < 0.05$ *vs* the control group. DN: Diabetic nephropathy; HG: High glucose; miR: microRNA; NC: Negative control; RT-qPCR: Real-time quantitative polymerase chain reaction; ICA: Icariin; L: Low; M: Medium; H: High; SIRT4: Sirtuin 4.

Table 4 Identification of mRNAs that may bind to miR-503 by sequencing results combined with the miRDB database

No.	Gene_id
1	SLC12A1
2	SIRT4
3	MLYCD
4	FBXL22
5	CCND1
6	MAP2K1
7	PCP4
8	RPS6KA3
9	EMC6
10	PPFIA3
11	TTC17
12	RAB11FIP1
13	GALNT2
14	NCS1
15	APLN
16	CEP85L
17	CLSTN1
18	KIF1C
19	PIGQ
20	BTRC
21	LOC691995
22	EGLN3
23	NABP1

HG-mediated promotion of miR-503 expression, which was reversed by mimic and enhanced by inhibitor (Figure 3B). These results confirmed that miR-503 may be a key pathway for ICA to improve HG-induced cell injury. The mechanism of miR-503 is still unclear.

miR-503 negatively regulates SIRT4

The sequencing results showed that 329 mRNAs could potentially bind to miR-503. Joint analysis of the sequencing results with the miRDB database (Figure 3C) revealed the intersection of 23 mRNAs (Table 4). Among them, prior results have suggested that SIRT4 can prevent glucose-induced apoptosis and cell damage[26,27]. We observed that SIRT4 expression and protein levels were downregulated in DM renal tissue or HG-induced PRKs (Figure 3D-G). The HG-induced downregulations were gradually recovered after low, medium, and high doses of ICA treatment (Figure 3H and I). The inhibitory effect of HG treatment on SIRT4 expression was enhanced by mimic and reversed by inhibitor. The inhibitory effect of ICA treatment on HG-induced SIRT4 expression was reversed by mimic and enhanced by inhibitor (Figure 3J). Therefore, the expression of miR-503 is negatively correlated with SIRT4.

SIRT4 is a direct target of miR-503

Typically, miRNAs bind to the 3'-UTR of downstream targets and inhibit transcriptional activity and translational levels, thereby affecting DN progression[28,29]. We constructed a SIRT4 overexpressing plasmid and transfected it into PRKs cells. The resulting expression and protein level of SIRT4 were upregulated in the ov-SIRT4 group (Figure 4A and B), confirming the successful ov-SIRT4. Sequencing results showed that miR-503 had a potential binding site with SIRT4 (Figure 4C), Dual luciferase results revealed that SIRT4 is a direct target of miR-503 (Figure 4D). The inhibition of SIRT4 expression by miR-503 mimic was reversed after transfection with ov-SIRT4 (Figure 4E and F). The findings indicate that miR-503 directly interacts with the 3'-UTR of SIRT4, inhibiting its transcriptional activity. Furthermore, our results suggest that the mechanism by which ICA restores viability and inhibits apoptosis of HG-induced PRKs cells is related to the miR-503/SIRT4 axis.

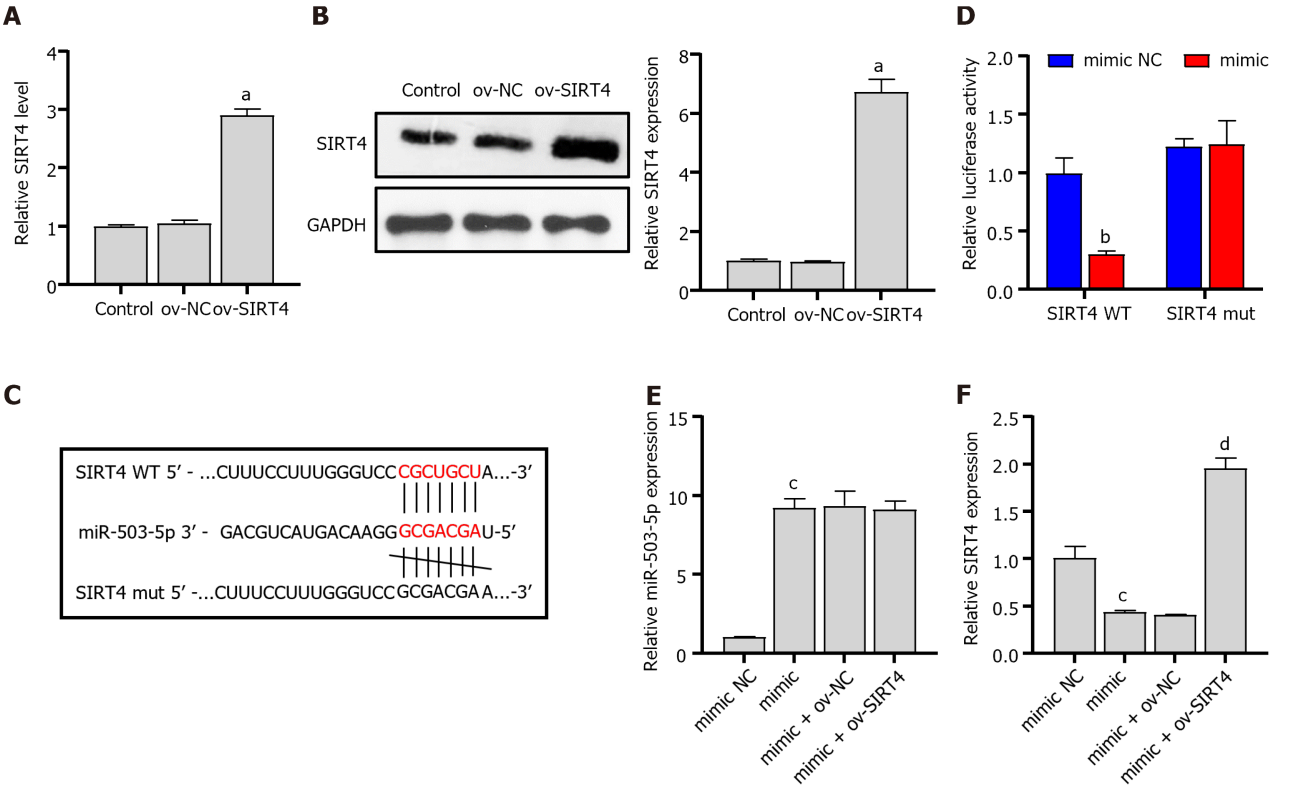

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Figure 4 Sirtuin 4 is a direct target of miR-503. A: Real-time quantitative polymerase chain reaction (RT-qPCR) verification of the validity of the ov-sirtuin 4 (SIRT4) plasmid; B: Western blot verification of the validity of the ov-SIRT4 plasmid; C: Potential binding sites of miR-503 to SIRT4; D: Dual luciferase analysis of the binding of miR-503 and SIRT4; E: RT-qPCR analysis of the effect of miR-503 mimic and ov-SIRT4 co-transfection on miR-503 expression; F: RT-qPCR analysis of the effect of miR-503 mimic and ov-SIRT4 co-transfection on SIRT4 expression. [a]*P* < 0.05 *vs* the ov-negative control (NC) group; [b]*P* < 0.05 *vs* the mimic NC group; [c]*P* < 0.05 *vs* the mimic group; [d]*P* < 0.05 *vs* the mimic + ov-NC group. miR: microRNA; NC: Negative control; RT-qPCR: Real-time quantitative polymerase chain reaction; ov: Overexpression; SIRT4: Sirtuin 4; WT: Wild type; mut: Mutant.

ICA regulates miR-503/SIRT4 axis to improve HG-induced cell injury and ER stress

To investigate the role of miR-503/SIRT4 axis in ICA treatment of HG-induced injury in PRKs, miR-503 mimic and ov-SIRT4 were co-transfected into PRKs. In PRKs co-treated with HG and ICA, miR-503 mimic promoted the expression/protein levels of ER stress associated factors caspase 12, CHOP, and GRP78 (Figure 5A-C) and inhibited the expression/protein levels of SIRT4 (Figure 5D). However, after co-transfection with ov-SIRT4, the effect of miR-503 mimic was reversed. In addition, in PRKs co-treated with HG and ICA, the inhibition of cell viability (Figure 5E) and promotion of apoptosis (Figure 5F) by miR-503 mimic were reversed after co-transfection with ov-SIRT4.

DISCUSSION

Recent research has suggested that improving protein folding may attenuate renal injury and that pharmacological treatment of ER stress is a promising therapeutic approach to prevent or halt the progression of kidney disease[6,30]. Studies have suggested that TCM is a safer treatment[31,32]. The use of TCM as combination therapy has been increasingly reported[33,34]. ICA is a flavonol glycoside isolated from Epimedium[35]. Long-term administration of ICA significantly improves behavioral performance[36], reduces neuronal apoptosis, and inhibits ER stress signaling[37]. Protein misfolding and ER stress are evident in various kidney diseases, including DN and chronic kidney disease[38,39]. Therefore, studying the effects of ICA on HG-treated PRKs may help uncover its potential cellular mechanisms, which could further the understanding of the potential effectiveness and reliability of ICA. The findings could suggest new avenues for potential therapeutic interventions relevant to DN.

We demonstrated HG-induced inhibition of proliferation, promotion of apoptosis, and ER stress in PRKs, suggesting that HG can induce renal cell damage, which may contribute to mechanisms relevant to DN[40]. These results are similar to previous results of ICA for ER stress in renal cells[41]. Since the overexpression of miR-503 may be the cause of the pathogenesis of DN[14], miR-503 was selected as a potential therapeutic target for DN from miRNA sequencing results. The expression of miR-503 increased after HG treatment, but was reversed under the action of ICA. Therefore, miR-503 may play an essential role in processes relevant to DN. To investigate the role of miR-503 in the pathology of HG-induced PRKs injury, we overexpressed and inhibited miR-503, and measured the levels of ER stress markers. The results demonstrated that the miR-503 mimic can accelerate HG-induced ER stress, while miR-503 inhibitor can reduce HG-

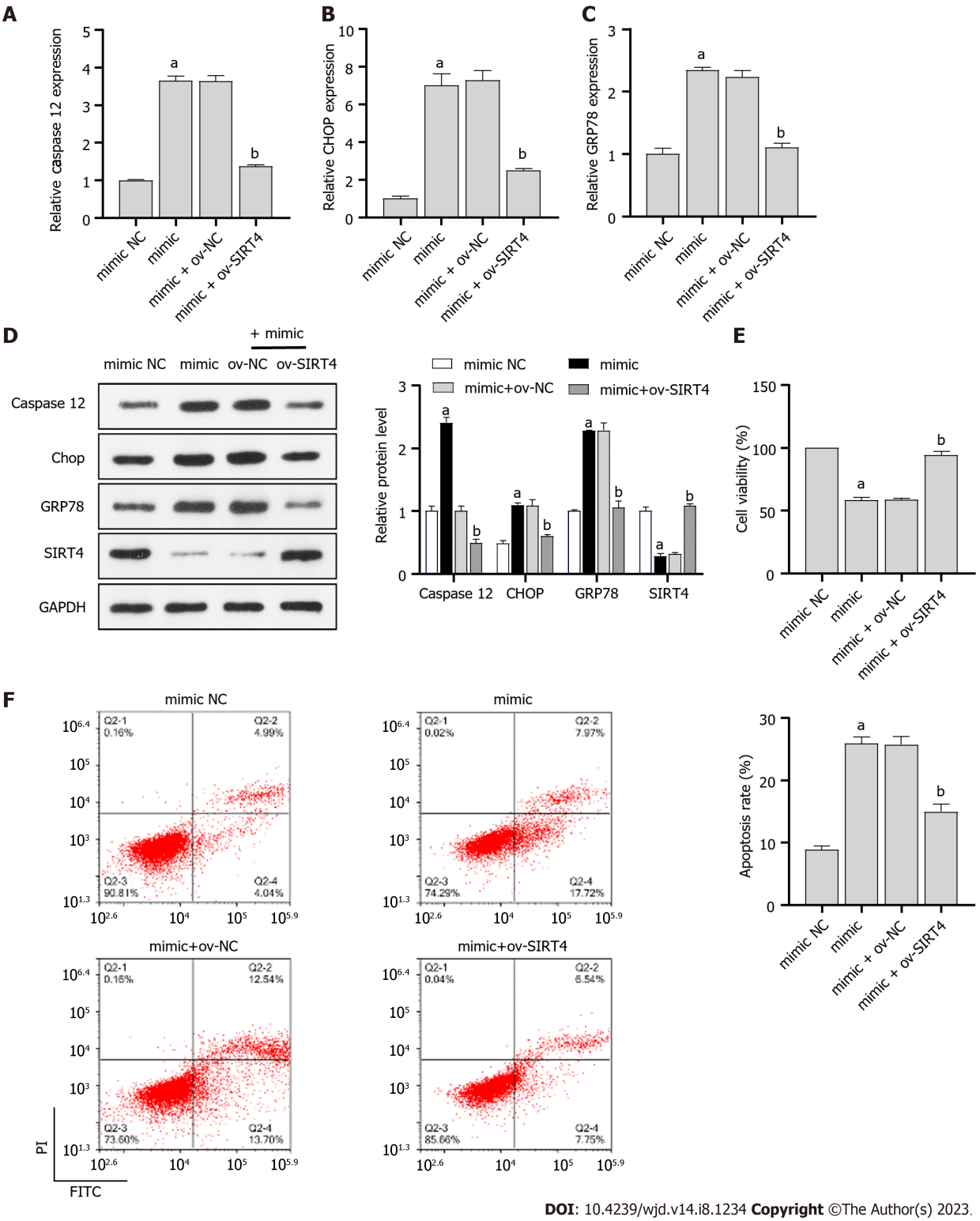

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Figure 5 Icariin regulates miR-503/sirtuin 4 axis to improve high glucose-induced cell injury and endoplasmic reticulum stress. A-C: Real-time quantitative polymerase chain reaction analysis of the effect of miR-503 mimic and ov-sirtuin 4 (SIRT4) co-transfection on Caspase 12 (A), C/EBP-homologous protein (CHOP) (B), and glucose regulated protein 78 (GRP78) (C) expression in primary rat kidney (PRKs) co-treated with high glucose (HG) and Icariin (ICA); D: Western blot analysis of the effect of miR-503 mimic and ov-SIRT4 co-transfection on Caspase 12, CHOP, and GRP78 protein levels in PRKs co-treated with HG and ICA; E: Cell Counting Kit 8 analysis of the effect of miR-503 mimic and ov-SIRT4 co-transfection on cell viability of PRKs; F: Flow cytometry analysis of the effect of miR-503 mimic and ov-SIRT4 co-transfection on apoptosis of PRKs. $^{a}P < 0.05$ *vs* the mimic negative control (NC) group; $^{b}P < 0.05$ *vs* the mimic + ov-NC group. HG: High glucose; miR: microRNA; NC: Negative control; RT-qPCR: Real-time quantitative polymerase chain reaction; CHOP: C/EBP-homologous protein; GRP78: Glucose regulated protein 78; SIRT4: Sirtuin 4; ICA: Icariin; FITC: Fluorescein isothiocyanate; PI: Propidium iodide; FCM: Flow cytometry; CCK8: Cell Counting Kit 8; ER: Endoplasmic reticulum.

induced ER stress.

It is well known that miRNAs function *via* targeting to the 3'-UTR of downstream targets[42]. Here, we report the first evidence of miR-503 directly targeting SIRT4. Through this mechanism, miR-503 regulates SIRT4-mediated growth of PRKs and ER stress. SIRT4 downregulation blocks the improvement and protection of renal function by forkhead box M1 in mice[26]. SIRT4 overexpression increases podocyte proliferation and inhibits apoptosis[27]. This could be attributed to the fact that SIRT4 induced by stresses and contributes to cell survival after stress[43]. In the present study, we observed HG-induced downregulation of SIRT4 expression and protein level in PRKs, which was increased after ICA treatment. Moreover, overexpression of SIRT4 reversed ER stress induced by miR-503 mimic. The dual luciferase assay revealed that SIRT4 is a direct target of miR-503. Therefore, HG-mediated upregulation of miR-503 inhibits the transcriptional activity and translation level of downstream target SIRT4, which damages PRKs and produces ER stress. However, ICA treatment blocked HG treatment, promoted the change of miR-503/SIRT4 axis in cells, and protected PRKs from HG-induced cell damage and ER stress.

We present novel evidence supporting the role of the ICA/miR-503/SIRT4 axis in the pathogenesis of HG-induced PRKs. Our findings expand the current understanding of HG-induced pathogenesis and suggest new potential molecular targets that could be explored in future therapeutic interventions related to conditions such as DN.

The study has several limitations. Firstly, while our results show a correlation between ICA, miR-503, and mechanisms related to DN, the causative role of miR-503 in the pathology of DN remains to be established. Secondly, although ICA treatment has shown promising effects in our *in vitro* study, the lack of clinical data supporting the therapeutic efficacy of ICA or miR-503 in conditions like DN is a clear limitation. Finally, while we have demonstrated an interplay between ICA and the miR-503-SIRT4 axis, validation in PRKs only does not provide broader insights. Subsequent studies are needed to expand the experimental scope in different cell types associated with diabetes (*e.g.*, podocytes or β-cells).

CONCLUSION

The *in vivo* and *in vitro* data demonstrate that ICA has the ability to safeguard PRKs against damage caused by HG-induced injury and ER stress. This protective effect is attributed to the ability of ICA to increase the proliferation of PRKs, while simultaneously inhibiting apoptosis. This is achieved by regulating the miR-503-SIRT4 axis. Moreover, the study findings provide an understanding of the molecular mechanisms potentially underlying the development of DN, specifically the role of miRNAs and their downstream targets. Based on these findings, ICA should be further explored in animal models to test whether it can still protect the kidney from diabetes as a reliable and efficient candidate for the treatment of DN.

ARTICLE HIGHLIGHTS

Research background

The study focuses on the effects of high glucose (HG) levels in diabetes and its implications on kidney function. It builds upon existing literature indicating that protein misfolding and endoplasmic reticulum (ER) stress are prevalent in kidney diseases, including diabetic nephropathy (DN) and chronic kidney disease. In addition, the flavonol glycoside Icariin (ICA), a traditional Chinese medicine (TCM), has shown potential in attenuating ER stress, which may potentially prevent or halt the progression of kidney diseases.

Research motivation

The research aimed to explore the potential of ICA as a treatment for HG-induced cellular damage, focusing on its interaction with specific microRNAs and proteins that contribute to renal cell damage. Given the increasing interest in the use of TCM as a safer and efficient alternative therapy, understanding the cellular mechanisms of ICA could provide valuable insights for potential therapeutic interventions in DN.

Research objectives

The primary goal was to investigate the effects of ICA on HG-treated kidney cells, with a particular emphasis on the role of miR-503 and sirtuin 4 (SIRT4) in the pathogenesis of HG-induced kidney injury. The study's findings could further the understanding of the mechanisms of ICA, paving the way for future research into its effectiveness and reliability as a treatment for DN.

Research methods

The research used *in vitro* experiments to study the effects of ICA on HG-induced cell injury and ER stress in renal cells. The methods adopted included overexpression and inhibition of miR-503 and measuring levels of ER stress markers. The study also conducted a dual luciferase assay to determine whether SIRT4 is a direct target of miR-503.

Research results

The study identified that ICA ameliorates HG-induced cell injury by reducing the expression of miR-503. This research also discovered that miR-503 directly targets SIRT4, a novel finding in the field. However, some problems remain, such as

establishing the causative role of miR-503 in DN and validating the results in other cell types associated with diabetes.

Research conclusions

This study proposes a new theory suggesting the role of the ICA/miR-503/SIRT4 axis in the pathogenesis of HG-induced renal cell injury. Additionally, it presents a new method of using ICA treatment to regulate the miR-503/SIRT4 axis, thereby protecting cells from HG-induced cell damage and ER stress.

Research perspectives

Future research should focus on validating these findings in animal models and different diabetic-associated cell types like podocytes or β-cells. Further studies should also explore the therapeutic efficacy of Icariin or miR-503 in clinical settings for conditions like DN, ultimately advancing our understanding of the ICA/miR-503/SIRT4 axis's role in managing diabetes.

FOOTNOTES

Author contributions: Su BL and Chen GY designed the study and interpreted the data; Wang LL and Zhang LY performed all experiments and drafted the manuscript; Zhang S and Li Q collected and analyzed the data; Su BL and Chen GY reviewed the manuscript.

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ORIGINAL ARTICLE

Basic Study

Impact of bariatric surgery on glucose and lipid metabolism and liver and kidney function in food-induced obese diabetic rats

Hong Long, Lei Zhao, Zhong-Sheng Xiao, Shu-Xiang Li, Qiu-Lin Huang, Shuai Xiao, Liang-Liang Wu

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Abstract

BACKGROUND

Obesity usually causes diabetes mellitus (DM) and is a serious danger to human health. Type 2 DM (T2DM) mostly occurs along with obesity. Foodborne obesity-induced DM is caused by an excessive long-term diet and surplus energy. Bariatric surgery can improve the symptoms of T2DM in some obese patients. But different types of bariatric surgery may have different effects.

AIM

To investigate the effect of bariatric surgery on glucose and lipid metabolism and liver and kidney function in rats.

METHODS

Male Sprague-Dawley rats aged 6-8 wk underwent Roux-en-Y gastric bypass surgery (RYGB), sleeve gastrectomy (SG), or gastric banding (GB). Glucose and insulin tolerance tests, analyses of biochemical parameters, histological examination, western blot, and quantitative real-time polymerase chain reaction were conducted.

RESULTS

In comparison to the sham operation group, the RYGB, SG, and GB groups had decreased body weight and food intake, reduced glucose intolerance and insulin insensitivity, downregulated biochemical parameters, alleviated morphological changes in the liver and kidneys, and decreased levels of protein kinase C β/P66shc. The effect in the RYGB group was better than that in the SG and GB groups.

CONCLUSION

These results suggest that RYGB, SG and GB may be helpful for the treatment of

foodborne obesity-induced DM.

Key Words: Diabetes mellitus; Obesity; Bariatric surgeries; Liver and kidney function

Core Tip: Bariatric surgery can improve the symptoms of type 2 diabetes mellitus (DM) in some obese patients. But different types of bariatric surgery may have different effects. In the current study, in comparison to the sham operation group, the Roux-en-Y gastric bypass surgery (RYGB), sleeve gastrectomy (SG), and gastric banding (GB) groups had decreased body weight and food intake, reduced glucose intolerance and insulin insensitivity, downregulated biochemical parameters, alleviated morphological changes in the liver and kidneys, and decreased levels of protein kinase C β/P66shc. The effect in the RYGB group was better than that in the SG and GB groups. Thus, bariatric surgeries are a helpful tool for the treatment of foodborn obesity-induced DM.

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INTRODUCTION

Diabetes mellitus (DM), a well-known chronic metabolic disease, is a substantial global problem characterized by a common outcome of hyperglycemia. Type 2 DM (T2DM), accounting for > 90% of all cases of DM, is considered the chief cause of diabetic complications, including diabetic nephropathy, diabetic neuropathy, cardiovascular disease, and diabetic retinopathy[1].

It is widely acknowledged that obesity, increasingly influenced by lifestyle factors, is an essential risk factor for the development of T2DM[2,3]. Obesity is involved in the upregulated circulating free fatty acids that play a distinct role in progressive dysfunction of pancreatic beta cells, damaging their ability to compensate for insulin resistance (IR) and thus contributing to T2DM pathogenesis[4]. The growing prevalence of T2DM has resulted in various approaches focusing on discovering novel therapeutic targets for treating hyperglycemia.

Higher blood glucose is an absolute risk factor for all-cause mortality, and bariatric surgery can increase survival rates of patients with obesity[5,6]. Bariatric surgery can promote sustained weight loss and is more efficacious than traditional medical strategies for long-acting control of T2DM[7]. Bariatric surgery quickly diminishes IR and blood glucose before any fathomable weight loss[8,9]. Bariatric surgery can ameliorate glycemic control and glucose homeostasis in patients with T2DM[10]. However, the underlying mechanism remains to be investigated.

Protein kinase C (PKC), a member of a family of serine/threonine protein kinases consisting of > 12 members, exerts a pivotal role in intracellular crosstalk and signal transduction[11]. It has been reported that pharmacological blockade or gene deletion of PKCβ can decrease infarct size, protect ischemic myocardium, and promote ventricular functional recovery[12]. The Shc adaptor protein family contains P46shc, P52shc, and P66shc, but only P66shc plays an essential role as a redox enzyme associated with the generation of mitochondrial reactive oxygen species (ROS) and the transformation of oxidative signals into apoptosis[13]. Hyperglycemic and oxidative stress can activate the PKCβ2 isoform to stimulate phosphorylation of P66shc at ser36 to transfer phosphorylated (p)-P66shc from the cytosol to the inner mitochondrial membrane, where p-P66shc can increase oxidative stress and catalyze the generation of ROS *via* cytochrome oxidation[14,15]. Therefore, we hypothesized that there may be a PKCβ/P66shc signaling pathway in the pathogenesis of DM.

In the current study, we investigated the effects of bariatric surgery, including Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), and gastric banding (GB), on the foodborne obesity diabetic rats and the possible mechanisms related to the PKCβ/P66shc signaling pathway.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats aged 6-8 wk with a body weight of 200-220 g were purchased from the Guangdong Medical Laboratory Animal Center and adapted to the environment for 7 d before the experiments. All rats were housed in specific pathogen-free cages with a 12-h light/dark cycle and had free access to drinking water and food.

Animal groups and bariatric surgery

All the rats were randomly divided into four groups: RYGB, SG, GB, and sham operation (SO), with 10 rats in each group. The rats were anesthetized with 0.5% pentobarbital (45 mg/kg) by intraperitoneal injection before the operation.

In the RYGB group, rats were routinely fasted with water 12 h before the operation. After weighing the rats, anesthesia was induced by intraperitoneal injection of 3% pentobarbital (0.15 mL/100 g). When the limbs were soft, we used an animal shaver to prepare the operation area, dipped a sterile cotton swab in iodophor, and disinfected the skin around the incision area three times. At the sterile area about 3 cm below the sternum of the rat, a longitudinal incision was made, the abdominal cavity was opened layer by layer, and an electrocoagulator was used to stop bleeding as needed. After entering the abdominal cavity, we confirmed the position of the distal ligament of Treitz. At a distance of 10-15 cm from the distal end of the ligament, we freed a segment of the small intestine to avoid damaging the mesenteric vessels and intestinal serosa, separated and cut off the jejunum, wiped off the digestive fluid with a cotton swab, and disinfected the distal and proximal intestinal tubes with iodophor. End-to-side full-thickness anastomosis was performed at the proximal jejunum 10 cm below the distal jejunum to keep the anastomosis unobstructed. We gently exposed the stomach body, esophagus, and cardia with a sterile cotton swab, and used the electrocoagulator to dissociate the stomach towards the lower part of the cardia. The stomach was severed at 10 cm at the distal end of the cardia, and < 20% of the gastric sacs were retained. The proximal gastric sacs were anastomosed with the distal jejunum laterally. After confirming the patency of the anastomosis, the distal remnant stomach was closed by suture. Both gastrojejunostomy and jejunojejunostomy were sutured with 6-0 absorbable sutures. Before closing the abdominal cavity, we flushed the abdominal cavity with normal saline solution containing gentamicin three times. Intermittent suture was used for abdominal closure.

In the SG group, preoperative treatment was the same as that in the RYGB group. We cut the skin and subcutaneous tissue layer by layer, exposed the esophagus, stomach, duodenum, and other organs, freed the stomach from the abdominal cavity, and ligated the vessels of the greater curvature according to the scope of resection. And 75%-80% of the whole stomach volume was cut off, including the fundus and most of the stomach body tissue. After resection, we cleaned the contents of the remnant stomach with a cotton swab. The stump stomach was sutured and closed, and the abdominal cavity was washed with physiological saline. After dipping the physiological saline with a cotton ball, the stump stomach was covered with part of the omentum, and the abdominal cavity was closed layer by layer.

In the GB group, preoperative treatment was the same as that in the RYGB group. The midline incision of the upper abdomen was 3 cm long. The inner diameter of the lower part of the upper gastric cardia was bound and fixed to one third of the original position with a buckle type silicon tape at 1 cm below the cardia. The proximal end formed a 20% small gastric sac. Routine abdominal closure was performed.

In the SO group, rats were fasted 12 h before the operation, and the jejunum and gastric body were cut at the same position as that in the RYGB group, and then the broken end was cut and anastomosed. The cross section of the gastrointestinal tract was performed at the site where gastrotomy was performed in RYGB, and the anastomosis was performed at the original cutting site. The operation time should be the same as that of RYGB, and normal saline containing gentamicin was used to wash the abdomen. The physiological flow of food through the gastrointestinal tract remained intact. After surgery, the rats were placed into a single cage, and wound care was applied.

Glucose and insulin tolerance tests

At 4 wk, the oral glucose tolerance test (OGTT) was performed as previously described[16] by glucose gavage (5 g D-glucose/kg) following an overnight fast. After the tail of rats was pierced using a needle, a drop of venous blood was collected to determine blood glucose concentration, and 300 μL of tail vein blood was gathered and centrifuged for 15 min at 2000 rpm to collect the serum for the measurement of insulin. Blood glucose was determined using a glucometer (Roche Diagnostics, Switzerland) following glucose gavage for 0 h, 1 h, and 2 h, and insulin was monitored at the same time points. The insulin tolerance test (ITT) was performed as previously described[17]. After fasting for 8 h, the rats were intraperitoneally injected with insulin (0.5 U/kg). The area under the curve (AUC) of the OGTT and ITT was also calculated.

Analysis of biochemical parameters

At 4 wk, blood samples gathered from the abdominal aorta of rats under anesthesia were centrifuged for 15 min at 3000 rpm to determine the serum concentrations of triglyceride (TG), total bile acids (TBA), alanine aminotransferase (ALT), and aspartate aminotransaminase (AST) with a microplate reader (Reitman-Frankel colorimetric assay) (Nanjing Jiancheng Corp., Nanjing, China).

Histological examination

Histological examination was performed as previously described[17]. Liver and kidney tissues were fixed in 4% paraformaldehyde solution, following embedding in paraffin blocks. Tissue sections were obtained using a microtome, and after staining with hematoxylin and eosin (HE), they were examined under a microscope (Olympus, Japan).

Western blot analysis

Western blot was performed as previously described[18]. Generally, protein samples were separated using 10% SDS-PAGE at 90 V for nearly 1.5 h, followed by electroblotting onto polyvinylidene difluoridemembranes for 2 h at 300 mA. The membranes were blocked with 5% bovine serum albumin (#9048-46-8, Beijing Solarbio Science & Technology Co., Ltd., Beijing, China) diluted in Tris-HCl buffer supplemented with 0.1% Tween-20 (TBST; pH = 7.4), followed by incubation with the primary antibodies rabbit anti-PKCβ (1:1000, #ab32026, Abcam Cambridge, United Kingdom) and rabbit anti-P66shc (1:1000, #ab33770, Abcam), overnight at 4 °C. The membranes were washed three times with TBST for 5 min each and then incubated with a horseradish peroxidase-conjugated goat anti-rabbit secondary antibody (1:5000, #ab288151, Abcam) diluted in TBST for 1 h at room temperature. After the membranes were washed with TBST three times for 5 min each, an enhanced chemiluminescence solution (Bio-Rad, Hercules, CA, United States) was used to

visualize the immunoreactive signals. Band intensity was quantified using ImageJ 5.0.

Quantitative real-time polymerase chain reaction

Quantitative real-time polymerase chain reaction (qRT-PCR) was performed as previously described[17]. After blood collection, the rats were killed, the liver and kidney tissues were quickly removed, and 15-20 mg of pancreatic tail tissue was separated on the ice bed for fluorescent qPCR detection. Liver and kidney tissues were treated with TRIzol reagent, cut, and homogenized on ice until complete lysis. The complementary DNA (cDNA) was generated based on the RNA templates by using a Transcriptor Reverse Transcriptase kit (Roche Applied Science, IN, United States). The mRNA levels of P66shc and PKCβ were determined by qPCR using a KAPA SYBR FAST qPCR Kit (Kapa Biosystems, Inc., MA, United States) and the Miniopticon™ Real-Time PCR Detection System (Bio-Rad, CA, United States). β-actin was used as the internal control. The relative mRNA level of each gene was analyzed by the $2^{-\Delta\Delta Ct}$ method. The sequences of each primer is shown in Table 1.

Statistical analysis

Data are shown as the mean ± SEM and were analyzed using GraphPad Prism v7.03 by one-way analysis of variance with the Dunnett's *post-hoc* test. Results were considered statistically significant at $P < 0.05$.

RESULTS

Serum biochemical analysis and physical conditions

The levels of serum total cholesterol (TC), TG, IR, and TBA were significantly upregulated in all four groups after the induction of foodborne obesity-induced diabetes at week 8 compared with before (week 1).

After 8 wk, body weight, blood glucose, and serum levels of TC, TG, IR, and TBA were not significantly different among the four groups ($P > 0.05$) (Figures 1A-F). One rat in the RYGB group died of massive hemorrhage during surgery, and one died on postoperative day 4. Anatomical analysis showed that the cause of death might be anastomotic leakage (Figures 1G and H), and one died of wound infection (Figure 1I). Seven survived until the end of the experiment. Two rats in the SG group died of wound infection 1 wk after the operation (Figure 1J). Eight survived until the end of the experiment. All rats in the GB and SO groups survived.

Effect of bariatric surgery on body weight and food intake in rats

In comparison to the SO group, the body weight in the RYGB, SG, and GB groups was significantly decreased. Among the latter three groups, body weight was lowest in the RYGB group and highest in the GB group ($P < 0.05$) (Figure 2A). There was a significant difference in body weight between any two of the groups. In comparison to the SO group, food intake in the RYGB, SG, and GB groups was significantly decreased. Among the latter three groups, food intake was lowest in the RYGB group and highest in the GB group ($P < 0.05$) (Figure 2B). There was a significant difference in food intake between any two of the groups.

Effect of bariatric surgery on glucose intolerance and insulin insensitivity in rats

In comparison to the SO group, fasting blood glucose in the RYGB, SG, and GB groups was significantly decreased ($P < 0.05$). Among the latter three groups, fasting blood glucose was lowest in the RYGB group and highest in the GB group (Figure 2C). There was a significant difference in fasting blood glucose between any two of the groups.

In comparison to the SO group, fasting blood IR level in the RYGB, SG, and GB groups was significantly decreased ($P < 0.05$). Among the latter three groups, fasting blood IR level in RYGB group was significantly than those in the GB and SG groups, but with no significant difference between the RYGB and SG groups (Figure 2D). In comparison to the SO group, blood glucose level in the OGTT in the RYGB, SG, and GB groups was significantly decreased ($P < 0.05$). Among the latter three groups, blood glucose level in the OGTT was lowest in the RYGB group and highest in the GB group. There was a significant difference in blood glucose level in the OGTT between any two of the groups (Figure 2E). A similar pattern of AUC of the OGTT was observed (Figure 2F).

In comparison to the SO group, the blood glucose level in the ITT in the RYGB, SG, and GB groups was significantly decreased ($P < 0.05$). Among the latter three groups, blood glucose level in the ITT was lowest in the RYGB group and highest in the GB group (Figure 2G). There was a significant difference in blood glucose level in the ITT between any two of the groups. A similar pattern of AUC of the ITT was observed (Figure 2H).

Effect of bariatric surgery on biochemical parameters in rats

In comparison to the SO group, the serum levels of TG, TC, TBA, ALT, and AST were significantly decreased in the RYGB, SG, and GB groups ($P < 0.05$). Among the latter three groups, the serum levels of TG, TC, TBA, ALT, and AST were lowest in the RYGB group and highest in the GB group (Figure 3). There was a significant difference in the serum levels of TG, TC, TBA, ALT, and AST between any two of the groups.

Effect of bariatric surgery on morphological changes in the liver and kidneys in rats

Grossly, the liver volume of rats in the SO group increased, with a milky white appearance, the edge became blunt, and the texture was soft; in the RYGB group, the liver was small and bright red, with sharp edges. HE staining showed a large number of fatty vacuoles in the liver of rats in the SO group, hepatic cord disorder, and narrowing of hepatic sinuses,

Table 1 Primers used for quantitative real-time polymerase chain reaction

Gene		5' to 3'	Product length (bp)
P66 shc	Forward	TTGCCCCTCCTCCAGGACAT	196
	Reverse	CGCAACCCATGTACCGAACC	
PKCβ	Forward	GACTTCATTTGGGGCTTCGGG	140
	Reverse	TTGCTCCGTGGGTCATCAGA	
β-actin	Forward	GTTGACATCCGTAAAGAC	168
	Reverse	ACCAATCCACACAGAGTA	

PKC: Protein kinase C.

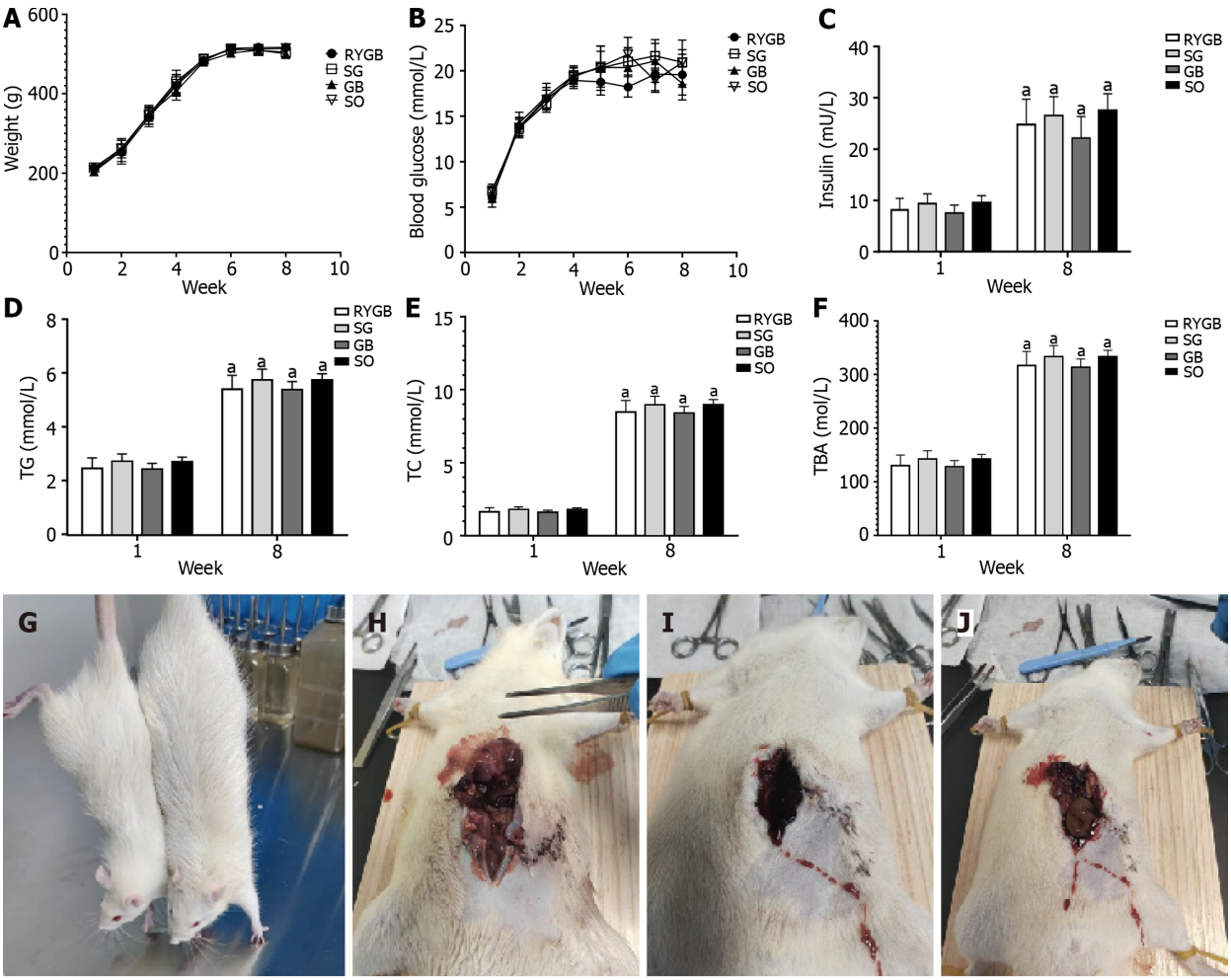

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Figure 1 Serum biochemical analysis and physical conditions. A-F: Different changes in body weight (A), blood glucose (B), insulin (C), triglyceride (D), total cholesterol (E) and total bile acids (F) in foodborne obese diabetic rats before and after modeling (n = 10); G: Representative images of body shape between obese diabetic and normal rats; H: One rat in the Roux-en-Y gastric bypass surgery (RYGB) group died of anastomotic fistula; I: One rat in the RYGB group died of wound infection; J: One rat in the SG group died of wound infection. $^{a}P < 0.05$. TG: Triglyceride; TC: Total cholesterol; TBA: Total bile acid; RYGB: Roux-en-Y gastric bypass surgery; SG: Sleeve gastrectomy; GB: Gastric banding; SO: Sham operation.

indicating the presence of severe fatty liver. Compared with the SO group, the number of fatty vacuoles in the SG and GB groups was significantly reduced, the hepatic cord was unclear, and the shape was curved, indicating mild fatty liver. In the RYGB group, the liver lobules were normal, the hepatic cords were orderly arranged, the hepatic sinuses were normal, and no obvious degeneration of hepatocytes was observed (Figures 4A-D).

In the SO group, renal tubular lesions were more obvious, and epithelial cells showed vacuolar lesions, glomerular mesangial injury, and shedding. The lesions in the SG and GB groups were significantly alleviated, and there was no obvious kidney disease in the RYGB group (Figures 4E-H).

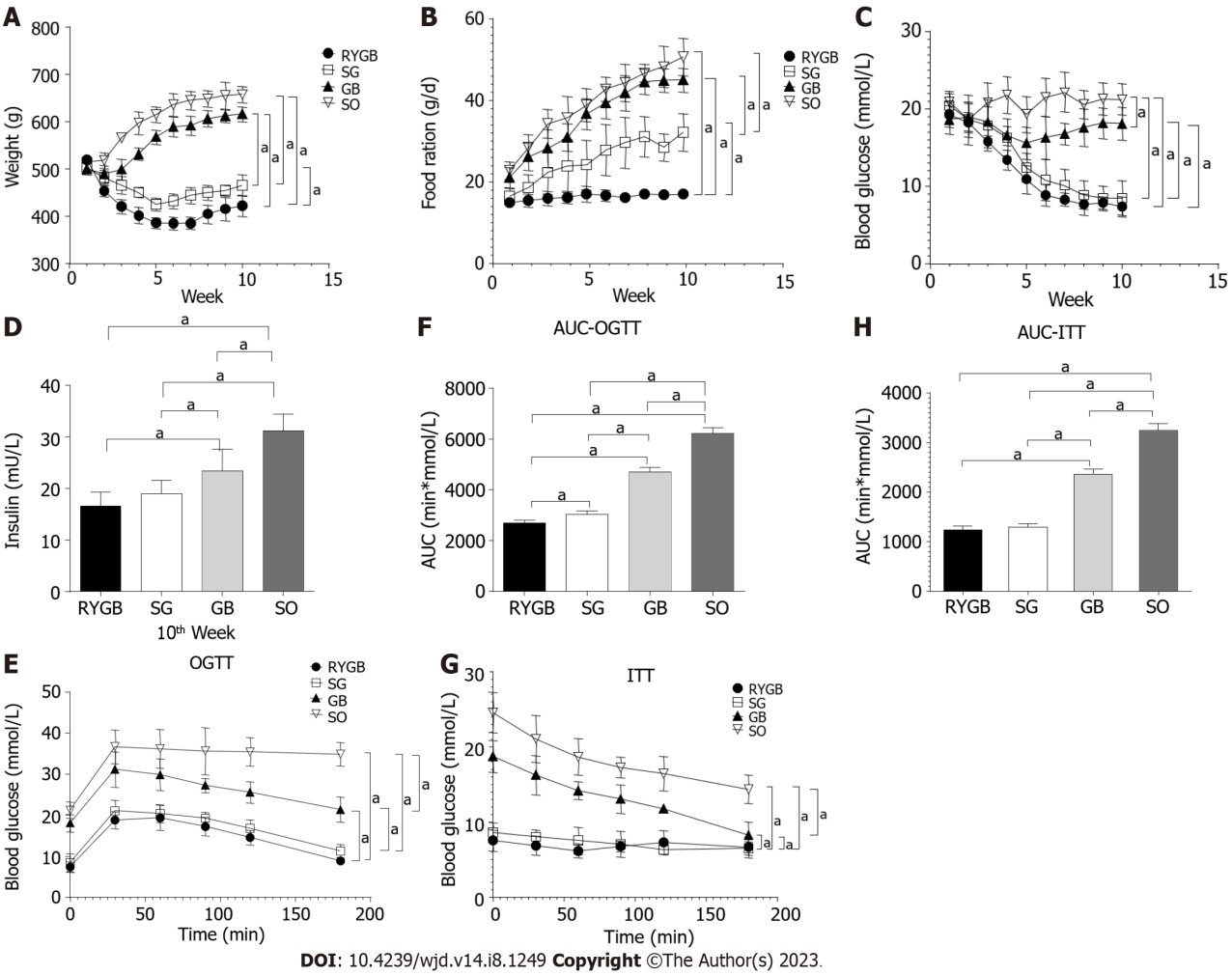

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Figure 2 Changes in blood glucose and insulin. A-H: Different changes in body weight (A), food intake (B), fasting blood glucose (C), fasting blood insulin (D), blood glucose in oral glucose tolerance test (OGTT) (E), area under the curve (AUC) of OGTT (F), blood glucose in insulin tolerance test (ITT) (G), and AUC of ITT in foodborne obese diabetic rats after bariatric surgery (H) (n = 10). $^{a}P < 0.05$. AUC: Area under the curve; RYGB: Roux-en-Y gastric bypass surgery; SG: Sleeve gastrectomy; GB: Gastric banding; SO: Sham operation.

Effect of bariatric surgery on PKCβ/P66shc pathway in rats

In comparison to the SO group, the protein expression levels of P66shc and PKCβ were significantly decreased in the RYGB, SG, and GB groups ($P < 0.05$). Among the latter three groups, the protein expression levels of P66shc and PKCβ were lowest in the RYGB group and highest in the GB group (Figures 5A-C). There was a significant difference in the protein expression levels of P66shc and PKCβ between any two of the groups.

In comparison to the SO group, the mRNA levels of P66shc and PKCβ were significantly decreased in the RYGB, SG, and GB groups ($P < 0.05$). Among the latter three groups, the mRNA levels of P66shc and PKCβ were lowest in the RYGB group and highest in the GB group (Figures 5D and E). There was a significant difference in the mRNA expression levels of P66shc and PKCβ between any two of the groups.

DISCUSSION

In previous studies, bariatric surgery promoted sustained weight loss, and achieved glycemic control and glucose homeostasis in patients with T2DM[7,10]. In the current study, we revealed that bariatric surgery, including RYGB, SG, and GB, can decrease body weight and food intake, reduce glucose intolerance and insulin insensitivity, downregulate biochemical parameters, alleviate morphological changes in the liver and kidneys, and diminish the expression levels of PKCβ and P66shc, suggesting that bariatric surgery may be a novel treatment for foodborne obesity-induced DM.

It is well-known that obesity predicts progression to T2DM, characterized by increased blood glucose, glucose intolerance, and IR[19,20]. Here, we observed that bariatric surgery decreased body weight and food intake, and reduced glucose intolerance and insulin insensitivity.

In complex diseases, including T2DM, there are multiple genes involved, affecting biological function in groups rather than alone. Therefore, to understand the signaling pathways involved in the pathological mechanisms and identify which of these pathways are affected in each patient may provide a better understanding of T2DM and could lead to new

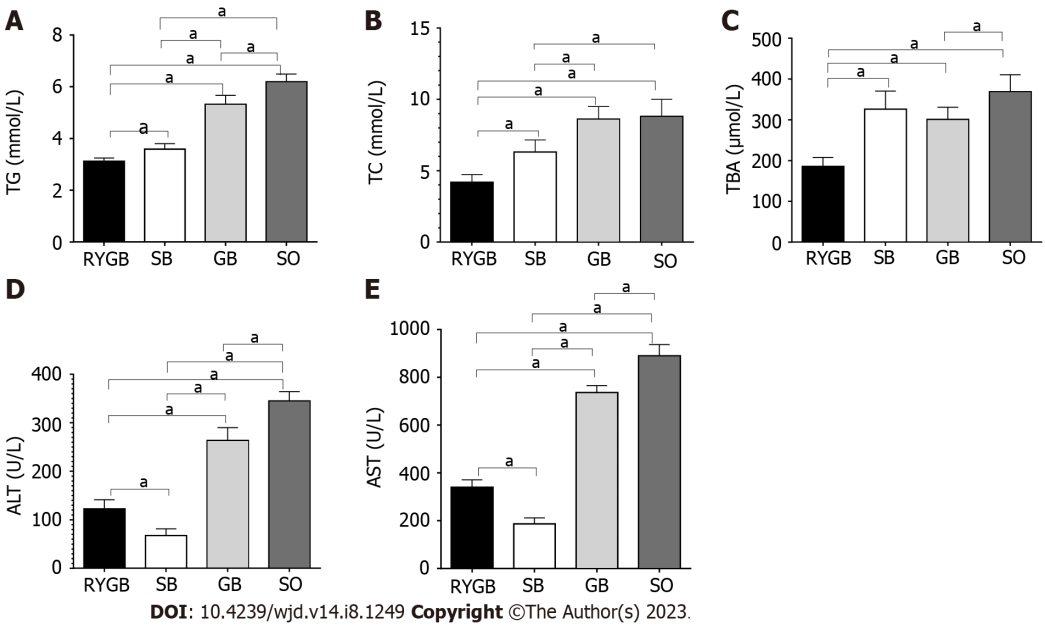

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Figure 3 Changes in biochemical indexes. A-E: Different changes in triglyceride (A), total cholesterol (B), total bile acids (C), alanine aminotransferase (D), and aspartate aminotransaminase (E) in foodborne obese diabetic rats after bariatric surgery (n = 10). $^{a}P < 0.05$. TC: Total cholesterol; TBA: Total bile acids; ALT: Alanine aminotransferase; AST: Aspartate aminotransaminase; RYGB: Roux-en-Y gastric bypass surgery; SG: Sleeve gastrectomy; GB: Gastric banding; SO: Sham operation.

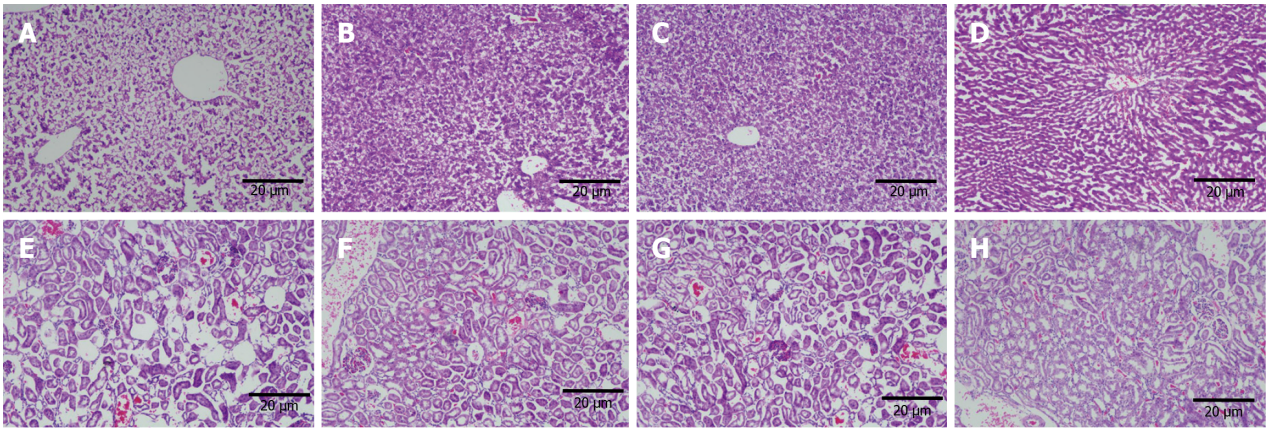

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Figure 4 Histomorphological changes in the liver and kidneys. A-H: Representative images of liver tissue in sham operation (SO) group (A), sleeve gastrectomy (SG) group (B), gastric banding (GB) group (C), and Roux-en-Y gastric bypass surgery (RYGB) group (D) in foodborne obese diabetic rats after bariatric surgery, as well as representative images of kidney tissue in SO group (E), SG group (F), GB group (G), and RYGB group (H) in foodborne obese diabetic rats after bariatric surgery are shown. Scale bars, 20 μm.

strategies for diagnosing, treating, and preventing this disease. It has been reported that acupuncture induced improvement of oxidative stress by regulating PKCβ/P66shc signaling in obese diabetic rats[21]. Here, we observed that bariatric surgery decreased the expression levels of PKCβ and P66shc.

Although these results look promising, each bariatric surgery, including RYGB, SG, and GB, has its own advantages and disadvantages. For RYGB, it has a small wound size, low risk, and good prognosis, and is generally less prone to recurrence. The way of food flow after surgery can also promote insulin secretion, effectively reduce the apoptosis of islet cells, restore the function of islets, and thus effectively treat diabetes. However, some rats undergoing RYGB will have abdominal discomfort, local inflammation of the anastomosis, and high blood sugar, which is easy to lead to incomplete healing of the surgical incision, infection, intestinal adhesion, and other complications. Some rats may also experience symptoms such as gastric paresis, gastrointestinal dysfunction, abdominal distension, and inability to eat, mainly related to the postoperative reduction of gastric volume.

For SG, it can effectively control T2DM and obesity related complications. By reducing the volume of the stomach, this surgery can reduce weight, improve T2DM, and reduce the risk of obesity related cardiovascular and cerebrovascular complications. However, SG completely removes the fundus of the stomach and may increase the risk of developing gastroesophageal reflux disease.

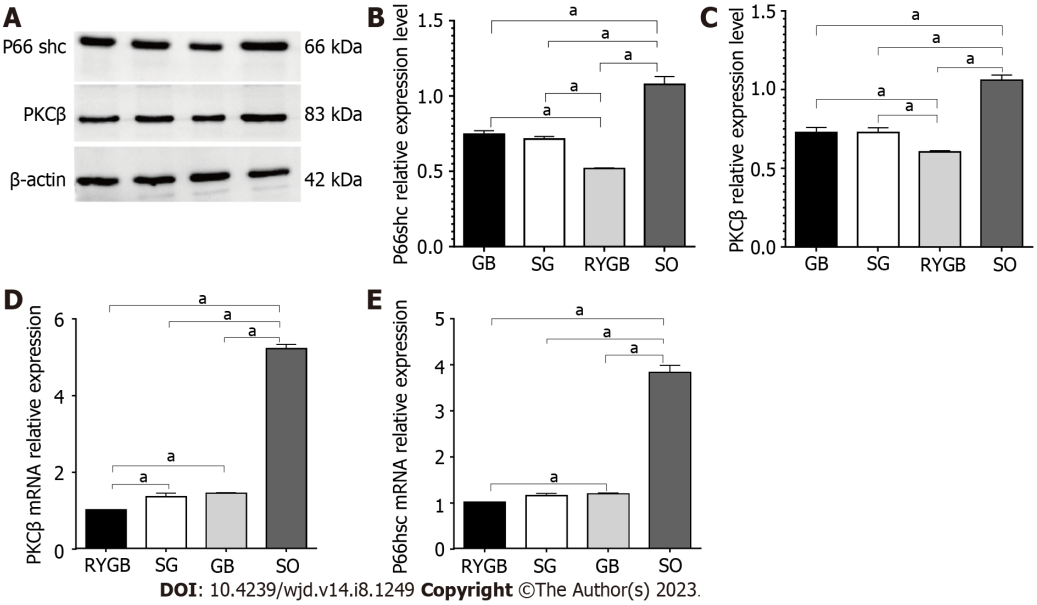

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Figure 5 Changes in protein and mRNA expression of kinase C β/P66shc. A-C: Western blot analysis of changes in P66shc and protein kinase C β protein expression; D and E: Quantitative polymerase chain reaction analysis of changes in protein kinase C β (D) and P66shc (E) mRNA expression in foodborne obese diabetic rats after bariatric surgery (n = 4). $^{a}P < 0.05$. PKC: Protein kinase C; RYGB: Roux-en-Y gastric bypass surgery; SG: Sleeve gastrectomy; GB: Gastric banding; SO: Sham operation.

For GB, like SG, it is a surgical method of reducing weight by reducing food intake. It reduces the entry passage for food by installing binding straps. The surgical damage is minimal, and there is no need to modify the digestive tract, resulting in faster postoperative recovery. However, the restraining strap is prone to displacement and expansion, and the surgical effect is not very good, resulting in limited weight loss.

CONCLUSION

Bariatric surgery may be a novel treatment for foodborne obesity-induced diabetes.

ARTICLE HIGHLIGHTS

Research background

Obesity usually causes diabetes mellitus (DM) and endangers human health seriously, and type 2 DM (T2DM) usually occurs along with obesity. Foodborne obesity-induced DM is caused by the excessive long-term diet and surplus energy.

Research motivation

Bariatric surgery can improve the symptoms of T2DM in some obese patients, but different types of bariatric surgery may have different effects.

Research objectives

To investigate the effect of different types of bariatric surgery on glucose and lipid metabolism, and liver and kidney function in rats, and to explore the underlying mechanisms.

Research methods

Male Sprague-Dawley rats aged 6-8 wk underwent Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), or gastric banding (GB). Glucose and insulin tolerance tests, analysis of biochemical parameters, histological examination, western blot, and quantitative real-time polymerase chain reaction were conducted.

Research results

In comparison to the sham operation group, the RYGB, SG, and GB groups had decreased body weight and food intake, reduced glucose intolerance and insulin insensitivity, downregulated biochemical parameters, alleviated morphological changes in the liver and kidneys, and decreased levels of protein kinase C (PKC)β/P66shc. Among the three groups, the effect in the RYGB group was better than that in the SG and GB groups.

Research conclusions

Bariatric surgeries, including RYGB, SG, and GB, can modulate the glucose and lipid metabolism, and liver and kidney function in food-derived obese diabetic rats *via* mediating the PKCβ/P66shc pathway.

Research perspectives

Bariatric surgery may be helpful for the treatment of foodborne obesity-induced DM.

FOOTNOTES

Author contributions: Long H, Zhao L, Li SX, and Wu LL designed the research; Long H and Wu LL performed the research and wrote the paper; Zhao L, Huang QL, and Xiao S supervised the report; Li SX contributed to the data analysis; Xiao ZS provided clinical advice.

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ARRIVE guidelines statement: All authors read the ARRIVE guidelines, and this manuscript was prepared and revised according to the ARRIVE guidelines.

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ORIGINAL ARTICLE

Case Control Study

Risk and predictors of severity and mortality in patients with type 2 diabetes and COVID-19 in Dubai

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Abstract

BACKGROUND

Globally, patients with diabetes suffer from increased disease severity and mortality due to coronavirus disease 2019 (COVID-19). Old age, high body mass index (BMI), comorbidities, and complications of diabetes are recognized as major risk factors for infection severity and mortality.

AIM

To investigate the risk and predictors of higher severity and mortality among in-hospital patients with COVID-19 and type 2 diabetes (T2D) during the first wave of the pandemic in Dubai (March–September 2020).

METHODS
In this cross-sectional nested case-control study, a total of 1083 patients with COVID-19 were recruited. This study included 890 men and 193 women. Of these, 427 had T2D and 656 were non-diabetic. The clinical, radiographic, and laboratory data of the patients with and without T2D were compared. Independent predictors of mortality in COVID-19 non-survivors were identified in patients with and without T2D.

RESULTS
T2D patients with COVID-19 were older and had higher BMI than those without T2D. They had higher rates of comorbidities such as hypertension, ischemic heart disease, heart failure, and more life-threatening complications. All laboratory parameters of disease severity were significantly higher than in those without T2D. Therefore, these patients had a longer hospital stay and a significantly higher mortality rate. They died from COVID-19 at a rate three times higher than patients without. Most laboratory and radiographic severity indices in non-survivors were high in patients with and without T2D. In the univariate analysis of the predictors of mortality among all COVID-19 non-survivors, significant associations were identified with old age, increased white blood cell count, lymphopenia, and elevated serum troponin levels. In multivariate analysis, only lymphopenia was identified as an independent predictor of mortality among T2D non-survivors.

CONCLUSION
Patients with COVID-19 and T2D were older with higher BMI, more comorbidities, higher disease severity indices, more severe proinflammatory state with cardiac involvement, and died from COVID-19 at three times the rate of patients without T2D. The identified mortality predictors will help healthcare workers prioritize the management of patients with COVID-19.

Key Words: Type 2 diabetes; COVID-19; Risk factors; Mortality; United Arab Emirates

Core Tip: Globally, patients with diabetes suffer from increased disease severity and mortality due to coronavirus disease 2019 (COVID-19). Old age, high body mass index (BMI), comorbidities, and complications of diabetes were recognized as major risk factors for infection severity and mortality. To identify the independent predictors of mortality in patients with type 2 diabetes (T2D) in Dubai, United Arab Emirates, we performed a cross-sectional nested case-control study during the first wave of the pandemic. It seems that the mortality of patients with T2D is driven by a significantly higher pro-inflammatory response to COVID-19 as evidenced by higher C-reactive protein, white blood cell, and lymphopenia. Mortality also seems to be synergistic with the comorbidities and complications of T2D in patients with COVID-19. The identified mortality predictors will help healthcare workers prioritize the management of patients with COVID-19.

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INTRODUCTION

It has been established that older age, higher body mass index (BMI), and comorbidities such as diabetes mellitus, hypertension, cardiovascular disease (CVD), and chronic kidney disease (CKD) are the major risk factors for severity and mortality of coronavirus disease 2019 (COVID-19) infection in patients in China[1,2], United Kingdom[3,4], United States [5-7], Sweden[8] and many other countries[9,10]. Evidence of higher severity and mortality of COVID-19 in patients with diabetes has been reported in many of the aforementioned studies and confirmed by others[11-14]. Systematic reviews [15] and meta-analyses[16-20] have established that the severity of COVID-19 in patients with diabetes is observed across all ethnicities. Similar observations were recorded in the United Arab Emirates during the first and subsequent waves of the pandemic[21-26].

The aim of this retrospective study was to determine the risk and predictors that drove the higher severity among in-hospital patients with COVID-19 and type 2 diabetes (T2D) and to describe the relationship between diabetes and all-cause mortality during the first wave of the pandemic in Dubai, United Arab Emirates.

MATERIALS AND METHODS

Study design

During the early phase of the COVID-19 pandemic, Dubai Hospital, where the study was conducted, was among the three main centers designated for the isolation and admission of all patients with COVID-19 in the Emirate of Dubai. Dubai Hospital is a specialized hospital equipped with 625 beds and incorporates 26 surgical and medical departments, including the intensive care unit (ICU), cardiology, oncology, nephrology, and endocrinology. During the first wave of the COVID-19 pandemic, most hospital wards were converted into isolation units. In this cross-sectional nested case-control study, 1083 patients with COVID-19 admitted to Dubai Hospital between March 21st and September 30th, 2020, were recruited.

Patients

All patients positive for COVID-19 were admitted to hospital. Patients were tested using reverse transcription-polymerase chain reaction (RT-PCR) using a nasopharyngeal swab for respiratory tract infection to test for COVID-19. A total of 1083 patients were randomly recruited for the study. This study included 890 men and 193 women. Of these patients, 427 had T2D and 656 did not.

Patients with type 1 diabetes were excluded. This was based on their previous medical history collected from the SALAMA Electronic Health Records (EHR) and confirmed upon admission. The following clinical data were obtained from the EHR: Age (13–87 years), sex (men/women), nationality (emirates/expatriates), and comorbidities [hypertension, ischemic stroke, cardiomyopathy, heart failure, chronic obstructive pulmonary disease, asthma, and diabetic ketoacidosis]. The following presenting symptoms were recorded at admission: Fever, cough, shortness of breath, sore throat, chest pain, myalgia, headache, chills, fatigue, malaise, loss of appetite, runny nose, abdominal pain, loss of taste, loss of smell, vomiting, diarrhea, dizziness, confusion, skin rash, and arthralgia. Noninvasive ventilation, intubation, and admission to the ICU were also recorded.

Clinical parameters

The mean ages of the patients were 51 and 39 years for those with and without T2D, respectively. Demographic features and the presence of co-morbidities, such as a prior diagnosis of cardiac disease, hypertension, diabetes, or respiratory disease, and any medication used were recorded. Patients were further categorized as asymptomatic, mild, moderate, severe, or critical according to the National Institutes of Health categorization of COVID-19 severity[26], as follows:

Asymptomatic: Patients have no symptoms but have tested positive for COVID-19.

Mild: Patients have symptoms and signs such as fever, cough, sore throat, malaise, headache, or muscle pain, but no shortness of breath, dyspnea, or abnormal chest radiography.

Moderate: Patients had clinical or imaging findings suggestive of lower respiratory disease but maintained an oxygen saturation of > 93% on room air.

Severe: The respiratory rate (RR) of the patients was above 30/min, oxygen saturation was ≤ 93%, PaO2/FiO2 was < 300, and/or pneumonic infiltrates involving > 50% of the lungs were observed.

Critical: Patients suffer respiratory failure, septic shock, and/or multiple organ dysfunction.

The vital signs recorded at the time of admission included blood pressure, heart rate, RR, SpO_2, and temperature.

Data collection

Data were collected from all patients with and without T2D from the Dubai Hospital SALAMA Electronic Medical Record System. The information collected was categorized into demographic data, medical and glycemic histories, physical examination results, comorbidities, laboratory investigation results, chest radiographs, complications, and treatment protocols. The collected data were entered into an SPSS data collection sheet explicitly designed for this study. All patient data were de-identified throughout the collection, categorization, and creation of the database. The reporting of this study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[27].

Laboratory and imaging data:

Laboratory measurements recorded for patients with COVID-19 included complete blood count, ferritin, absolute lymphocyte count, lactate dehydrogenase, procalcitonin, C-reactive protein (CRP), creatine phosphokinase, D-dimer, pro-BNP, serum creatinine, fasting blood glucose, and Hb_{A1C}.

Chest X-ray scoring: A chest radiograph severity scoring system was used to determine the severity of the pneumonia. The images were also classified as exhibiting ground-glass opacities, reticular patterns, or consolidations and as normal, mild, moderate, or severe.

Treatment protocol

The management and Treatment of COVID-19 followed the United Arab Emirates Guidelines[28]. which are based on the National Institutes of Health (NIH) guidelines (NIH, 2021)[29]. After a thorough assessment of clinical severity, all patients with COVID-19 were treated (March–September 2020) with a standard combination of hydroxychloroquine

sulfate and Kaletra antiviral (lopinavir/ritonavir). Therefore, there were no differences in drug management between patients with and without T2D. Patients were considered cured after two consecutive negative (determined through RT-PCR) nasopharyngeal swabs following clinical recovery.

Statistical analysis

Data were analyzed using SPSS for Windows version 28.0 (SPSS Inc., Chicago, IL, United States). Categorical variables are described as percentages. Continuous variables were described using a measure of tendency and dispersion. Continuous data were tested for normality using the Kolmogorov-Smirnov test. The Mann-Whitney U test and *t*-test were used when appropriate to compare the means between continuous variables. Categorical variables were cross-tabulated to examine the independence between variables, the χ^2 test or Fisher's exact test was used as appropriate.

Kaplan-Meier estimates were used to examine the effect of T2D on survival. The estimate was based on the serial time to death of patients with T2D and controls. The results of the computed model are visualized in a survival plot (Figure 1). In addition to the Kaplan-Meier analysis, univariate and multivariate analyses containing all the variables that differed statistically between survivors and non-survivors were performed to identify the independent predictors of mortality among patients with COVID-19 and T2D. Statistical significance was set at $P < 0.05$.

RESULTS

Demographic characteristics

A total of 1083 patients (890 men and 193 women) diagnosed with COVID-19 were enrolled in this study. Among the men, 378 (42%) had T2D, whereas among the women, only 49 (25%) had T2D. The mean age of patients with T2D is 51.4 (± 11.2), whereas for patients without T2D is 39.4 (± 13.5) ($P < 0.001$). There was also a significant difference in BMI between patients with T2D [28.80 (± 5.47)] compared to patients without T2D [27.20 (± 4.94)] ($P < 0.001$).

The demographic characteristics and comorbidities of patients with T2D and patients without are shown in Table 1. Patients with T2D and COVID-19 had higher rates of comorbidities, such as hypertension, ischemic heart disease, and heart failure compared to patients with COVID-19 without T2D.

Presenting symptoms and signs

Only dyspnea, cough, sore throat, and headache were significantly more frequent in patients with T2D (Table 1).

Laboratory measurements

All 18 Laboratory measurements indicative of disease severity were significantly higher among patients with T2D (Table 1).

Radiographic and severity indices of chest infection

Chest radiographs of patients with COVID-19 and T2D exhibited significantly more lung consolidation, ground-glass appearance, and severity than patients without (Table 1). Consequently, COVID-19 patients with T2D had significantly lower SpO_2 saturation and required more noninvasive assisted ventilation as well as frequent mechanical ventilation. They also had more life-threatening complications, such as diabetic ketoacidosis and acute kidney failure. Therefore, these patients had longer hospital stays and significantly higher mortality rates.

Treatment protocols

All patients with COVID-19 were treated (March-September 2020) with a standard combination of hydroxychloroquine sulfate and Kaletra antiviral medication (lopinavir/ritonavir). Therefore, there were no differences in drug management between patients with and without T2D.

The frequency and/or absolute values of independent predictors of mortality between survivors and non-survivors of COVID-19, with and without T2D

In general, patients with COVID-19 with T2D were 12 years older than those without T2D (Table 1). In addition, non-survivors were older than survivors in both groups (Table 2). On admission, there were no significant differences in the symptoms between the two groups.

Most laboratory indicators of disease severity were equally high among the COVID-19 non-survivors in each group (Table 2). The association of radiographic and severity indices of chest infection with mortality in patients with COVID-19 was also equally high among the patients in each group. Therefore, most risk factors for severity and predictors of mortality in T2D non-survivors and controls were similar, with few exceptions (Table 2).

The relationship between glycemic control and mortality

The relationship between random blood glucose, fasting blood glucose and blood Hb_{A1C}, and mortality among patients with COVID-19 and T2D was tested using the Mann-Whitney U test and found to be statistically insignificant.

Predictors of mortality among non-survivors of COVID-19 with T2D

Predictors of mortality were determined in non-survivors of COVID-19 with and without T2D, using univariate analysis.

Table 1 Demographic characteristics, comorbidities, symptoms, signs, laboratory measurements, radiographic and severity indices of chest infection, and disease outcome observed in coronavirus disease 2019 patients with and without type 2 diabetes; in Dubai

Characteristics	T2D (*n* = 427)	Without T2D (*n* = 656)	*P* value[a]
A: Demographics and comorbidities [*n* (%)]			
Gender	No (%)		
Male	378 (42.5)	512 (57.5)	
Female	49 (25.4)	144 (74.6)	< 0.001
Nationality			
United Arab Emirates	23 (59)	16 (41)	
Expatriate	404 (38.7)	640 (61.3)	0.009
Hypertension	165/427 (38.6)	88/656 (13.4)	< 0.001
Ischemic heart disease	21/427 (4.9)	3/656 (0.5)	< 0.001
Cardiomyopathy	2/427 (0.5)	0/656	0.155
Heart failure	13/427 (3)	4/656 (0.6)	0.002
COPD	2/427 (0.5)	1/656 (0.2)	0.344
Asthma	10/427 (2.3)	18/656 (2.7)	0.421
B: Symptoms and signs [*n* (%)]			
Fever	358 (85.9)	528 (82.8)	0.105
Cough	303 (72.7)	388 (60.8)	< 0.001
Sore throat	52 (12.5)	150 (23.5)	< 0.001
Running nose/rhinorrhoea	17 (4.1)	40 (6.3)	0.079
Shortness of breath (dyspnoea)	276 (66.2)	250 (39.2)	< 0.001
Chest pain	22 (5.3)	29 (4.5)	0.344
Chills	13 (3.1)	35 (5.5)	0.047
Headache	24 (5.8)	74 (11.6)	< 0.001
Fatigue	92 (22.1)	116 (18.2)	0.071
Malaise	8 (1.9)	15 (2.4)	0.405
Nausea	11 (2.6)	17 (2.6)	0.572
Loss of appetite/anorexia	19 (4.6)	22 (3.4)	0.226
Loss of taste	1 (0.2)	6 (0.9)	0.164
Anosmia/loss of smell	1 (0.2)	6 (0.9)	0.164
Abdominal pain	12 (2.9)	46 (7.2)	0.001
Vomiting	39 (9.4)	47 (7.4)	0.150
Diarrhoea	26 (6.2)	34 (5.3)	0.312
Myalgia	123 (29.5)	180 (28.2)	0.351
Arthralgia/joint pain	1 (0.2)	2 (0.2)	0.635
Dizziness	10 (2.4)	21 (3.3)	0.259
Confusion	4 (1.0)	2 (0.3)	0.216
Skin rash	1 (0.2)	1 (0.2)	0.635
C: Laboratory measurements [mean (± SD)]			
Haemoglobin (g/dL)	12.42 (2.07)	13.45 (1.84)	< 0.001
MCV (fL)	85.66 (37.79)	84.54 (7.74)	0.01
WBC (10^9/L)	9.62 (7.87)	8.31 (7.25)	< 0.001

Lymphocyte (%)	14.57 (8.52)	18.46 (10.08)	< 0.001
Absolute lymphocyte count	1.05 (0.82)	1.26 (0.78)	< 0.001
Random blood glucose (mg/dL)	222.53 (114.59)	119.16 (42.75)	< 0.001
Fasting blood glucose POCT (mg/dL)	192.06 (88.88)	126.77 (48.38)	< 0.001
Hb_{A1C} (%)	9.26 (2.44)	5.74 (0.47)	< 0.001
CRP (mg/L)	86.38 (88.05)	50.23 (64.68)	< 0.001
Troponin (ng/mL)	180.10 (917.58)	18.29 (64.11)	< 0.001
D-Dimer (mcg/mL)	4.14 (6.43)	2.46 (5.04)	< 0.001
Pro-calcitonin (ng/mL)	0.97 (4.2)	0.61 (3.18)	< 0.001
Pro-BNP (pg/mL)	1948.56 (4602.46)	1533.62 (6449.57)	0.008
Ferritin (mcg/L)	1526.7 (2153.81)	1231.68 (3268.65)	< 0.001
LDH (U/L)	444.93 (371.05)	355.55 (243.98)	< 0.001
LDH-Peak (U/L)	429.27 (393.39)	366.62 (585.83)	< 0.001
CPK peak (U/L)	597.8 (1090.39)	505.5 (2055.57)	0.022
Creatinine (mg/dL)	1.87 (2.12)	1.16 (1.44)	< 0.001
D: Chest radiographs, ventilation and disease outcome [No (%)]			
Normal chest radiograph	16 (3.8)	99 (16.5)	< 0.001
Mild consolidation [1-2 zones]	174 (41.7)	342 (57.1)	
Moderate consolidation [2-3 zones]	183 (43.9)	125 (20.9)	
Severe consolidation [3-4 zones]	44 (10.6)	33 (5.5)	
E: SpO_2 on admission			
≤ 94	84 (19.7)	64 (9.8)	< 0.001
> 94	343 (80.3)	592 (90.2)	
F: Ventilation and/or intubation			
O_2 mask	58 (13.6)	43 (6.6)	< 0.001
Nasal canula	311 (72.8)	361 (55)	< 0.001
Intubation	42 (9.8)	15 (2.3)	< 0.001
G: Complications & Outcomes			
Diabetic keto acidosis	7 (4.5)	0	0.01
Chronic kidney failure	37 (10.5)	16 (3)	< 0.001
Length of hospital stay, mean (days)	14.90 (17.31)	7.49 (10.22)	< 0.001
Death: No (%)	63/427 (14.8)	32/656 (4.9)	< 0.001

[a]*t*-test, Mann-Whitney and Chai Square.

COPD: Chronic obstructive pulmonary disease; WBC: White blood cell; CRP: C-reactive protein; LDH: Lactate dehydrogenase; T2D: Type 2 diabetes; MCV: Mean corpuscular volume; POCT: Point of care testing; CPK: Creatine phospho-kinase.

Among the eight clinical and 12 Laboratory risk factors (Table 2), significant associations of mortality of COVID-19 in patients with and without T2D were identified with advanced age, increased total white blood cell (WBC) count, lymphopenia, and elevated serum troponin. In multivariate analysis, only lymphopenia was identified as a predictor of mortality in patients with T2D.

Survival analysis of COVID-19 patients based on T2D status using Kaplan-Meier estimates.

Kaplan-Meier analysis was used to compare survival against serial time to death between patients with and without T2D (Figure 1). The median time of death among patients without T2D is less than that among patients with T2D [42 d with 95%CI: 32.2–51.8 and 54 d with 95%CI (23.3–84.7)]; respectively. This difference was not statistically significant because 95% of the CIs overlapped. However, the number of deaths was significantly higher among patients with T2D [63 (14.8%)] than among patients without T2D [36 (5.5%)], with $P < 0.001$ (Table 3).

Table 2 The association between demographic characteristics, comorbidities, symptoms, signs, laboratory measurements, radiographic and severity indices of chest infection and disease outcome observed in coronavirus disease 2019 patients with and without type 2 diabetes in Dubai

Characteristics	T2D (*n* = 427)			Without T2D (*n* = 656)		
	Survivors (*n* = 364)	Non-survivors (*n* = 63)	*P* value	Survivors (*n* = 624)	Non-survivors (*n* = 32)	*P* value[a] < 0.001
A: Demographics and comorbidities [*n* (%)]						
Males: No (%)	325 (86)	53 (14)	0.164	484 (94.1)	30 (5.9)	0.072
Females: No (%)	39 (79.6)	10 (20.4)		140 (98.6)	2 (1.4)	
Age: Yr (± SD)	50.76 (10.92)	54.86 (12.58)	0.02	38.83 (13.42)	48.58 (12.43)	< 0.001
BMI (±SD)	28.81 (5.53)	28.69 (5.08)	0.841	27.15 (4.95)	28.03 (5.05)	0.400
Hypertension, No (%)	137 (37.6)	28 (44.4)	0.188	77 (12.4)	11 (30.6)	0.005
B: Symptoms and signs [*n* (%)]						
Fever	306 (86.4)	52 (82.5)	0.26	502 (82.8)	26 (81.0)	0.484
Cough	256 (72.3)	47 (74.6)	0.418	359 (59.2)	29 (90.6)	< 0.001
Sore throat	50 (14.1)	2 (3.2)	0.007	146 (24.1)	4 (12.5)	0.093
Dyspnea	224 (63.3)	52 (82.5)	0.002	222 (36.6)	28 (87.5)	< 0.001
Headache	23 (6.5)	1 (1.6)	0.097	73 (12)	1 (3.1)	0.095
C: Laboratory measurements [mean (± SD)]						
Hemoglobin (g/dL)	12.69 (2.06)	10.95 (1.36)	< 0.001	13.6 (1.7)	10.7 (1.2)	< 0.001
MCV (fL)	85.98 (41)	83.95 (7.28)	0.815	84.4 (7.6)	86.2 (10)	0.223
WBC (10^9/L)	9.02 (6.56)	12.86 (12.41)	< 0.001	7.6 (4.75)	18.9 (20.4)	< 0.001
Lymphocytes (%)	15.48 (8.59)	9.55 (6.1)	< 0.001	18.79 (9.7)	13.1 (13.3)	< 0.001
Absolute lymphocyte	1.13 (0.84)	0.57 (0.5)	< 0.001	1.3 (0.7)	1.2 (1.6)	< 0.001
Random glucose (mg/dL)	221.52 (115.69)	227.94 (109.3)	0.442	118.8 (43.6)	124.4 (62.3)	0.026
Fasting glucose (mg/dL)	107.46 (114.85)	118.1 (121.74)	0.191	118.8 (43.6)	52.5 (68)	< 0.001
Hb_{A1C} (%)	9.32 (2.4)	8.87 (2.64)	0.13	5.73 (0.5)	5.9 (0.4)	0.586
CRP (mg/L)	76.23 (77.72)	141.1 (116.77)	< 0.001	44.6 (56)	138 (108)	< 0.001
Troponin (ng/mL)	167.19 (990.22)	238.21 (470)	< 0.001	15.9 (64.5)	37.6 (58.4)	< 0.001
D-Dimer (mcg/mL)	3.09 (4.53)	9.56 (10.79)	< 0.001	1.78 (3.84)	8.9 (9.1)	< 0.001
Procalcitonin (ng/mL)	0.83 (4.32)	1.75 (3.45)	< 0.001	0.51 (3.01)	1.9 (4.72)	< 0.001
Pro-BNP (pg/mL)	1225.01 (3572)	3862.9 (6248.31)	0.007	1324.5 (7323)	2109.1 (2985.8)	< 0.001
Ferritin (mcg/L)	1277.9 (1599.2)	2888 (3749)	< 0.001	856.2 (1179)	5549.9 (10016)	< 0.001
LDH (U/L)	416.41 (365.96)	611.04 (360.04)	< 0.001	321.1 (164.7)	785 (521.5)	< 0.001
LDH-Peak (U/L)	402.02 (394.6)	605.2 (339.82)	< 0.001	346.3 (587.3)	644.1 (491.3)	< 0.001
CPK peak (U/L)	464.9 (970.7)	1163.5 (1369.5)	< 0.001	432.8 (2145.6)	1041.2 (1085)	< 0.001
Creatinine (mg/dL)	1.61 (2.01)	3.22 (2.17)	< 0.001	1.02 (1.22)	3.2 (2.55)	< 0.001
D: Chest radiographs, ventilation and disease outcome [*n* (mean ± SD)]						
E: Chest radiograph						
Normal X-ray	15 (4.2)	1 (1.6)	0.021	99 (17.4)	0	< 0.001
Mild	156 (43.9)	18 (29)		335 (59)	7 (22.6)	
Moderate	152 (42.8)	31 (50)		11 (19.5)	14 (45.2)	

Severe	32 (9)	12 (19.4)		23 (4)	10 (32.3)	
F: SpO_2 on admission						
≤ 94	56 (15.4)	28 (44.4)		574 (92.6)	18 (50)	< 0.001
> 94	308 (84.6)	35 (55.6)	< 0.001	46 (7.4)	18 (50)	
G: Ventilation and/or intubation						
O_2 mask	32 (8.8)	26 (41.3)	< 0.001	23 (3.7)	20 (55.6)	< 0.001
Nasal canula	269 (73.9)	42 (66.7)	0.15	340 (54.8)	21 (58.3)	0.408
Intubation	21 (5.8)	21 (33.3)	< 0.001	6 (1.0)	9 (25)	< 0.001
H: Complications & outcomes						
Diabetic ketoacidosis	3 (2.3)	4 (14.3)	0.02			
Chronic kidney failure	19 (6.4)	18 (31)	< 0.001	11 (2.2)	5 (15.2)	0.002
Length of hospital stay: Mean (SD)	14.47 (17.9)	17.02 (14)	0.005	6.47 (8.53)	32 (20.06)	< 0.001

[a]*t*-test, Mann-Whitney and Chai Square.
BMI: body mass index; WBC: White blood cell; CRP: C-reactive protein; LDH: Lactate dehydrogenase; T2D: Type 2 diabetes; MCV: Mean corpuscular volume; CPK: Creatine phospho-kinase.

Table 3 Comparison of the rate of mortality of COVID-19 patients, with and without type 2 diabetes; in successive 5-day intervals of hospital admission, in Dubai

	Total number of patients (*n* = 1083)	Patients with T2D (*n* = 427)	Patients without T2D (*n* = 656)	Ratio: T2D:Non-T2D
0-5 d	15	10	5	3.1
6-10 d	18	12	6	3.1
11-15 d	20	15	5	4.6
16-20 d	8	4	4	1.53
21-25 d	13	9	4	3.5
26-30 d	8	7	1	10.8
> 30 d	13	6	7	1.3
Total	95	63	32	3.1

T2D: Type 2 diabetes.

Rate of mortality of patients with COVID-19 with and without T2D

The overall ratio of COVID-19 patients who died among patients with T2D was three times that of patients without T2D (Table 3). The ratio remained high in each successive 5-d interval for the first 4 wk of admission but decreased thereafter.

DISCUSSION

In this cross-sectional nested case-control study, we determined the risk factors and predictors that drove higher disease severity and mortality among in-hospital patients with COVID-19 and T2D during the first wave of the pandemic in Dubai, United Arab Emirates. Patients with T2D and COVID-19 seem to have higher rates of comorbidities such as hypertension, ischemic heart disease, and heart failure compared to patients with COVID-19 without T2D. Older men with T2D and high BMI were more prone to severe COVID-19. Dyspnea, cough, sore throat, and headache were significantly more frequent in patients with T2D. All laboratory measurements indicative of disease severity were significantly higher in patients with T2D. On chest radiographs, patients with COVID-19 infection with T2D showed significantly more lung consolidation, glassy appearance, and severity than patients without T2D. Consequently, patients with COVID-19 with T2D had significantly lower SpO_2 saturation and required more noninvasive assisted ventilation as well as frequent mechanical ventilation. They also had more life-threatening complications, such as diabetic ketoacidosis and acute kidney failure. Therefore, these patients had more ICU admissions, longer hospital stays, and significantly higher mortality rates.

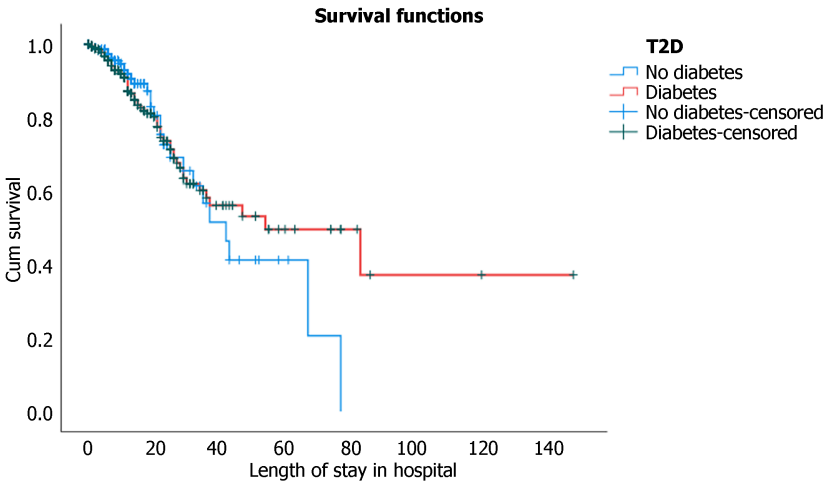

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Figure 1 The Kaplan-Meier plot relating survival against serial time to death between coronavirus disease 2019 patients with and without type 2 diabetes. T2D: Type 2 diabetes.

Most laboratory indicators and radiographic and severity indices of chest infection in non-survivors were equally high in patients with COVID-19 with and without T2D. Therefore, we used Kaplan-Meier analysis to explain survival against serial time to death between patients with and without T2D. Although the median time of death among patients without T2D is lower than that among patients with T2D (42 *vs* 54 d), the number of deaths was significantly higher among patients with T2D [63/427 (14.8%)] than among patients without T2D [32/656 (4.9%)]. The overall ratio of patients with T2D dying is three times higher than that of patients without T2D. The ratio remained high in each successive 5-d interval for the first 4 wk of admission, but, decreased thereafter.

In addition to Kaplan-Meier analysis of the effect of T2D on survival, univariate and multivariate analyses were performed, including all the variables that differed statistically between survivors and non-survivors, to identify independent predictors of mortality among patients with COVID-19. Initially, predictors of mortality were examined using univariate analysis. Among eight clinical and 12 Laboratory risk factors, significant associations of mortality of COVID-19 in patients with and without T2D were identified with advancing age, increased total WBC count, lymphopenia, and elevated serum troponin. In multivariate analysis, only lymphopenia was identified as a predictor of mortality in patients with T2D.

In this study, we found no relationship between glycemic control and mortality. It cannot be implied that the poorer the glycemic control, the higher the mortality rate. Hyperglycemia *per se* is not an independent predictor of mortality. In contrast, it seems that the mortality of patients with T2D is driven by a much higher inflammatory response to COVID-19 as evidenced by higher CRP levels, higher WBC counts, and lymphopenia. It is also possible that mortality is associated with cardiac damage as evidenced by elevated serum troponin and synergized by the large number of comorbidities and complications observed in patients with T2D[30].

Similar investigations conducted overseas[1-20] and in the United Arab Emirates[21-26], have reported that the prevalence of diabetes in patients with COVID-19 does not differ from that in the general population, indicating that the primary risk of COVID-19 infection is not increased in patients with diabetes. It seems that the increased risk of COVID-19 severity and mortality in patients with diabetes is due to older age and comorbidities, such as hypertension, CVD, CKD, and obesity, in addition to a severe proinflammatory state and cardiac involvement. The risk that patients with diabetes face is that they are more likely to have worse complications and not have a greater chance of contracting the virus[31].

This study demonstrated that patients with COVID-19 with T2D had more comorbidities, higher disease severity, and died at three times the rate of patients without T2D. Identifying the predictors of mortality may allow healthcare workers to prioritize vaccination and implement early management strategies for patients with COVID-19 patients and T2D to offset this calamity.

Limitations

The authors acknowledge the several limitations of this study. It is possible that there was a selection bias in this study, as it was a short-term cross-sectional nested case-control study in which data were collected over a short period in a pandemic environment. In this cross-sectional study, it was not possible to establish causal inferences or analyze temporal changes. Patients could not be followed-up with after discharge, limiting the possibility of further outcomes. Despite these limitations, this study provided data on a large cohort of patients with COVID-19 and T2D with results similar to those of many internationally acknowledged studies.

CONCLUSION

Patients with COVID-19 and T2D were older with higher BMI, more comorbidities, higher disease severity indices, more severe proinflammatory state with cardiac involvement, and died from COVID-19 at three times the rate of patients without T2D. The identified mortality predictors will help healthcare workers prioritize the management of patients with COVID-19.

ARTICLE HIGHLIGHTS

Research background

Patients with diabetes suffer higher morbidity and mortality from corona virus disease 2019 (COVID-19). Despite better outcomes due to vaccination, many patients with diabetes continue to suffer from the disease. It is imperative therefore, to continue investigating the risk and predictors of COVID-19 severity in this vulnerable group, to help shaping better management of the disease.

Research motivation

Identifying independent predictors of mortality from COVID-19 will allow healthcare workers to prioritize vaccination, implement early management strategies for patients with COVID-19 and type 2 diabetes (T2D), and offset disease severity and mortality.

Research objectives

To identify independent mortality predictors among in-hospital patients with COVID-19 and T2D during the first wave of the pandemic (March–September 2020) in Dubai, United Arab Emirates.

Research methods

In this cross-sectional nested case-control study, a total of 1083 patients with COVID-19 were recruited. Of these, 427 had T2D and 656 were non-diabetic. The clinical, radiographic, and laboratory data of the patients with and without T2D were compared. Independent predictors of mortality in COVID-19 non-survivors were identified in patients with and without T2D.

Research results

Patients with T2D and COVID-19 were older and had a higher body mass index than patients without T2D. They had higher rates of comorbidities such as hypertension, ischemic heart disease, heart failure, and more life-threatening complications. All laboratory parameters of disease severity were significantly higher than in those without T2D. Therefore, these patients had a longer hospital stay and a significantly higher mortality rate. These patients died from COVID-19 at three times the rate of patients without T2D. In the univariate analysis of the independent predictors of mortality among all COVID-19 non-survivors, significant associations were identified with old age, increased white blood cell count, lymphopenia, and elevated serum troponin levels. In multivariate analysis, only lymphopenia was identified as an independent predictor of mortality among T2D non-survivors.

Research conclusions

It seems that the increased severity and mortality of patients with COVID-19 and T2D is due to older age and comorbidities such as hypertension, cardiovascular disease, chronic kidney disease, and obesity, with an added severe proinflammatory state.

Research perspectives

It is necessary to further investigate the factors that heighten the pro-inflammatory state, driving higher mortality among patients with T2D and COVID-19.

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FOOTNOTES

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Informed consent statement: Patients' informed consent was waived by DSREC as part of the policy to garner information about the COVID-19 pandemic. Therefore, patient consent was not obtained.

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Data sharing statement: All primary data is available on request at https://www.mbru.ac.ae//college-of-medicine/.

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ORIGINAL ARTICLE

Retrospective Study

Conbercept combined with laser photocoagulation in the treatment of diabetic macular edema and its influence on intraocular cytokines

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Abstract

BACKGROUND

The prevalence of diabetes mellitus (DM) in China is high, and the base is broad. Diabetic retinopathy (DR) is a critical condition affecting the life and health of a nation and its economic development. DR is a common complication of DM.

AIM

To investigate the efficacy of laser photocoagulation combined with intravitreal injection of conbercept for treating macular edema.

METHODS

Overall, 130 patients with diabetic macular edema (DME) hospitalized in The Third People's Hospital of Changzhou from January 2019 to June 2022 were retrospectively included. According to the treatment plan, 130 patients with DME were categorized into an observation and a control group, with 65 patients in each group. The control group received laser photocoagulation, and the observation group received laser photocoagulation with intravitreal injection of conbercept. Observe changes in vision, cytokines in the eye and so on.

RESULTS

The total efficacy rate in the observation group (93.85%) was higher than that in the control group (78.46%) ($P < 0.05$). In both groups, the best corrected visual acuity correction effect improved after treatment, and the observation group was superior to the control group ($P < 0.05$). Retinal thickness and central macular thickness improved after treatment, and the observation group was superior to the control group ($P < 0.05$). The levels of vascular endothelial growth factor, interleukin-6, soluble intercellular adhesion molecule-1, and basic fibroblast growth factor in both groups improved after treatment, and the observation group was superior to the control group ($P < 0.05$).

CONCLUSION

In patients with macular edema, combining laser photocoagulation and intravitreal injections of conbercept for DME is a more effective and safer strategy to improve vision, and lower intraocular cytokine levels.

Key Words: Conbercept; Laser photocoagulation; Diabetes treatment; Diabetic retinopathy; Diabetic macular edema; Intraocular cytokines

Core Tip: This study investigated the efficacy of intravitreal injection of conbercept combined with retinal laser photocoagulation in treating diabetic retinopathy (DR) with macular edema and compared the effectiveness of conbercept injection based on laser photocoagulation in the treatment of DR. It also provides a new scheme for clinical treatment of DR with macular edema. The results showed that intravitreal injection of conbercept combined with laser photocoagulation could be more effective in treating diabetic macular edema, shortening the treatment process, and reducing the level of cytokines in the eye. Thus, this treatment plan warrants further promotion.

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INTRODUCTION

Diabetic retinopathy (DR) is a common complication in patients with diabetes. DR is a critical factor affecting people's lives, health, and economic development. Furthermore, there are many reasons for vision loss in patients with DR, including diabetic macular edema (DME). However, the etiology of DME is unknown and may be related to reduced retinal barrier function in macular DME, which mainly appears as a retinal thickening and can cause patients to develop significant DME, primarily manifesting as a retinal thickening and can cause patients to develop substantial visual impairment, which requires active treatment[1]. Historically, the main clinical treatment strategy for DME has been laser photocoagulation of the retina under glycemic control, where laser energy causes protein denaturation and coagulation, capillary and outer retinal wall occlusion, and reduced macular blood flow[2]. Laser photocoagulation is important in treating retinal vascular diseases and cannot be completely replaced by various intraocular drugs. The predominant technique in the clinical treatment of DR is laser photocoagulation because it inhibits intraocular vascular growth, reduces macular edema, and improves visual acuity[3].

DR is primarily caused by metabolic abnormalities and organ dysfunction due to diabetes. Therefore, laser photocoagulation alone improves symptoms and effectively prevents DR[4]. As research progresses, it is currently known that the development of DME is closely related to vascular endothelial growth factor [hereafter referred to as vascular endothelial growth factor (VEGF)]. Intravitreal administration of anti-VEGF drugs can rapidly improve DME symptoms and has attracted significant clinical attention. Conbercept is a humanized anti-VEGF drug manufactured domestically and with a strong presence in the domestic market, available for treating ocular vascular diseases with remarkable results[5]. This study aimed to evaluate the combined effects of conbercept intravitreal administration and laser retinal photocoagulation for DME, compare the effects of combined treatment and laser photocoagulation alone, and propose a new clinical treatment system for DME in DR.

MATERIALS AND METHODS

General information

Overall, 130 patients with DME who were hospitalized in The Third People's Hospital of Changzhou between January 2019 and June 2022 were retrospectively included. According to the treatment plan, 130 patients with DME were categorized into an observation and a control group, with 65 patients in each group. The observation group comprised 39 males (39 diseased eyes) and 26 females (26 diseased eyes). The age of the patients in this group was 33-79 (51.07 ± 12.50) years. The disease duration in the selected patients ranged from 1 to 4 (2.49 ± 0.34) wk. The control group comprised 36 males (48 diseased eyes) and 29 females (39 diseased eyes). The age of the patients in the control group ranged from 34 to 78 (52.48 ± 11.37) years. Their disease duration ranged from 1 to 4 (2.58 ± 0.37) wk. No significant differences were found in the general characteristics (sex, age, or disease duration) between the two groups ($P > 0.05$).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Age ³18, met diagnostic criteria for DR; (2) met DME diagnostic standards, best corrected visual acuity (BCVA) < 0.6, and central macular thickness (CMT) ≥ 250 μm; and (3) no severe organ

dysfunction, such as heart, liver, and kidney.

The exclusion criteria were as follows: (1) Previous cataract or other eye surgeries; (2) other types of maculopathy; and (3) patients who could not undergo eye surgery[6].

Therapeutic method

Intravitreal injection of conbercept and laser photocoagulation treatment were used in the observation group; antibiotic eye drops were routinely used 5 d preoperatively. Intravitreal injections of conbercept included disinfection of a drapery, topical anesthesia, eyelid opener, povidone-iodine solution (5%), conjunctival sac disinfection, and normal saline irrigation. A 1-mL disposable syringe was connected to a 30 G needle to suction 0.05 mL conbercept injection. The tip of the needle was perpendicular to the eyeball wall, and the needle was inserted approximately 1 cm from the flat part of the ciliary body 3.5-3.8 mm behind the superior temporal limbus.

The needle was confirmed to reach the vitreous cavity from the pupil area, slowly push the injection, pull it out after completion, and gently press the needle eye with a cotton swab for 2 min. Tobramycin and Dexamethasone Eye Ointment were applied to the conjunctival sac, a bandage was used, and antibiotics were administered for 3 d[7].

The 532 nm laser pan-retinal photocoagulation: 1 wk after intravitreal injection of conbercept, laser system (California, Lumenis, United States), wavelength 532 nm, spot diameter 200-300 μm, exposure time 0.2-0.3 s, power level I-III, and Spaced one spot diameter apart. First, photocoagulation of the uncovered part of the vitreous hemorrhage was performed 3-4 times at 1-wk intervals as the accumulated blood was absorbed. The total effective photocoagulation volume was 1200-1500 points. It was completed by senior doctors of the same specialty[8].

The control group was treated with 532 nm laser photocoagulation, and the procedure was the same as that of the observation group.

Detection methods of related indicators

(1) BCVA was measured according to the international standard eye chart; (2) retinal thickness was measured using optical coherence tomography (OCT, Heidelberg, Germany); (3) CMT was measured using OCT; (4) a 5-mL was collected in the morning in a common vacuum tube and centrifuged at 3500 rpm for 15 min at a centrifuge radius of 8 cm. The upper serum was collected, and the level of VEGF was measured using ELISA; (5) vitreous fluid from patients was collected and diluted, and interleukin-6 (IL-6) expression and soluble intercellular adhesion molecule-1 (sICAM-1) and basic fibroblast growth factor (BFGF) levels were measured using ELISA; and (6) the adverse reactions during treatment were recorded in both groups[9].

The criterion of therapeutical effect

Significant effect: Fundus fluorescein angiography showed retinal capillaries, arteriolar non-perfusion area, and no neovascularization and visual acuity reached 5.0 or improved more than 2 lines; effective: Retinal capillaries, arteriolar non-perfusion area, and neovascularization significantly reduced, visual acuity improved 1 line; ineffective: retinal capillaries, arteriolar non-perfusion area, and neovascularization did not decrease or aggravate, and visual acuity did not improve. Ametropia refers to corrected visual acuity. Total effective rate = (effective + markedly effective)/total cases × 100%[10].

Observation target

(1) The BCVA was measured using an international standard visual acuity chart at four-time points: Before treatment, 1 mo after treatment, 3 mo after treatment, and 6 mo after treatment; (2) the retinal thickness was measured using an OCT scanner at four-time points: Before treatment, 1 mo after treatment, 3 mo after treatment, and 6 mo after treatment; (3) CMT was measured using OCT before treatment, 1 mo of treatment, 3 mo of treatment, and 6 mo after treatment; (4) cytokine levels: before treatment, after 1 mo of treatment, after 3 mo of treatment, and after 6 mo of treatment, 0.2 mL of vitreous fluid was collected from the patient, diluted, and assayed using enzyme-linked immunoassay for VEGF and IL-6 and sICAM-1 and BFGF[11]. Adverse events also need to be recorded: The occurrence of adverse reactions during treatment in both groups, such as elevated intraocular pressure, endophthalmitis, vitreous hemorrhage, and retinal detachment, among others[12].

Statistical analysis

The clinical data were analyzed using SPSS statistical software. The test data followed a normal distribution and were expressed as mean ± SD regarding homogeneity of variance and compared using independent sample *t*-tests. Count data were expressed as *n* (%) using the c^2 test; statistical significance was set at $P < 0.05$.

RESULTS

Clinical effects

The patients in both groups showed high efficacy; however, the total efficacy rate in the observation group was higher than that in the control group ($P < 0.05$) (Table 1).

Comparison of two groups of BCVA

The BCVA of the control and observation groups before treatment was not significantly different ($P > 0.05$). After 1 mo of

Table 1 Clinical effects

Group	Number of cases	Invalid, *n* (%)	Valid, *n* (%)	Excellent, *n* (%)	Total effective rate (%)
Control group	65	14 (21.54)	41 (63.08)	10 (15.38)	78.46
Observation group	65	4 (6.15)	41 (63.08)	20 (30.77)	93.85
$\chi 2$ value					8.88
P value					0.04

treatment, the BCVA in both groups improved. After 3 mo and 6 mo of treatment, the BCVA in both groups improved significantly, and that in the observation group was superior to that in the control group. According to the independent samples *t*-test, the changes in BCVA in the two groups were statistically different at the three-time points after treatment and were comparable ($P < 0.05$), as shown in Table 2.

Retinal thickness

No significant difference was observed in the retinal thickness between the two groups before treatment ($P > 0.05$). After 1 mo of treatment, it was visually evident from the images that the retinal thickness of both groups improved. Retinal thickness in both groups improved significantly after 3 and 6 mo of treatment, and the effect in the observation group was better than that in the control group. According to the *t*-test, a significant variation existed in retinal thickness changes between the two groups at the three time points after treatment ($P < 0.05$) (Table 3).

Comparison of CMT between two groups of patients

The difference in CMT between the two groups before treatment was not statistically significant ($P > 0.05$). The CMT in both groups improved after 1 mo of treatment. The CMT in both groups could be found to be substantially improved after 3 mo and 6 mo of treatment, and the effect of the observation group was better than that of the control group. Notably, the changes in CMT in both groups at the two-time points were statistically different ($P < 0.05$) (Table 4).

Cytokine levels

The data showed no statistical discrepancy in the levels of VEGF, IL-6, sICAM-1, and BFGF between the observation control group before treatment ($P > 0.05$). The cytokine levels in both groups gradually decreased after 1 mo, 3 mo, and 6 mo of treatment. According to the independent samples *t*-test, VEGF, IL-6, sICAM-1, and BFGF levels were statistically different between the observation and control groups at the three time points after treatment ($P < 0.05$), as shown in Tables 5-8.

Untoward effect

The two groups had 2 and 3 cases of intraocular pressure hypertension and 1 and 1 case of vitreous injection site hemorrhage, respectively. Retinal detachment or fundus lesions were not observed in either group. The total incidence of adverse events in the control and observation groups was 4.61% and 6.15% (control and observation), respectively, and no significant difference was found between the two groups in the total incidence of adverse events. ($\chi^2 = 2.222$, $P > 0.05$).

DISCUSSION

Studies have demonstrated that approximately 6.8% of patients with diabetes experience vision loss due to DME. Clinically, DME is defined as a retinal thickening or hard exudation within 1.5 mm of the fovea. The mechanism of DME may involve a local inflammatory reaction or oxidative stress reaction[13]. It damages the retinal barrier and increases retinal permeability. Some proteins and water molecules enter the parenchymal layer from outside the retina, increasing intercellular space[14]. If these components converge into the macular area, they will cause retinal thickening and visual impairment in the macular area[15]. Intravitreal injection of anti-VEGF drugs and laser photocoagulation are options for treating DME; however, both methods have limitations. Photocoagulation has a long history of use in treating DR. Photocoagulation can inhibit blood vessel proliferation, relieve hypoxia in the inner retina, and improve visual function. Patients with DR still experience vision loss shortly after simple photocoagulation treatment, which is related to the failure to eliminate the underlying cause of DR formation. Abnormal angiogenesis plays a key role in the occurrence and development of DR. Retinal laser photocoagulation is used to transform laser energy into heat energy and then use its consistency and strong directionality to form scars at specific locations in the retina to repair eye tissue[16]. However, it has the risk of burning the retinal fovea and damaging the retinal pigment epithelial cells, and the treatment effect in moderate to severe DME is not ideal[17]. Anti-VEGF drugs reduce angiogenesis by inhibiting the binding of VEGF to its receptors[18]. Some patients do not respond to anti-VEGF drugs. Although anti-VEGF drugs can improve the visual acuity and anatomical structure in patients with DME, they cannot replace retinal laser photocoagulation. Therefore, laser photocoagulation in combination with the injection of an anti-VEGF is recommended. Conbercept, which is a fusion protein extracted from hamster ovarian cells, has antiangiogenic and antiproliferative effects on endothelial cells. It has been successfully used to treat wet age-related macular degeneration[19]. Therefore, this study used a combination

Table 2 Comparison of best-corrected visual acuity before and after treatment

Group	Number of cases	BCVA			
		Prior treatment	One month of treatment	Three months of treatment	Treatment for 6 mo
Control group	65	0.07 ± 0.02	0.22 ± 0.08[1]	0.30 ± 0.16[1,2]	0.49 ± 0.20[1,2,3]
Observation group	65	0.07 ± 0.02	0.21 ± 0.06[1]	0.44 ± 0.16[1,2]	0.62 ± 0.22[1,2,3]
t value		1.224	-5.221	-6.804	-4.439
P value		0.223	< 0.001	< 0.001	< 0.001

[1]Indicates the intra-group comparison with that before treatment, $P < 0.05$.
[2]Indicates that compared with 1 mo after treatment, $P < 0.05$.
[3]Indicates [a]$P < 0.05$, in the group compared with 3 mo of treatment.
BCVA: Best-corrected visual acuity.

Table 3 Retinal thickness before and after treatment

Group	Number of cases	Retinal thickness (μm)			
		Prior treatment	One month of treatment	Three months of treatment	Treatment for 6 mo
Control group	65	637.20 ± 101.96	431.12 ± 90.22[1]	320.16 ± 88.71[1,2]	241.92 ± 70.43[1,2,3]
Observation group	65	638.39 ± 103.16	316.31 ± 86.72[1]	221.43 ± 90.22[1,2]	170.62 ± 72.34[1,2,3]
t value		-0.492	6.216	6.535	5.863
P value		0.624	< 0.001	< 0.001	< 0.001

[1]Indicates the intra-group comparison with that before treatment, $P < 0.05$.
[2]demonstrates that compared with 1 mo after treatment, $P < 0.05$.
[3]Indicates $P < 0.05$, in the group compared with 3 mo of treatment.

Table 4 Before and after central macular thickness treatment

Group	Number of cases	CMT (μm)			
		Prior treatment	One month of treatment	Three months of treatment	Treatment for 6 mo
Control group	65	360.60 ± 41.62	307.32 ± 39.42[1]	270.38 ± 34.67[1,2]	236.71 ± 32.31[1,2,3]
Observation group	65	357.63 ± 42.51	249.31 ± 36.21[1]	221.62 ± 31.62[1,2]	183.26 ± 33.32[1,2,3]
t value		0.493	8.949	8.611	9.175
P value		0.623	< 0.001	< 0.001	< 0.001

[1]Indicates the intra-group comparison with that before treatment, $P < 0.05$.
[2]Indicates that compared with 1 mo after treatment, $P < 0.05$.
[3]Indicates intra-group comparison with 3-mo treatment, $P < 0.05$.
CMT: Central macular thickness.

treatment protocol for DME and examined its efficacy and safety to explore a more economical and effective treatment scheme for DME[20].

Analysis of the data before and after the four treatment periods revealed that laser photocoagulation combined with conbercept injection had a better treatment effect on DME, which can effectively improve the visual quality of patients and inhibit retinal thickening[21]. Retinal laser photocoagulation reduces macular edema in the following two ways: One is by blocking the capillary network through the thermal effect of the laser, which decreases the permeability of the retina and reduces the infiltration rate; and other is in the retinal epithelium that damages the photoreceptor cells in the retina and decreases their VEGF expression, which decreases angiogenesis in the retina and improves its hypoxic state. This has proven to be a practical and effective treatment method; however, its treatment time is considerably long and can cause visual field defects, thereby reducing its effectiveness[22]. In combination with retinal laser photocoagulation, DME can be treated from the following two perspectives: inhibition of macular effusion and multitargeted inhibition of VEGF expression. In our study, we found that compazepib significantly increased laser penetration during retinal laser photocoagulation and enhanced its efficacy[23].

Table 5 Levels of vascular endothelial growth factor before and after treatment

Group	Number of cases	VEGF (ng/mL)			
		Prior treatment	One month of treatment	Three months of treatment	Treatment for 6 mo
Control group	65	423.73 ± 76.35	336.73 ± 65.28[1]	170.30 ± 41.32[1,2]	106.32 ± 10.71[1,2,3]
Observation group	65	424.32 ± 77.31	301.62 ± 63.78[1]	110.32 ± 36.72[1,2]	66.79 ± 10.21[1,2,3]
t value		-0.151	3.512	8.707	21.818
P value		0.880	< 0.001	< 0.001	< 0.001

[1]Indicates the intra-group comparison with that before treatment, $P < 0.05$.
[2]Indicates that compared with 1 month after treatment, $P < 0.05$.
[3]Indicates intra-group comparison with 3-mo treatment, $P < 0.05$.
VEGF: Vascular endothelial growth factor.

Table 6 Interleukin-6 levels before and after treatment

Group	Number of cases	IL-6 (ng/mL)			
		Prior treatment	One month of treatment	Three months of treatment	Treatment for 6 mo
Control group	65	76.31 ± 11.76	66.31 ± 11.76[1]	52.34 ± 8.71[1,2]	42.91 ± 5.93[1,2,3]
Observation group	65	75.24 ± 12.03	60.12 ± 8.03[1]	45.71 ± 7.62[1,2]	34.73 ± 5.63[1,2,3]
t value		0.196	4.476	3.981	8.309
P value		0.845	< 0.001	< 0.001	< 0.001

[1]Indicates the intra-group comparison with that before treatment, $P < 0.05$.
[2]Indicates that compared with 1 mo after treatment, $P < 0.05$.
[3]Indicates intra-group comparison with 3-mo treatment, $P < 0.05$.
IL-6: Interleukin-6.

Table 7 Levels of soluble intercellular adhesion molecule-1 before and after treatment

Group	Number of cases	sICAM-1 (ng/mL)			
		Prior treatment	One month of treatment	Three months of treatment	Treatment for 6 mo
Control group	65	373.37 ± 83.12	313.71 ± 54.62[1]	236.42 ± 37.91[1,2]	205.71 ± 20.31[1,2,3]
Observation group	65	376.39 ± 83.83	280.18 ± 54.62[1]	200.73 ± 37.91[1,2]	180.31 ± 20.72[1,2,3]
t value		-0.043	3.850	5.325	7.120
P value		0.966	< 0.001	< 0.001	< 0.001

[1]Indicates the intra-group comparison with that before treatment, $P < 0.05$.
[2]Indicates that compared with 1 mo after treatment, $P < 0.05$.
[3]Indicates intra-group comparison with 3-mo treatment, $^{a}P < 0.05$.
sICAM-1: Soluble intercellular adhesion molecule-1.

Studies have also shown[24] that intravitreal injection of conbercept combined with pan-retinal photocoagulation is more effective in treating severe non-proliferative DR with macular edema. Placental growth factor (PIGF) has various biological effects that induce endothelial cell proliferation and stimulate angiogenesis. It also increases vascular permeability by enhancing endothelial cell migration. Studies[25] have found that PIGF is highly expressed in pathological conditions, such as inflammation, tumors, tissue ischemia, and hypoxia, which may be related to the occurrence and development of DME. Another reason for the enhanced efficacy of the combined treatment of the two DME methods in this study may be associated with the inhibition of PIFG expression. VEGF is a glycoprotein with a molecular mass of 36 kDa to 46 kDa that induces cell mitosis and promotes angiogenesis. This is an important cellular factor associated with DME. When the retina is ischemic and hypoxic, related cells secrete a large amount of VEGF, which can interact with the tight junction proteins of endothelial cells, thereby destroying the structure and function of the blood-retinal barrier, eventually leading to retinal capillary leakage and macular edema. A critical component of the DME disease process is the inflammatory response, and various pro-inflammatory factors can affect each other and aggravate

Table 8 Levels before and after serum basic fibroblast growth factor treatment

Group	Number of cases	BFGF (g/L)			
		Prior treatment	One month of treatment	Three months of treatment	Treatment for 6 mo
Control group	65	52.16 ± 8.17	49.31 ± 7.28[1]	40.21 ± 6.22[1,2]	32.41 ± 3.21[1,2,3]
Observation group	65	53.07 ± 8.02	44.12 ± 7.16[1]	33.34 ± 5.98[1,2]	23.62 ± 3.16[1,2,3]
t value		-0.201	3.675	6.601	11.661
P value		0.841	< 0.001	< 0.001	< 0.001

[1]Indicates the intra-group comparison with that before treatment, $P < 0.05$.
[2]Indicates that compared with 1 mo after treatment, $P < 0.05$.
[3]Indicates intra-group comparison with 3-mo treatment, $P < 0.05$.
BFGF: Basic fibroblast growth factor.

DME[26].

Previous studies have demonstrated[27] that microglia are bifurcated and distributed in the inner retina under normal physiological conditions and mainly monitor retinal immunity. When there is local inflammation in the retina, microglia are activated, become amebic, and gather at the site of inflammation, causing an inflammatory cascade, releasing many inflammatory mediators, and causing changes in vascular permeability. Additionally, inflammation can alter the function of retinal Müller cells, reduce the efficiency of intracellular fluid clearance, and cause fluid accumulation. IL-6 is a classic pro-inflammatory factor that induces apoptosis in retinal cells and increases their permeability by activating the nuclear factor-kB pathway. It is also an important inflammatory factor in DME[28]. sICAM-1 is an immunoglobulin, and in this study, the levels of VEGF, IL-6, sICAM-1, and BFGF in the vitreous fluid of the observation group were significantly reduced at three-time points after treatment-induced DME, and the efficacy was better. The intravitreal syringe of conbercept combined with laser photocoagulation improved the hypoxic state, reduced the inflammatory response, and enhanced treatment efficacy.

When conbercept and ranibizumab were compared in DME, it was found that both anti-VEGF drugs inhibited the expression of VEGF and IL-6[29]. The results showed that the use of conbercept in DR was safer and more credible. Therefore, to prevent DME, we should increase screening and health promotion for people at risk of DME (patients with poor glycemic control, combined hypertension, combined hyperlipidemia, kidney disease, anemia, and pregnancy) so that they know the specific means of preventing and cultivating good habits.

CONCLUSION

Conbercept, combined with laser photocoagulation, is a highly effective therapeutic agent for DR. Its action mechanism may be achieved by downregulating the expression of VEGF, IL-6, sICAM-1, BFGF, and other genes. Although the study had positive results, it also had some limitations. Among them, the sample size is small, which makes the research results lack sufficient representativeness. Second, the short duration of the study may lead to the lack of long-term validation of the results. In order to better generalize the results of this study, follow-up studies need to focus on these limiting factors, which could help guide clinical treatment.

ARTICLE HIGHLIGHTS

Research background

China has a high prevalence of diabetes and a large base of diabetes. Diabetic retinopathy (DR) seriously affects the patients' quality of life.

Research motivation

DR is an important condition affecting people's lives, health, and economic development. Therefore, effective and efficient treatment programs are required.

Research objectives

To provide better treatment for DR with macular edema.

Research methods

We selected 130 patients with diabetic macular edema who were hospitalized between January 2018 and May 2020 and assigned them to the following two groups according to treatment: the observation and control groups. The control group

was treated with laser photocoagulation, and the observation group received laser photocoagulation with an intravitreal injection of conbercept (65 patients in each group). Clinical efficacy was evaluated, and seven indicators were measured.

Research results

The total efficacy rate in the observation group (93.85%) was higher than that in the control group (78.46%). In both groups, the BCVA correction effect was better after treatment, and that in the observation group was superior to that in the control group. Retinal thickness and CMT improved after treatment, and the observation group was superior to the control group. The levels of VEGF, IL-6, sICAM-1, and BFGF in both groups improved after treatment, and the observation group was superior to the control group.

Research conclusions

In patients with macular edema, the combination of laser photocoagulation and intravitreal injections of Conbercept for DME is a more effective and safer way to improve vision, reduce retinal thickness, and lower intraocular cytokine VEGF levels.

Research perspectives

It is more effective in treating DR with macular edema and is worthy of widespread promotion.

FOOTNOTES

Author contributions: Zhan HQ designed and performed the research and wrote the paper; Gu CY designed the research and supervised the report; Zhou JL designed the research and contributed to the analysis; Zhang J and Wu D provided clinical advice.

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ORIGINAL ARTICLE

Observational Study

Effects of glucagon-like peptide-1 receptor agonists on glucose excursion and inflammation in overweight or obese type 2 diabetic patients

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Abstract

BACKGROUND

Currently, the lack of comparative studies between weekly and daily formulations of glucagon-like peptide-1 receptor agonists (GLP-1RAs) for glucose excursion is worth investigation.

AIM

To investigate the effects of weekly and daily formulations of GLP-1RA on glucose excursion and inflammation in overweight and obese patients with type 2 diabetes.

METHODS

Seventy patients with type 2 diabetes mellitus who were treated at our hospital between January 2019 and January 2022 were enrolled in this retrospective analysis. All patients were treated with metformin. We evaluated changes in blood glucose levels and a series of important indicators in patients before and after treatment with either a weekly or daily preparation of GLP-1RA (group A; n = 33 and group B; n = 37).

RESULTS

The degree of decrease in the levels of fasting blood glucose, mean blood glucose, mean amplitude of glycemic excursions, total cholesterol, triglycerides, tumor necrosis factor-α, interleukin-6, and high-sensitivity C-reactive protein after treatment in group A was higher than that in group B ($P < 0.05$), whereas the 2-h postprandial blood glucose levels decreased more so in group B than in group A ($P < 0.001$). However, there were no statistically significant differences in the levels of glycated hemoglobin, standard deviation of blood glucose, coefficient of

variation, absolute mean of daily differences, percentage of time with 3.9 mmol/L < glucose < 10 mmol/L, and high- and low-density lipoproteins between the two groups ($P > 0.05$). The incidence of adverse reactions was significantly lower in group A than in group B ($P < 0.05$).

CONCLUSION

The effect of the weekly preparation of GLP-1RA in controlling blood glucose levels in the patients, suppressing inflammation, and reducing adverse reactions was significantly higher than that of the daily preparations, which is worthy of clinical promotion.

Key Words: Glucagon-like peptide-1 receptor agonists; Weekly preparation; Daily preparation; Overweight or obese; Type 2 diabetes mellitus; Glucose excursion; Inflammation

Core Tip: Weekly formulation of glucagon-like peptide-1 receptor agonists (GLP-1RAs) exhibited superior efficacy in treating obese patients with type 2 diabetes mellitus compared to the daily formulation. It effectively controls blood glucose levels, better regulates blood lipids, inhibits inflammatory reactions, and reduces adverse reactions. Therefore, the weekly formulation of GLP-1RA is a promising treatment option worthy of clinical promotion.

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INTRODUCTION

The prevalence of diabetes is increasing worldwide, with nearly 500 million people living with diabetes and is expected to increase by 25% by 2030 and 51% by 2045[1]. Currently, the prevalence of diabetes in China is as high as 11.2% and patients with type 2 diabetes mellitus (T2DM) account for > 90% of the population. However, the awareness rate (36.5%), treatment rate (32.2%), and control rate (49.2%) of diabetes are low, and the prevalence of diabetes in obese and overweight individuals has increased dramatically; therefore, standardized diagnosis and treatment of the disease is vital[2]. Glucose excursion has become a new and important indicator for assessing glycemic control in treating diabetes. Numerous studies have confirmed that the occurrence and development of chronic complications of diabetes are not only related to overall blood glucose levels but also more closely associated with glycemic fluctuations, which are independent risk factors for chronic complications of diabetes[3]. Continuous glucose monitoring systems can monitor blood glucose fluctuations continuously for 24 h, detect nocturnal asymptomatic hypoglycemia and postprandial hyperglycemic states that are easily overlooked by self-glucose monitoring, and accurately assess fluctuating changes in blood glucose in diabetic patients[4].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have received much attention because of their unique glucose-lowering mechanisms, which mainly include a glucose concentration-dependent approach to promote insulin release, inhibit glucagon secretion, protect β-cells to increase their numbers, reduce hepatic glucose output, suppress appetite to increase satiety, and delay gastric emptying and gastrointestinal motility to lower blood glucose levels and reduce body weight[5-7]. In addition to these mechanisms, the role of GLP-1RAs in suppressing inflammation is currently receiving widespread attention. Diabetes mellitus is a complex chronic metabolic disease that requires continuous medical management with glycemic control along with multifactorial risk reduction strategies (*e.g.*, blood pressure, lipid, and weight control)[8,9].

GLP-1RA is another injectable agent other than insulin in the treatment of T2DM, which is divided into two categories: daily and long-acting weekly agents according to the duration of action, among which the clinical use of weekly agents greatly reduces the number of injections and increases patient compliance, which is one of the important factors for long-term glycemic control in diabetic patients[10]. The weekly formulation has good prospects for clinical application as a once-weekly injection regimen. The current lack of comparative studies between weekly and daily formulations of GLP-1RAs on glucose excursion is worth in-depth exploration, especially for providing a new avenue for improving patient compliance and glycemic control in clinical treatment.

MATERIALS AND METHODS

Clinical data

Seventy patients with T2DM who were treated at our hospital between January 2019 and January 2022 were enrolled in

this retrospective analysis. All patients were treated with metformin. Specifically, patients were treated with either a weekly or daily preparation of GLP-1RA (group A; n = 33 and group B; n = 37). This study was approved by our Medical Ethics Committee.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Patients with symptoms who met the latest World Health Organization diagnostic criteria for diabetes mellitus[11]; (2) 18-60-years-old; (3) metformin monotherapy of up to 1500 mg in the last 3 mo for substandard glucose control; (4) 7.5%-10.0% glycated hemoglobin (HbA1c); and (5) 24 kg/m^2 ≤ body mass index (BMI) ≤ 35 kg/m^2.

Exclusion criteria: (1) Type 1 diabetes or other specific types of diabetes; (2) T2DM combined with acute complications of diabetes, infection, or stress; (3) severe liver, kidney, and gastrointestinal diseases (alanine aminotransferase and aspartate aminotransferase 2.5 times higher than the upper limit of normal, bilirubin 1.5 times higher than the upper limit of normal, and blood creatinine > 106 μmol/L); (4) myocardial infarction and chronic cardiac insufficiency (New York Heart Association [NYHA] classes III-IV); (5) history of acute or chronic pancreatitis; (6) patients with thyroid disease or serum calcitonin levels > 20 pg/mL; and (7) pregnancy, lactation, or planning a pregnancy in the near future.

Treatment options

All patients received an education on diabetes knowledge from dedicated staff, followed by the diet and appropriate amount of post-meal exercise as specified by a physician; they could skillfully apply the blood glucose meter for self-measurement, and all blood glucose meters were calibrated before use. This was combined with 500 mg metformin three times daily. Patients in group A were started with dulaglutide (S20190021; Eli Lilly Nederland B.V., The Netherlands) 0.75 mg subcutaneously once a week and increased to 1.5 mg once per week after 1 wk if formamidopyrimidine DNA glycosylase (FPG) > 7.0 mmol/L or 2-h plasma glucose (2hPG) > 11.0 mmol/L was measured. Patients in group B started with 0.6 mg liraglutide subcutaneously once daily and increased to 1.2 mg twice daily if FPG > 7.0 mmol/L or 2hPG > 11.0 mmol/L was measured after 1 wk and increased to 1.8 mg once daily if FPG > 7.0 mmol/L or 2hPG > 11.0 mmol/L was measured after 1 wk. Patients who were originally taking oral antihypertensive and lipid-regulating drugs continued the original regimen.

Ambulatory glucose monitoring indicators

Patients wore a 72-h ambulatory continuous glucose monitor (CGM; MMT-7745; Medtronic, Minneapolis, MN, United States) before and after 12 wk of treatment, and monitored three times a day before meals and before bedtime as well as fasting fingertip glucose to calibrate ambulatory glucose values. The software analysis system was used to process the blood glucose data to derive the following parameters: 24-h mean blood glucose (MBG), 24-h standard deviation of blood glucose (SDBG), coefficient of variation (CV%), mean amplitude of glycemic excursions (MAGEs), absolute mean of daily differences (MODDs), and percentage of time with 3.9 mmol/L < glucose < 10 mmol/L (TIR).

Outcome measures

The main outcome measures were as follows: blood glucose levels (plasma fasting blood glucose [FBG], 2-h postprandial blood glucose [PBG], and HbA1c) were compared before and after treatment between the two groups. The changes in ambulatory glucose monitoring indices, including MBG, SDBG, CV%, MAGE, MODD, and TIR, were compared between the two groups.

The secondary outcome measures were as follows: the baseline clinical data of the two groups were compared. The incidence of adverse reactions and changes in lipid indices (total cholesterol and triglyceride levels) were compared between the two groups. The levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) were compared between the two groups before and after treatment using an enzyme-linked immunosorbent assay, and the changes in BMI were compared before and after treatment.

Before and after 12 wk of treatment, the patient was equipped with a 72-h ambulatory CGM (Medtronic), which monitored fasting fingertip blood glucose three times a day before meals and before bedtime. A software analysis system was used to process blood glucose data to obtain the following parameters: MBG, SDBG, CV%, MAGE, MODD, and TIR.

Statistical analyses

The counting data are expressed as rates and counted by the χ^2 test. The measurement data are expressed as the mean ± standard deviation, and the paired samples t-test was used for intra-group comparison before and after treatment, and the independent samples t-test was used for intergroup comparison. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 20.0 software.

RESULTS

Clinical baseline data

The clinical data of the two groups were compared. There was no statistical difference in age, sex, course of disease, BMI, and history of hypertension and smoking between patients in group A and group B ($P > 0.05$; Table 1).

Table 1 Comparison of clinical baseline data

Factor	Group A, *n* = 33	Group B, *n* = 37	*P* value
Age in yr			
≥ 60	13	17	0.580
< 60	20	20	
Sex			
Male	22	35	0.447
Female	11	12	
Course of disease in yr			
≥ 5	19	20	0.767
< 5	14	17	
BMI in kg/m^2			
≥ 30	25	30	0.587
< 30	8	7	
History of hypertension			
Yes	8	10	0.790
No	25	27	
History of smoking			
Yes	22	35	0.447
No	11	12	

BMI: Body mass index.

Changes in blood glucose levels

Comparison of the changes in blood glucose levels between the two groups revealed that FBG, 2h PBG, and HbA1c were significantly decreased in both groups after treatment ($P < 0.05$). Among them, FBG decreased more in group A than in group B after treatment, and 2h PBG decreased more in group B than in group A ($P < 0.001$; Figure 1). There was no difference in HbA1c between the two groups after treatment ($P > 0.05$).

Changes in dynamic indicators of patients' blood glucose

The dynamic indicators of blood glucose before and after treatment in the two groups were found to be statistically non-different in MBG, SDBG, CV%, MAGE, MODD, and TIR before treatment in the two groups ($P > 0.05$; Figure 2). Patients were treated with a significant decrease in MBG, SDBG, CV%, MAGE, and MODD in both groups compared to pre-treatment, whereas TIR increased dramatically ($P < 0.001$; Figure 2). Further comparison revealed that MBG and MAGE were significantly lower in group A than in group B ($P < 0.01$; Figure 2), but there was no statistical difference in SDBG, CV%, MODD, and TIR between both groups ($P > 0.05$; Figure 2).

Changes in patients' blood lipid indexes

In this study, we also examined the changes in the lipid indexes of patients. Total cholesterol, triglyceride and low-density lipoprotein (LDL) levels were significantly lower and high-density lipoprotein (HDL) levels were significantly higher ($P < 0.01$) in both groups after treatment compared to those before treatment. Among them, total cholesterol and triglyceride levels decreased more in group A than in group B after treatment ($P < 0.05$; Figure 3), but there was no difference between HDL and LDL ($P > 0.05$).

Changes in inflammatory factor levels in patients

In this study, we also detected changes in inflammatory factors in patients. The levels of TNF-α, IL-6, and hs-CRP were significantly lower in both groups after treatment compared with those before treatment ($P < 0.01$). Among them, the level of TNF-α, IL-6, and hs-CRP decreased to a greater extent in group A than in group B after treatment ($P < 0.05$; Figure 4).

Analyses of adverse reactions

Comparison of the adverse reactions between the two groups revealed that the incidence of adverse reactions was significantly lower in group A than in group B. There was a statistical difference ($P < 0.05$; Table 2).

Table 2 Statistics of adverse reactions

Group	Nausea	Vomiting	Diarrhea	Total incidence
Group A, n = 33	1 (3.03%)	1 (3.03%)	0 (0.00%)	2 (6.06)
Group B, n = 37	4 (10.80%)	3 (8.10%)	2 (5.40)	9 (24.30)
χ^2 value				4.393
P value				0.036

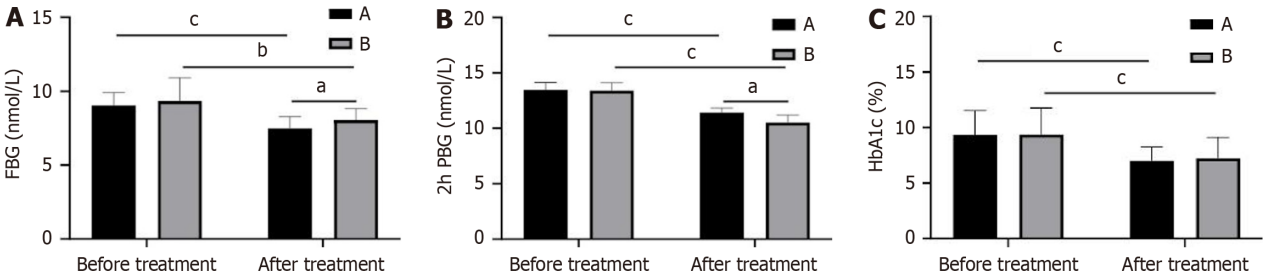

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Figure 1 Changes in blood glucose levels before and after treatment in patients. A: Fasting blood glucose (FBG); B: 2-h postprandial blood glucose (2hPBG); C: Glycated hemoglobin (HbA1c). [a]P < 0.05; [b]P < 0.01; [c]P < 0.001.

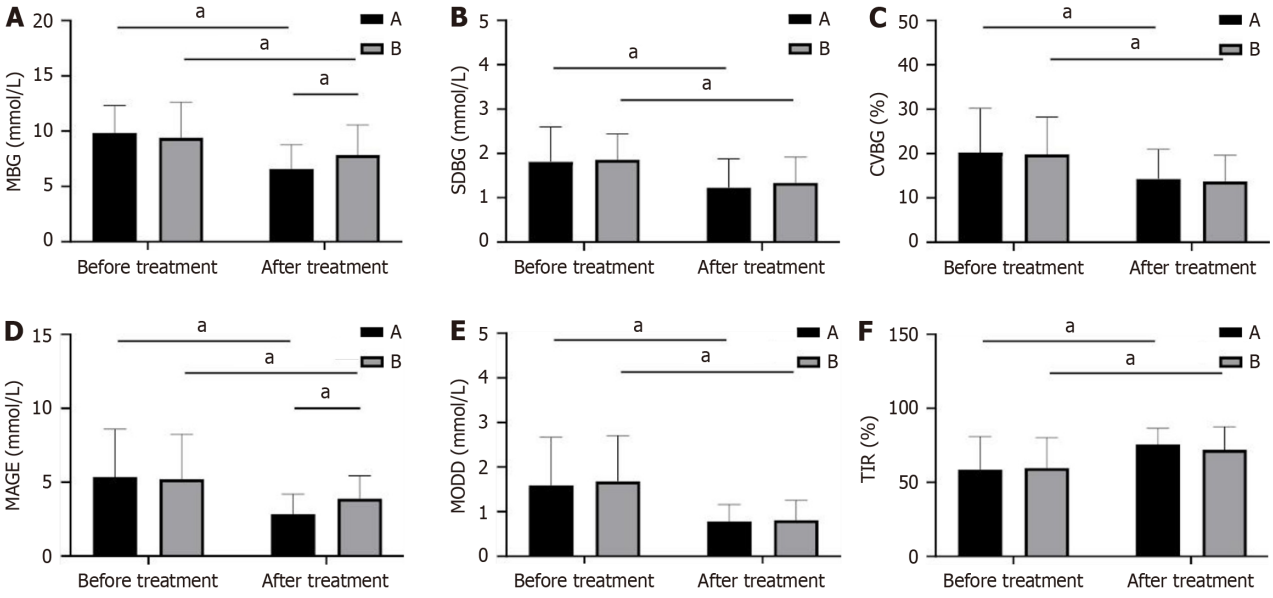

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Figure 2 Changes in blood glucose level and islet cell function of patients before and after treatment. A: 24-h mean blood glucose (MBG); B: 24-h standard deviation of blood glucose (SDBG); C: Coefficient of variation (CV%); D: Mean amplitude of glycemic excursions (MAGEs); E: Absolute mean of daily differences (MODD); F: Percentage of time (TIR) with 3.9 mmol/L < glucose < 10 mmol/L before and after treatment in the two groups. [a]P < 0.001.

Changes in BMI after treatment

In this study, we also examined the changes in BMI before and after treatment in both groups. Patients in both groups showed a significant decrease in BMI through treatment (P < 0.05), with patients in group A showing a higher decrease in BMI after treatment than those in group B (P < 0.001, Table 3).

DISCUSSION

Studying the causes of T2DM has expanded from the well-known deficiency of islet β-cell secretion, increased hepatic glycogen output, and decreased muscle glucose uptake to lipid metabolic disorder, weakening of the effect of intestinal

Table 3 Change in body mass index

Group	BMI in kg/m²		*t* value	*P* value
	Before treatment	After treatment		
Group A, *n* = 33	33.29 ± 4.05	26.89 ± 1.59	8.096	< 0.001
Group B, *n* = 37	33.35 ± 3.29	30.22 ± 1.48	5.099	< 0.001
t value	0.125	8.999		
P value	0.900	< 0.001		

BMI: Body mass index.

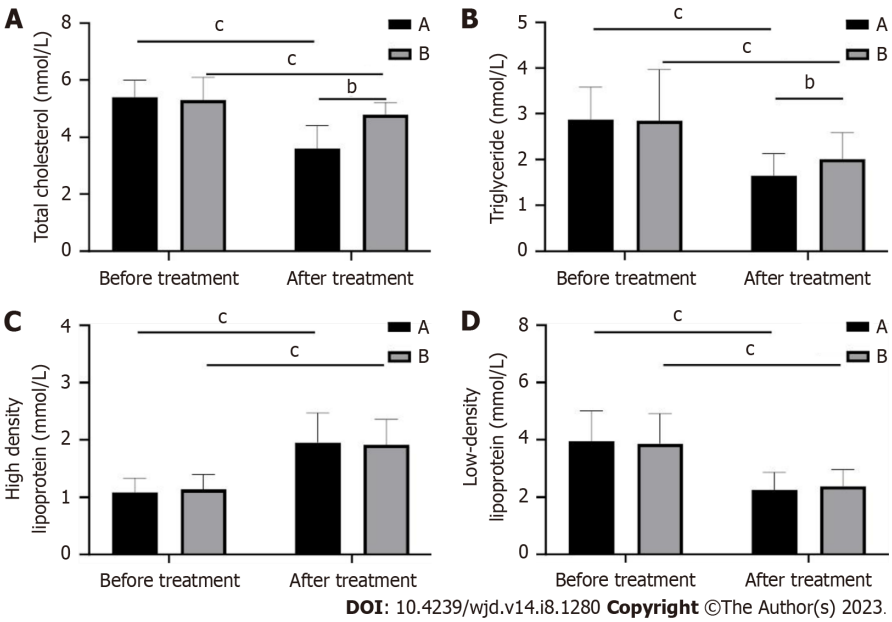

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Figure 3 Changes in patients' blood lipid indexes before and after treatment in both groups. A: Total cholesterol; B: Triglycerides; C: High-density lipoprotein; D: Low-density lipoprotein. $^{b}P < 0.01$; $^{c}P < 0.001$.

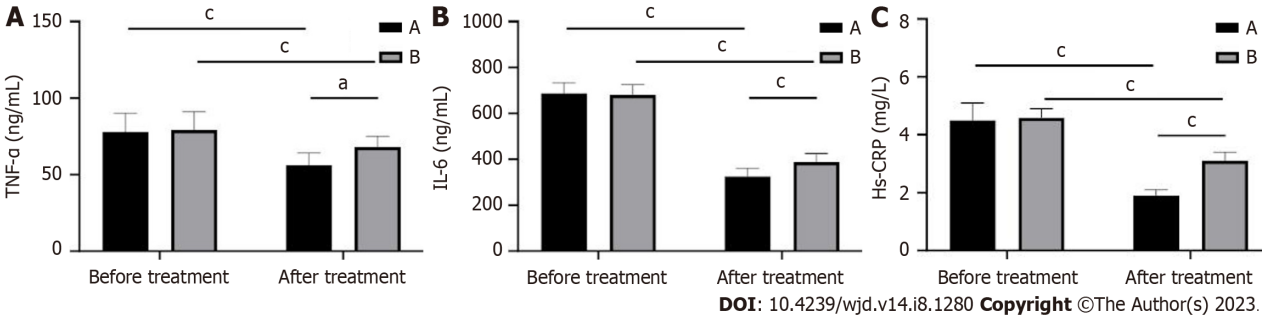

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Figure 4 Changes in inflammatory factor levels in patients before and after treatment in the two groups. A: Tumor necrosis factor-alpha (TNF-α); B: Interleukin-6 (IL-6); C: High-sensitivity C-reactive protein (hs-CRP). $^{a}P < 0.05$; $^{c}P < 0.001$.

glucagon, inappropriate secretion of glucagon in islet α-cells, increase of glucose reabsorption by renal tubules, and hypothalamic regulatory disorder of blood glucose[12-14].

Numerous types of drugs are available for the treatment of T2DM including insulin promoters, insulin sensitizers, α-glucosidase inhibitors, insulin or insulin analogs, dipeptidyl peptidase 4 inhibitors, and sodium-glucose co-transporter 2 inhibitors[15-17]. However, most of these drugs are not only ineffective in maintaining blood glucose in the long term but also have side effects such as weight gain, progressive pancreatic β-cell failure, liver and renal impairment, gastrointestinal reactions, and an increased risk of hypoglycemia[18,19]. GLP-1RA corrects the multiple pathophysiological mechanisms of T2DM and exert their biological effects by binding to GLP-1 receptors *in vivo*[20]. GLP-1 receptors are

widely distributed in several organs or tissues throughout the body including the central nervous system, gastrointestinal tract, cardiovascular system, liver, adipose tissue, muscle, and pancreas. There is a current lack of domestic and foreign research on the effects of weekly and daily formulations of GLP-1RA on blood glucose fluctuation; weekly formulations have good clinical application prospects to improve patient treatment compliance, and more clinical experience and safety data need to be obtained in future clinical practice.

In the present study, we compared the blood glucose control effects of weekly GLP-1RA administration with that of daily GLP-1RA administration and analyzed glucose excursion and inflammation in overweight or obese patients with T2DM. After treatment, FBG, MBG, MAGE, total cholesterol, triglyceride, and TNF-α levels were measured in patients in group A. The decrease in IL-6 and hs-CRP levels was greater in group A than in group B. We also found through glucose dynamic tests that the MBG, SDBG, CV%, MAGE, and MODD of patients in the two groups were decreased significantly after treatment compared to those before treatment, whereas TIR increased in both groups. This indicates that both treatment schemes can improve blood glucose drift in patients. However, we found that the MBG and MAGE levels in group A were significantly lower than those in group B. Previously, in a meta-analysis performed by Yang *et al*[21], it was found that the use of a GLP-1RA weekly formula was superior to the daily formula in improving HbA1c and FBG levels in patients with T2DM, which is consistent with our findings. This is because weekly preparations can effectively control FBG levels by stimulating insulin secretion and inhibiting glucagon secretion, whereas daily preparations mainly rely on delaying gastric emptying and slowing glucose absorption in the duodenum, mainly to lower PBG levels. In addition, weekly preparations have a half-life of several days and can continuously agitate GLP-1R to produce hypoglycemic effects; therefore, the hypoglycemic efficacy of weekly preparations, especially for FBG control, is better than that of daily preparations[22]. Most of the initially diagnosed obese patients with T2DM have inflammation, and inflammatory factors such as TNF-α, IL-6, and hs-CRP are abnormally elevated, and this inflammation leads to insulin resistance and increases the risk of cardiovascular disease, so it is significant to control inflammation in the body[23]. The results of the current study showed that after treatment, the levels of TNF-α and IL-6 in group A were lower than those in group B, indicating that the use of weekly preparations of GLP-1RA for treating obese patients with T2DM is more effective, facilitates the reduction of inflammatory factors, and has a higher safety for clinical application.

GLP-1 receptors are expressed on cardiomyocytes, vascular smooth muscle cells, and vascular endothelial cells. GLP-1RA can inhibit smooth muscle cell proliferation and high glucose-induced apoptosis in endothelial cells, promote endothelial cell proliferation, stabilize the endothelial environment, and reduce injury, which directly affects the cardiovascular system and ultimately the outcome of patients with T2DM[24]. GLP-1RA acts on the hypothalamic feeding center to delay the emptying of food into the stomach, suppressing the appetite of patients with a significant weight loss effect, and thus reducing the risk of cardiovascular disease[25]. In addition, GLP-1RA inhibitors directly participate in lipid metabolism and accelerate fat mobilization. The present study showed that the levels of total cholesterol and triglycerides post-treatment were lower in patients treated with the weekly formulation of GLP-1RA than in those treated with the daily formulation, suggesting that both drugs are suitable for obese patients with high lipid levels, but that the weekly formulation is the most effective.

This study had some limitations. First, we did not conduct patient follow-up sessions. Second, this study was retrospective, which may have introduced a recall bias in the analysis of the results. Finally, only the short-term treatment effects of the two drugs were analyzed, and it remains unclear whether there are differences in the long-term. Future studies should address these limitations through extensive clinical trials to refine our conclusions.

CONCLUSION

In conclusion, the effect of weekly preparations of GLP-1RA in controlling the blood glucose levels in obese patients with T2DM, inhibiting inflammation, and reducing adverse reactions was significantly higher than that of daily preparations, which is worthy of clinical promotion.

ARTICLE HIGHLIGHTS

Research background

The background of the research is the increasing prevalence and challenges associated with type 2 diabetes mellitus (T2DM). The study explores the causes of T2DM and the limitations of current treatment options.

Research motivation

The motivation behind the research is to address the limitations of existing drugs for T2DM treatment and explore the potential of glucagon-like peptide-1 receptor agonists (GLP-1RAs) as a more effective therapeutic option.

Research objectives

The objectives of the research are to compare the blood glucose control effects of weekly and daily formulations of GLP-1RAs, analyze glucose excursion and inflammation in overweight or obese patients with T2DM, and evaluate the safety and clinical application prospects of the weekly formulation.

Research methods

The study involved administering weekly and daily formulations of GLP-1RA to the participants and measuring various parameters such as fasting blood glucose, mean blood glucose, glucose excursion, lipid levels, and inflammation markers. Glucose dynamic tests were conducted to assess blood glucose fluctuations.

Research results

The results indicated that the weekly formulation of GLP-1RA had superior blood glucose control effects compared to the daily formulation. It resulted in lower mean blood glucose levels, reduced glucose excursion, and improved lipid profiles. Additionally, the weekly formulation showed a greater decrease in inflammation markers.

Research conclusions

Based on the findings, the research concludes that the weekly formulation of GLP-1RA is more effective in controlling blood glucose levels, inhibiting inflammation, and reducing adverse reactions in obese patients with T2DM. It suggests that the weekly formulation has promising clinical applications and should be considered for wider implementation.

Research perspectives

To investigate the effects of weekly and daily formulations of GLP-1RA on glucose excursion and inflammation in overweight and obese patients with type 2 diabetes.

FOOTNOTES

Author contributions: Pan TR took part in the study coordination; Huang XM took part in the study execution, data collection, and discussions; Zhong X, Du YJ, Guo YY, and Pan TR took part in the study design, supervision, and drafting of the manuscript; Zhong X, Du YJ, and Guo YY contributed to the data analyses.

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Informed consent statement: All study participants provided informed written consent prior to study enrolment.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No additional data are available.

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META-ANALYSIS

Prognostic role of metformin in diabetes mellitus type 2 patients with hepatocellular carcinoma: A systematic review and meta-analysis

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is among the commonest malignancies associated with significant cancer-related death. The identification of chemo-preventive agents following HCC treatments with the potential to lower the risk of HCC adverse course is intriguing. Metformin, a first-line agent used in the treatment of type 2 diabetes mellitus (T2DM), has been associated with inhibition of HCC growth.

AIM

To determine whether metformin can prevent adverse events (*i.e.,* death, tumor progression, and recurrence) after any HCC treatment in T2DM patients.

METHODS

A systematic review of the published literature was undertaken focused on the role of metformin on outcomes in patients with T2DM and HCC receiving any tumor therapy. A search of the PubMed and Cochrane Central Register of Controlled Trials Databases was conducted.

RESULTS

A total of 13 studies (n = 14886 patients) were included in this review. With regard to the risk of death, a decreased risk was reported in cases receiving metformin, although this decrease was not statistically significant [odds ratio (OR) = 0.89, P =

0.42]. When only patients treated with curative strategies were considered, a more marked correlation between metformin and favorable cases was reported (OR = 0.70, *P* = 0.068). When analyzing palliative treatment, there was no statistical significance in terms of the correlation between metformin and favorable cases (OR = 0.74, *P* = 0.66). As for the risks of progressive disease and recurrence, no obvious correlation between metformin use and reduced risk was reported. When sub-analyses were performed for patients from different regions, the results for patients from Eastern countries showed a tendency for decreased risk of death in T2DM cases receiving metformin (OR = 0.69, *P* = 0.17), but the same was not seen in patients from Western countries (OR = 1.19, *P* = 0.31).

CONCLUSION

Metformin failed to show a marked impact in preventing adverse effects after HCC treatment. A trend was reported in T2DM cases receiving curative therapies in relation to the risk of death, especially in patients from Eastern regions. Great heterogeneity was reported among the different studies. Further large studies are required to definitively clarify the real impact of metformin as a chemopreventive agent for HCC.

Key Words: Hepatocellular carcinoma; Metformin; Type 2 diabetes mellitus; Death; Recurrence; Progression; Treatment

Core Tip: The identification of chemopreventive agents following hepatocellular carcinoma (HCC) treatments with the potential to lower the risk of its adverse course is of paramount relevance. Among them, metformin has been recently examined in this setting. The present systematic review and meta-analysis aim to determine the role of metformin in preventing HCC adverse events (*i.e.*, death, tumor progression, and recurrence). Metformin only showed statistical significance as a protective factor for the risk of death in patients receiving curative therapies for HCC, but failed as a protective agent for progressive disease and recurrence. Further large studies are required to definitively clarify the real impact of metformin as a chemopreventive agent for HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC), with an estimated incidence of > 1 million cases, is among the commonest malignancies worldwide and is still associated with significant cancer-related death[1,2]. The major risk factor for developing HCC is advanced liver disease due to various etiologies such as alcohol or viral disease (hepatitis C and B). In addition, non-alcoholic steatohepatitis (NASH), associated with metabolic syndrome, obesity, and diabetes mellitus, is becoming increasingly important for HCC development. In addition, it represents the fastest-growing cause of HCC in westernized and sedentary-lifestyle regions of the world. Moreover, the comorbidities associated with nonalcoholic fatty liver disease (NAFLD) and cardiovascular diseases promote HCC development and negatively influence patients' outcomes[3-6]. Indeed, while HCC predominantly occurs in the setting of chronic liver disease and cirrhosis (80%), in up to 20% of cases, especially those with metabolic syndrome [obesity, type 2 diabetes mellitus (T2DM), and NAFLD] it emerges much earlier, during non-cirrhotic liver disease stages[7].

Several proposed mechanisms explain the relationship between NAFLD-associated comorbidities and HCC development. Among them, insulin resistance, insulin-like growth factor (IGF) related factors, chronic inflammation and proinflammatory cytokines, oxidative stress, dysbiosis of gut microbiota, intrahepatic fat accumulation, inhibition of cell apoptosis and autophagy together with enhanced angiogenesis might play a key link[8-10]. A large retrospective cohort study following over 85000 patients with NAFLD and concomitant diabetes for an average of 10 years showed that good glycemic control (hemoglobin A1c < 7%) not only results in a reduction of micro- and macrovascular diabetes-related complications but can also lower the risk of HCC by 31% [hazard ratio = 0.69; 95% confidence interval (CI): 0.62-0.78][11].

In addition to being a significant risk factor for HCC development, diabetes mellitus has been linked to unfavorable prognosis in HCC patients, including recurrence of HCC after curative approaches and mortality[12]. When possible, surgery, including hepatic resection or liver transplantation, is the first line of treatment, but unfortunately, the incidence of tumor recurrence is still high. Therefore, the role of adjuvant therapy to preclude relapse is a medical need, and different chemopreventive agents following hepatic resection with the potential to lower the risk of HCC recurrence are being investigated[13].

Metformin, a first-line agent used in the treatment of T2DM, has been associated with inhibition of the growth of different cancer types[14,15]. A cohort study by Libby *et al*[16] analyzing patients with T2DM showed that new users of metformin might have a lower risk of overall incident cancer by 30% to 50% while on standard clinical doses of metformin (1500-2250 mg/d in adults).

Similarly, data from epidemiological studies suggest metformin might also lower the risk of HCC in diabetic patients [17-21]. In addition, as an adjuvant treatment for different cancers, metformin might also improve patients' survival by acting synergistically with chemo- and radiotherapy. On the other hand, data on HCC patients treated with sorafenib suggest tumor aggressiveness and therapy resistance in the case of chronic metformin use[22-25], while a recent study, using propensity score matching, suggested improved survival and reduced HCC recurrence in hepatitis B virus-induced HCC patients with T2DM receiving metformin[26]. Overall, whether metformin improves long-term outcomes in the HCC setting is still unclear. Therefore, we performed a systematic review and meta-analysis to further examine its chemopreventive role in HCC patients.

MATERIALS AND METHODS

Search sources and study design

A systematic review of the published literature was undertaken focused on the role of metformin in patients with T2DM and HCC receiving any tumor therapy. The search strategy was performed following the PRISMA guidelines[27]. The study has been registered on the International Prospective Register of Systematic Reviews (code CRD42023416686).

The specific research questions formulated in the present study included the following Patients, Intervention, Comparator, Outcome components: Patient: Patient with HCC and T2DM receiving metformin. Intervention: Any HCC therapy. Comparison: Patient with HCC with T2DM not receiving metformin. Outcome: Death, or progressive disease, or recurrence.

A search of the PubMed and Cochrane Central Register of Controlled Trials Databases was conducted using the following terms: (Recurrence or death or surv*) and (diabetes or DM2 or T2DM) and (metformin) and (HCC or hepatocellular cancer or hepatocellular carcinoma or hepatoma). The search period was from "2000/01/01" to "2022/08/11".

The systematic qualitative review included only English studies involving human patients. Published reports were excluded based on several criteria: (1) Data on animal models; (2) Lacked enough clinical details; and (3) Had non-primary source data (*e.g.*, review articles, non-clinical studies, letters to the editor, expert opinions, and conference summaries). In the case of studies originating from the same center, the possible overlap of clinical cases was examined, and the most informative study was considered eligible.

Data extraction and definitions

Following a full-text review of the eligible studies, two independent authors (Giovanardi F and Lai Q) performed the data extraction and crosschecked all outcomes. During the selection of articles and extraction of data, potential discrepancies were resolved following a consensus with a third reviewer (Mrzljak A). Collected data included the first author of the publication, year of publication, country, and the number of treated patients and those with recurrence according to the different therapies adopted.

Quality assessment

Selected studies were systematically reviewed with the intent to identify potential sources of bias. The quality of each study was assessed using the Risk of Bias In Non-randomized Studies of Interventions (Robins-I) tool[28].

Statistical analysis

Study results were expressed as odds ratio (OR) with 95%CIs. The statistical heterogeneity was evaluated with the Higgins statistic squared (I^2). I^2 values of 0%-25% were considered an index of low heterogeneity between studies, 26%-50%: Moderate heterogeneity, and ≥ 51%: High heterogeneity. The fixed-effects model was used when low or moderate (0%-50%) heterogeneity was detected between studies, while the random effects model was preferred when high heterogeneity was present. Subgroup analyses (for different types of HCC treatment and different ethnicities) were used to investigate the source of the heterogeneity.

Sensitivity analysis was used to assess the stability of the study. The funnel plot was used to evaluate publication bias. The rank correlation test and the regression test, using the standard error of the observed outcomes as predictor, were used to check for funnel plot asymmetry. A value $P < 0.05$ was considered indicative of statistical significance. The meta-analysis was performed using OpenMetaAnalyst (http://www.cebm.brown.edu/openmeta/index.html).

RESULTS

Search results and study characteristics

The PRISMA flow diagram schematically depicts the article selection process (Figure 1). Among the 107 articles screened, a total of 13 studies were finally included in this review[24-26,29-38]. All the studies included in the analytic cohort were published during the last decade. Eight articles (61.5%) were from Asia, of which three (23.1%) were from Taiwan or Korea, respectively. The remaining studies were from Europe (n = 3, 23.1%) and North America (n = 2, 15.4%) (Table 1).

Qualitative assessment of the included studies

Eleven (84.6%) studies were retrospective analyses, while two (15.4%) were prospective studies. The ROBINS-I tool

Table 1 Characteristics of included studies for the risk of overall cause of death

Ref.	City	Country	Study period	Design	*N*	Therapy	DM (no metformin)	Number of events	DM (metformin)	Number of events
Chen *et al*[29], 2011	Taichung	Taiwan	June 2003 to July 2009	Retro	53	RFA	32	18	21	6
Bhat *et al*[25], 2014	Rochester	United States	January 2005 to June 2011	Retro	263	No therapy	207	133	56	37
Jang *et al*[30], 2015	Seoul	Korea	March 2003 to December 2012	Retro	48	RT	29	13	19	5
Casadei Gardini *et al*[31], 2015	Meldola	Italy	March 2008 to August 2014	Retro	42	Sorafenib	11	5	31	22
Seo *et al*[32], 2016	Seoul	Korea	January 2005 to December 2011	Retro	751	HR	218	111	533	169
Chan *et al*[33], 2017	Taipei	Taiwan	January 1995 to December 2011	Retro	4610	HR	2978	1335	1632	612
					7813	No surgery	5884	3858	1929	1437
Casadei Gardini *et al*[24], 2017	Meldola	Italy	May 2007 to September 2015	Retro	86	Sorafenib	34	26	52	45
Chung *et al*[34], 2018	Seoul	Korea	January 2009 to December 2016	Retro	63	Sorafenib + HR	23	23	40	30
					31	Sorafenib + LT	17	14	14	13
Luo *et al*[26], 2020	Nanchang	China	January 2000 to December 2013	Retro	250	HR	184	129	66	49
Cho *et al*[35], 2021	Kaohsiung	Taiwan	April 2001 to June 2016	Retro	222	HR	86	15	136	26
Tangjarusritaratorn *et al*[36], 2021	Bangkok	Thailand	January 2006 to June 2014	Prosp	327	Multiple therapies	165	84	162	60
Elsayed *et al*[37], 2021	Atlanta	United States	2014-2018	Retro	40	TARE	21	8	19	8
Hydes *et al*[38], 2022	Birmingham	United Kingdom	January 2007 to March 2012	Prosp	287	Multiple therapies	139	58	148	63
Total					14886		10028	5830	4858	2582

DM: Diabetes mellitus; Retro: Retrospective; Prosp: Prospective; RFA: Radiofrequency ablation; RT: Radiotherapy; HR: Hepatic resection; LT: Liver transplantation; TARE: Trans-arterial radio-embolization.

quality assessment showed that all the studies had a low risk of bias (Figure 2).

Review of the eligible studies

Data extracted from the selected articles are reported in detail in Tables 1-3. All the studies investigated the risk of death for any reason observed after any HCC treatment (Table 1)[24-26,29-38]. In seven (53.8%) studies, a curative therapy (*i.e.*, thermoablation, resection or transplantation) was performed[26,29,32,34,37]. The risk of progressive tumor disease was reported in four (30.8%) studies (Table 2)[24,30,31,34]. Tumor recurrence was investigated in three (23.1%) studies (Table 3)[29,33,35]. Overall, only one (7.7%) study was based on a population of patients including more than 1000 cases [33].

Death in HCC patients with T2DM receiving vs not receiving metformin

According to the data shown in Table 1, 13 studies reported post-treatment death rates in HCC patients with T2DM treated or not treated with metformin. A total of 14886 patients were considered, with 8412 (56.5%) deaths. In detail, 2582/4858 (53.1%) and 5830/10028 (58.1%) deaths were observed in the metformin group and no metformin group, respectively.

Great heterogeneity was observed among the selected studies, with an I^2 = 82.6% (P < 0.001). The summary OR (95%CI) showed a decreased risk of death in T2DM cases receiving metformin, although this value did not reach statistical significance (OR = 0.89, 95%CI: 0.67-1.18; P = 0.42) (Figure 3A). Sensitivity analysis indicated no change in the direction of

Table 2 Characteristics of included studies for the risk of progressive tumor disease

Ref.	City	Country	Study period	Design	*N*	Therapy	DM (no metformin)	Number of events	DM (metformin)	Number of events
Jang *et al*[30], 2015	Seoul	Korea	March 2003 to December 2012	Retro	48	RT	29	24	19	9
Casadei Gardini *et al*[31], 2015	Meldola	Italy	March 2008 to August 2014	Retro	42	Sorafenib	11	9	31	28
Casadei Gardini *et al*[24], 2017	Meldola	Italy	May 2007 to September 2015	Retro	86	Sorafenib	34	33	52	47
Chung *et al*[34], 2018	Seoul	Korea	January 2009 to December 2016	Retro	63	Sorafenib + HR	23	23	40	40
					31	Sorafenib + LT	17	17	14	14
Total					270		114	106	156	138

DM: Diabetes mellitus; Retro: Retrospective; RT: Radiotherapy; HR: Hepatic resection; LT: Liver transplantation.

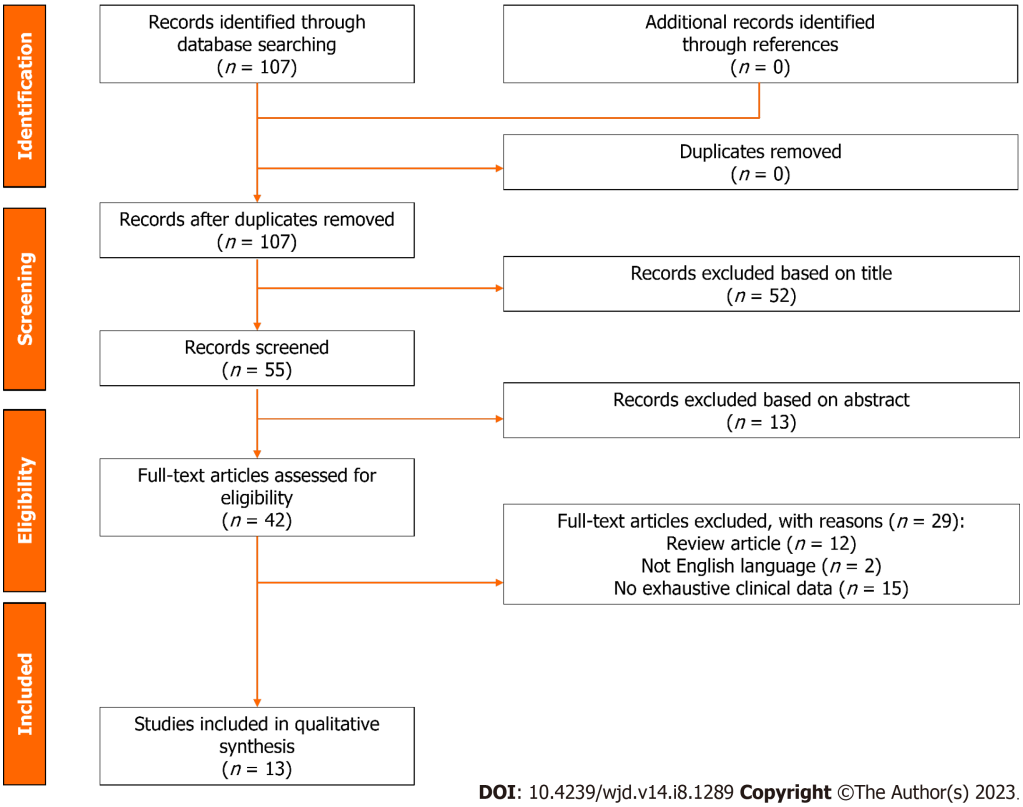

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Figure 1 PRISMA summarizing the trial flow.

effect when any one study was excluded from the meta-analysis. Funnel plot did not indicate a significant risk of publication bias (Figure 4). Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.20 and P = 0.86, respectively).

When only patients treated with curative strategies were considered, the heterogeneity reduced; however, it remained relevant (I^2 = 67.8%, P = 0.005). The summary OR (95%CI) showed a more marked correlation between metformin and favorable cases, with an OR = 0.70 (95%CI: 0.47-1.03; P = 0.068) (Figure 3A). Despite the correlation between metformin and positive clinical course being more evident, statistical significance was not reached in this sub-analysis.

When only patients treated with palliative strategies were considered, the heterogeneity was high (I^2 = 90.8%, P < 0.001). The summary OR (95%CI) did not show statistical significance in terms of the correlation between metformin and favorable cases, with an OR = 0.74 (95%CI: 0.19-2.85; P = 0.66). A sub-analysis focused on the region in which the studies were published was also performed. In patients from Eastern countries, great heterogeneity was observed among the studies, with an I^2 = 67.9% (P < 0.001). The summary OR (95%CI) showed a decreased risk of death in T2DM cases

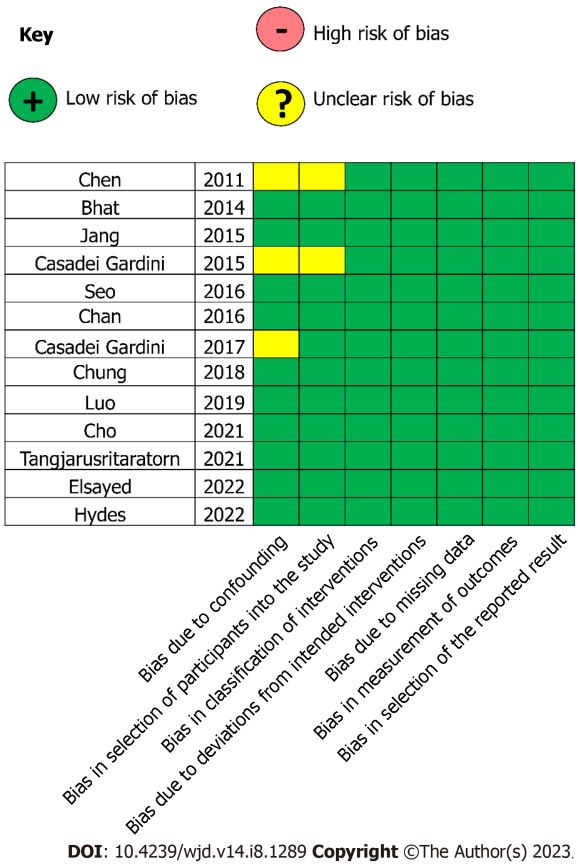

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Figure 2 Results of the risk of bias in non-randomized studies of interventions tool for the extracted articles.

receiving metformin, although this value did not reach statistical significance (OR = 0.69, 95%CI: 0.40-1.17; P = 0.17). In Western patients, heterogeneity was not present (I^2 = 0; P = 0.60). Also in this case, the summary OR (95%CI) did not show any correlation between metformin and favorable cases (OR = 1.19, 95%CI: 0.85-1.65; P = 0.31).

Progressive disease in HCC patients with T2DM receiving vs not receiving metformin

According to the data shown in Table 2, four studies reported post-treatment progressive disease rates in HCC patients with T2DM treated or not treated with metformin[24,30,31,34]. A total of 270 patients were considered, with 244 (90.4%) patients having progressive disease. In detail, 138/156 (88.5%) and 106/114 (93.0%) patients with progressive disease were observed in the metformin and no metformin group, respectively.

Low heterogeneity was observed among the selected studies, with an I^2 = 16.0% (P = 0.31). The summary OR (95%CI) showed a decreased risk of progressive disease in T2DM cases receiving metformin, although this correlation did not reach statistical significance (OR = 0.47, 95%CI: 0.16-1.37; P = 0.17) (Figure 3B).

Recurrence in HCC patients with T2DM receiving vs not receiving metformin

According to the data shown in Table 3, three studies reported post-treatment recurrence rates in HCC patients with T2DM receiving or not receiving metformin[29,33,35]. A total of 12698 patients were considered, with 6130 (48.3%) recurrences. In detail, 1777/3718 (47.8%) and 4353/8980 (48.5%) recurrences were observed in the metformin and no metformin group, respectively. Great heterogeneity was observed among the selected studies, with an I^2 = 95.8% (P < 0.001). The summary OR (95%CI) showed no evident correlation between metformin use and reduced risk of recurrence (OR = 0.95, 95%CI: 0.57-1.58; P = 0.85) (Figure 3B).

DISCUSSION

HCC, even after potentially curative treatment, is still associated with significant mortality. Therefore, identifying adjuvant agents that might decrease this risk is important. As T2DM imposes a significant risk for HCC, the role of metformin in this setting is of relevance. Data including information on 14886 patients with T2DM and HCC included in 13 studies, regardless of the treatment option used, showed a numerical decrease in the death rate in those on metformin, although no statistical significance was reported. When the survival results were analyzed for T2DM patients treated with curative strategies, similar results were reported, although the suggested correlation between the use of metformin and favorable prognosis was close to statistical significance (P = 0.068).

Table 3 Characteristics of included studies for the risk of hepatocellular carcinoma recurrence

Ref.	City	Country	Study period	Design	*N*	Therapy	DM (no metformin)	Number of events	DM (metformin)	Number of events
Chen *et al* [29], 2011	Taichung	Taiwan	June 2003 to July 2009	Retro	53	RFA	32	18	21	12
Chan *et al* [33], 2017	Taipei	Taiwan	January 1995 to December 2011	Retro	4610	HR	2978	1615	1632	698
					7813	No surgery	5884	2668	1929	982
Cho *et al* [35], 2021	Kaohsiung	Taiwan	April 2001 to June 2016	Retro	222	HR	86	52	136	85
Total					12698		8980	4353	3718	1777

DM: Diabetes mellitus; Retro: Retrospective; RFA: Radiofrequency ablation; HR: Hepatic resection.

The results mentioned were promising but never reached statistical significance, showing that the real protective effect of metformin is questionable. Unfortunately, the present study could not definitively clarify this potential protective effect due to several confounding factors related to tumor burden and the severity of cirrhosis, which are not well described in the studied population. Therefore, it was impossible to perform a meta-regression focused on these aspects.

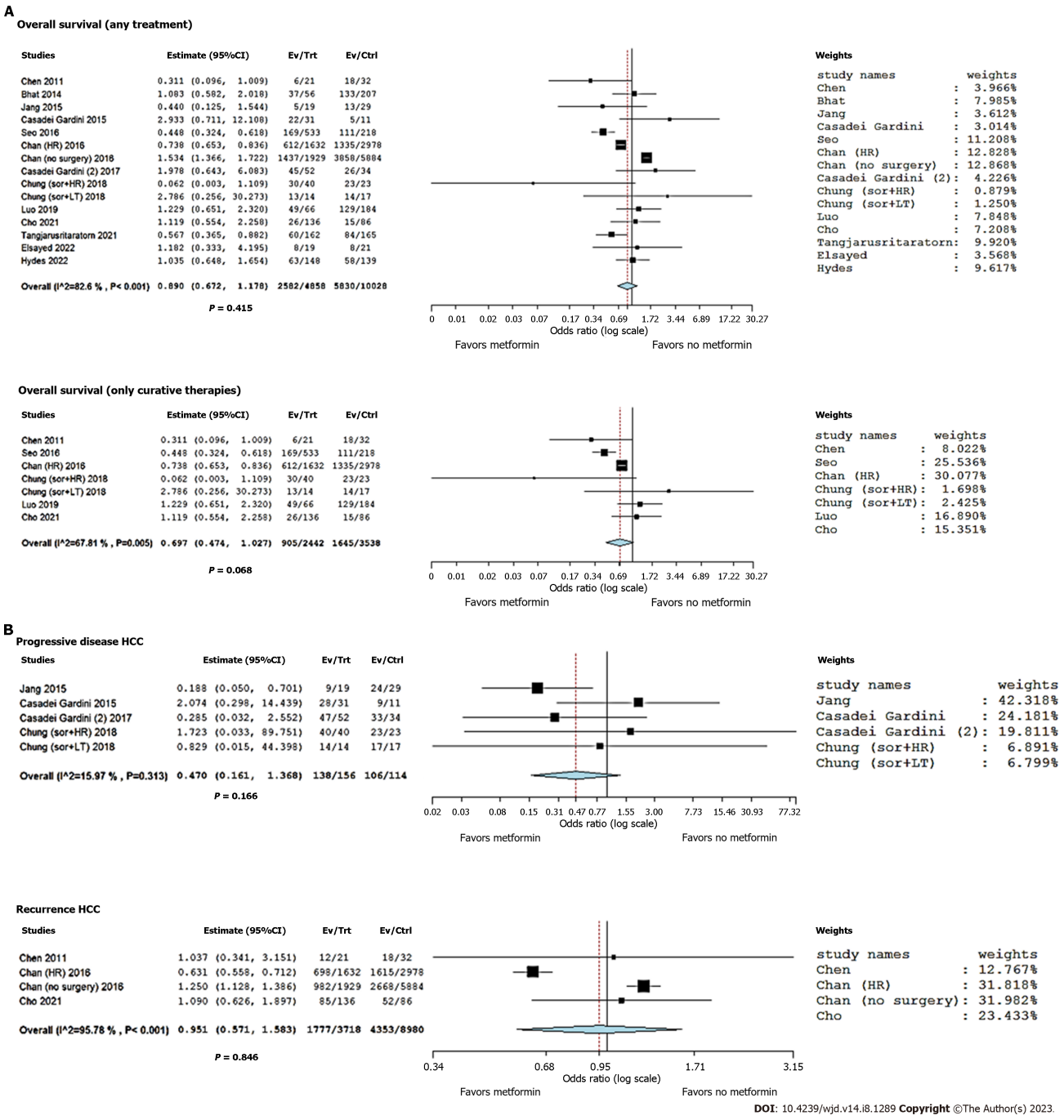
Moreover, there was no specific investigation on the HCC-related death concerning the timing of curative treatment (1-, 2-, 5-year period), or the metformin dose, which also limited data interpretation. Specific studies exploring these aspects showed a positive effect of metformin. For example, use of metformin in high doses before cancer diagnosis reduced the likelihood of death in colorectal patients comparing T2DM and non-T2DM patients not receiving metformin [39].

Due to these promising results, metformin has also been used in non-diabetic cancer patients, and available data suggest its benefits in terms of Ki-67 reduction (positive effects on tumor cell proliferation and apoptosis) and insulin level reduction when given to non-diabetic breast cancer patients in standard doses[40,41]. Whether the suppressive effect of metformin on cancer is caused by a direct preventive effect or is due to the cancer-diabetes association, relying on lowering hyperglycemia and insulin levels, remains unclear[42]. An interesting clinical study suggests metformin has a preventive role in colorectal precancerous lesions in non-diabetic patients even when used in very low doses (250 mg/d) [43]. The actual mechanism behind the metformin anti-tumor effect is still intriguing. In the case of HCC, activating adenosine monophosphate-activated protein kinase and increasing p53 gene expression, which then induces the senescence of cancer cells, might be the key player in the anti-tumor role[44]. Besides inhibition of the mechanistic target of rapamycin signaling, effects on insulin and IGF-1 are also interesting potential pathways[45,46]. Data regarding metformin use in non-diabetic HCC patients is lacking. Also, in the present meta-analysis, all the enrolled cases had a diagnosis of T2DM. The correlation between metformin and HCC appears intriguing for numerous reasons related to the connection of T2DM and metabolic associated fatty liver disease/NASH and obesity, together with the potential lowering of hyperglycemia and hyperinsulinemia known factors in HCC development.

The effects of metformin on tumor progression and tumor recurrence are best studied in pancreatic cancer. A recently published meta-analysis including 38772 patients with T2DM and pancreatic adenocarcinoma showed a significant survival benefit of those taking metformin during early and mixed stages of the disease, for patients receiving surgical treatment but not for those at an advanced stage or those receiving chemotherapy[47]. Similar improvements in survival were described earlier by Li *et al*[48] and related only to patients with locally advanced pancreatic cancer and coexisting T2DM when taking metformin.

In the present study, patients with T2DM and HCC receiving metformin had a decreased risk of progressive disease, although this correlation did not reach statistical significance (OR = 0.47, 95%CI: 0.16-1.37; P = 0.17). In addition, the role of metformin on tumor recurrence showed no evident correlation between its use and reduced risk of recurrence (OR = 0.95, 95%CI: 0.57-1.58; P = 0.85). The negative results might relate to the previously reported biases deriving from the high rate of heterogeneity observed among the studies. Moreover, only a few studies explored the role of metformin on tumor progression and recurrence, with a consequently limited number of cases investigated.

As previously reported, the present study has some limitations. First, studies examining the effect of metformin in HCC patients have been carried out exclusively in T2DM patients. No specific studies investigating non-diabetic cases have been published, therefore identifying a potential new area of interest to be explored with specific prospective research. Second, the heterogeneity of the studies limits our ability to clarify the real effect of metformin, mainly on outcomes (*i.e.*, recurrence and progressive disease) with a limited number of enrolled cases. Therefore, more studies are needed specifically focused on these aspects, to better clarify whether the role of metformin is marginal for the risk of post-curative recurrence. Third, despite the potential effect on death prevention after curative therapies, many confounders were reported, requiring a meta-regression to clarify the real positive effect of metformin. Unfortunately, in many cases, the data needed to perform such an analysis is insufficient or lacking. New studies to clarify these aspects or an individual participant data meta-analysis are required. Other relevant aspects not explorable in the extracted studies are the metformin dose, HCC-related death, and the time-to-event data to perform inferential analyses. Also, in this case, the publication of new studies on these aspects or an individual participant data meta-analysis are needed. Lastly, HCC



DOI: 10.4239/wjd.v14.i8.1289 **Copyright** ©The Author(s) 2023.

Figure 3 Forest plots and meta-analyses results. A: The occurrence of death after any hepatocellular carcinoma (HCC) treatment and only after curative therapies: Metformin *vs* no metformin in type 2 diabetes mellitus (T2DM) patients; B: The occurrence of progressive tumor disease and HCC recurrence after any HCC treatment: Metformin *vs* no metformin in T2DM patients. HCC: Hepatocellular carcinoma.

patients often present an underlying liver disease, with different degrees of severity. Metformin is contraindicated in patients which severe liver injury, therefore adding a potential bias in the results reported.

CONCLUSION

In conclusion, no definitive answer can be given on the real protective effect of metformin in diabetic patients receiving therapies for HCC. A trend for a protective effect regarding death after curative treatments has been reported. However, many confounders exist, reducing the relevance of the reported results. More studies are needed to resolve these relevant confounders.

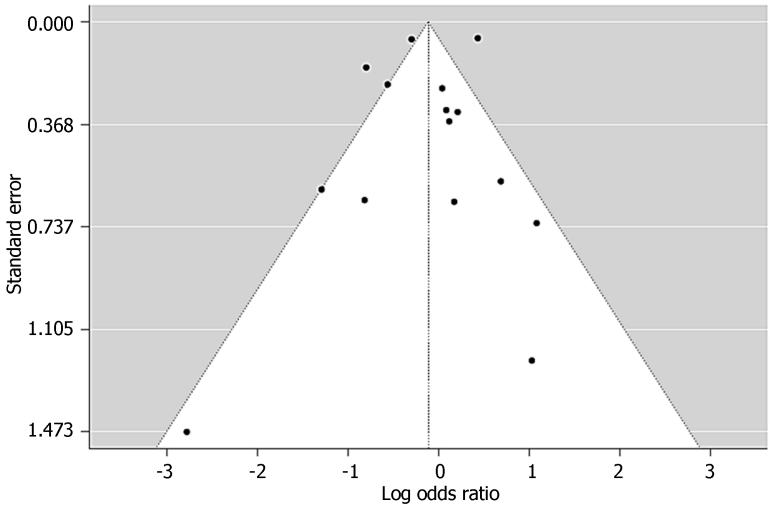


Figure 4 Funnel plot of the studies selected in the present meta-analysis.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is a common malignancy associated with significant cancer-related death. Therefore, it is important to identify chemopreventive potential to lower the risk of an HCC adverse course. Metformin has been associated with a lower risk of HCC development, but its role in prevention of death, tumor progression, and recurrence after any HCC treatment in type 2 diabetes mellitus (T2DM) patients is still inconclusive.

Research motivation

Metformin is a first-line therapeutic option for T2DM, with expanded re-purposing in the treatment of different cancer types. Whether it can improve long-term outcomes in the HCC setting is still unclear. Therefore, we performed a systematic review and meta-analysis to further explore its chemopreventive role in HCC patients.

Research objectives

We focused on the role of metformin in patients with T2DM and HCC in terms of outcomes (death, or progressive disease, or recurrence) receiving any tumor therapy. Moreover, we performed subgroup analyses (including different types of HCC treatment and different ethnicities).

Research methods

We performed a systematic review *via* a search of PubMed and Cochrane Central Register of Controlled Trials Databases of the published literature focused on the role of metformin in patients with T2DM and HCC receiving any tumor therapy.

Research results

We included 13 studies (n = 14886 patients) in this review. A decreased risk was reported in cases receiving metformin, although this value did not reach statistical significance [odds ratio (OR) = 0.89, P = 0.42]. When only patients treated with curative strategies were considered, a more marked correlation between metformin and favorable cases was reported (OR = 0.70, P = 0.068). In the case of a palliative treatment, there was no correlation between metformin and favorable cases (OR = 0.74, P = 0.66). With regard to the risk of progressive disease and recurrence, no obvious correlation between metformin use and reduced risk was reported. Moreover, there was a tendency for a decreased risk of death with metformin use in patients from Eastern countries (OR = 0.69, P = 0.17), but the same was not seen in patients from Western countries (OR = 1.19; P = 0.31).

Research conclusions

Metformin failed to have a relevant impact on preventing adverse effects after HCC treatment. A trend was reported in T2DM cases receiving curative therapies in relation to the risk of death.

Research perspectives

Further large studies are required to definitively clarify the real impact of metformin as a chemopreventive agent for HCC.

FOOTNOTES

Author contributions: Lai Q and Mrzljak A contributed to the conception and design of the study; Giovanardi F and Lai Q contributed to the acquisition of data; Lai Q and Giovanardi F analyzed and interpreted the data; Mrzljak A and Cigovski Berkovic M drafted the article; Lai Q critically revised the manuscript; and all authors approved the final version.

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META-ANALYSIS

New environmental factors related to diabetes risk in humans: Emerging bisphenols used in synthesis of plastics

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Abstract

BACKGROUND

Diabetes mellitus (DM) is one of the largest global health emergencies of the 21st century. In recent years, its connection with environmental pollutants, such as bisphenol A (BPA), has been demonstrated; consequently, new structurally similar molecules are used to replace BPA in the plastics industry (BPS, BPF and BPAF).

AIM

To carry out a systematic review to allow coherent evaluation of the state of the

art. Subsequently, a meta-analysis was performed to unify the existing quantitative data.

METHODS
Firstly, a systematic review was carried out, using the terms "(bisphenol) AND (Diabetes OR Hyperglycemia)", to maximize the number of results. Subsequently, three authors analyzed the set of articles. Finally, a meta-analysis was performed for each BP, using RevMan software. In addition, funnel plots were developed to study publication bias.

RESULTS
The systematic analysis of the literature revealed 13 recent articles (2017–2023) related to the study paradigm. The qualitative analysis showed interesting data linking diabetes to the three most widely used substitute BPs in the industry: BPS, BPF and BPAF. Finally, the meta-analysis determined a positive relationship with BPS, BPF and BPAF, which was only statistically significant with BPS.

CONCLUSION
There is a need to apply the precautionary principle, regulating the use of new BPs. Therefore, replacing BPA with BPS, BPF or BPAF is unlikely to protect the population from potential health risks, such as DM.

Key Words: Bisphenol S; Bisphenol F; Bisphenol AF; Diabetes mellitus; Systematic review; Meta-analysis

Core tip: The present study analyzed the potential dangers that society faces with the replacement of bisphenol A (BPA) by new BPs. Thus, using PRISMA methodologies, a systematic review and meta-analysis of the relationship between new BPs and diabetes mellitus (DM) in humans was carried out. The results showed a positive relationship between BPS, BPF and BPAF and DM, which was statistically significant only with BPS. Consequently, new BPs could represent a health risk equivalent to that of BPA.

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INTRODUCTION

Diabetes mellitus (DM) is one of the largest global health emergencies of the 21st century[1]. The prevalence of DM in recent decades has increased substantially. In 1980, the number of people affected was around 108 million adults aged 20–79 years; currently, the prevalence is 10.5% of the world population (536 million people affected), and it is estimated that could increase to 12.2% in 2045 (783.2 million)[2]. DM risk factors include numerous environmental and/or genetic factors, including covariates such as age, weight, diet, and smoking[3]. Therefore, the idea that environmental pollutants could play a role in the development or progression of the disease is coherent. In the literature, there is evidence that suggests a possible relationship between DM and environmental pollutants[4].

Plastics are one of the main environmental pollutants that modern society faces. Thanks to their multiplicity of uses and low cost, plastics have become one of the main axes of modern industry. The central element of the plastics industry is bisphenol A (BPA); a monomer of epoxy resins and polycarbonates used as an additive and improver of the physical properties of different polymers[5]. In the mid-1970s, BPA was part, directly or indirectly, of all major American industries[6]. Currently, the production volume of plastics has increased from 2 million tons (in 1950) to 368 million tons in 2019[7]. Economic studies estimate that plastic production will double in the next 20 years[8].

In recent years the scientific community has highlighted the potential health risks associated with BPA exposure, related with numerous pathologies, such as hormonal alterations[9,10], DM[11], obesity[12], hypertension[13], chronic kidney disease/diabetic nephropathy[14,15] or even with disorders of embryonic development[16,17]. For this reason, the new emerging regulations limit the use of BPA in various contexts, such as baby products[18,19], thermal paper (used in purchase receipts)[20], or containers[21]. Consequently, industries are replacing BPA with substitute molecules with similar structure and molecular weight. The three most important molecules in the plastic industry are BPS, BPF and BPAF[22-24]. In terms of European legislation, BPA is the only monomer that has a harmonized EU classification as toxic to reproduction 1B, H360F (may damage fertility). However, BPS is self-classified under REACH (EU chemicals legislation) as toxic to reproduction 2 (H361f), and BPAF is self-classified as toxic to reproduction 1B (H360F)[25]. BPF has not been classified, but it also has the potential to induce reproductive toxicity[25], showing a hormonal activity as active

as BPA or BPS[22]. Despite the small number of publications exploring the possible effects of these new molecules on human health, their presence has already been detected in air, water, and food of many parts of the world[24,26-28].

The present study was a systematic review of the literature to allow a coherent evaluation of the state of the art. Subsequently, a meta-analysis was performed to unify the existing quantitative data. The primary outcome measures were serum/plasma or urinary BPs (except BPA) in relation to DM. The analysis was limited to humans and English language, but no restriction was applied in the academic search engines.

MATERIALS AND METHODS

Selection of studies

The study was conducted using the PRISMA guidelines[29,30] as a methodological basis. The main objective of the study was to identify and analyze the state of the art of the new bisphenols–diabetes paradigm. In recent years, the number of evidence related to BPA has increased; however, the new BPA substitute molecules continue to be relegated to the background in the literature, with a small amount of available evidence. For this reason, all those original studies that studied the possible implications of any BP (except for BPA), in the context of human populations, were selected. From the set of publications selected for the qualitative analysis, manuscripts with logistic regression analyzes were selected to quantitative analysis.

Strategies and search criteria

The search for articles of interest was performed in December 2022, using the reference academic search engines PubMed (PubMed.ncbi.nlm.nih.gov, accessed on 20 December 2022) and Web of Science (webofscience.com/wos/alldb/basic-search, accessed on 20 December 2022). To maximize the results and avoid losing potential articles of interest, a strategy focused on the generic terms was used. The terms "(Bisphenol) AND (Diabetes OR Hyperglycemia)" were used, without adding any restrictions in academic search engines. The search was carried out by three researchers independently (RMGT, MDM and ACC) and their decisions in each of the bibliographic search and evaluation steps were determined by consensus.

After removal of duplicate articles using the Mendeley bibliography manager (Mendeley Ltd., Elsevier, London, UK), the articles were evaluated by title/abstract. All the articles that were not original (such as reviews), *in vitro* or *in vivo* research models, exclusively BPA study models, or studies of compounds that were not BPs (such as phthalates), and all those articles that did not study DM, were excluded (Table 1). Subsequently, the full text of the manuscripts was analyzed and evaluated.

Selection of articles for qualitative and quantitative analysis

After the full-text analysis, a descriptive analysis of the selected articles was performed. In addition, relevant data for the qualitative study and subsequent quantitative analysis were extracted. All the studies that provided odds ratio (OR) and 95% confidence interval (CI) were selected. Studies that performed correlations, linear regressions, or multivariate analyzes were only included in the descriptive analysis. Discrepancies between independent reviews were resolved by consensus.

RMGT, MDM, ACC, CGC, NA, BJG, IH, RRC, LT and LB extracted the data for Tables 2 and 3: first author, year of publication, country, population group, number of individuals included, age, study period, type of study (Table 2), BP, biological fluid analyzed, analysis method, detection frequency, and metabolite concentration determined (Table 3).

Meta-analysis

Review Manager software (RevMan 5.3, Cochrane, London, UK) was used to perform the inverse variance method. An analysis was performed for each type of BP present in the literature (BPS, BPF and BPAF). Heterogeneity between studies was calculated by applying the ^{2} and I^2 tests. The I^2 statistic was calculated as a percentage, and the results were interpreted as low, medium or high heterogeneity, reaching 25%, 50% and 75%, respectively[31]. The fixed-effect model was used when no heterogeneity was detected among studies, while the random-effect model was preferred when variance existed. $P < 0.05$ was considered statistically significant for all the analyses performed.

Risk of bias

The individual quality of the articles was evaluated considering the use of urinary creatinine or urine gravity as a normalization factor for glomerular filtration rate, and the use of covariates related to diabetes in the development of binomial and multinomial logistic regression models. For the evaluation of publication bias in the meta-analysis, funnel plots were used to identify symmetry or asymmetry in the distribution of results.

RESULTS

Selection of articles

The initial search identified 472 articles in PubMed and 816 in Web of Science. After exporting the set of references to the Mendeley desktop application and removing duplicates, a total of 928 items were obtained. The first analysis carried out

Table 1 Inclusion and exclusion criteria for the analysis of academic literature

Criteria	Description
Inclusion criteria	Studies published in peer-reviewed journals
	Studies published as original article accepted and published
	Studies conducted in human populations, regardless of the population subgroup
	Studies focused on bisphenols, except BPA
Exclusion criteria	Reviews, hypotheses, proyect reports, letters or comments
	In vitro or *in vivo* study models
	Studies performed only on BPA, or on compounds other than bisphenols
	Studies not developed in diabetes

BPA: Bisphenol A.

Table 2 Characteristics of included studies

Ref.	Country	Poblation group	*N*	Age	Study period	Type of study
Kataria *et al*[32], 2017	USA	Healthy children	41 (19 males; 22 females)	10-13	2013-2014	Cross-sectional
Li *et al*[33], 2018	Saudi Arabia	Diabetic *vs* Control	54 (28 males and 26 females) *vs* 47 (20 males and 27 females)	28-68	2015-2016	Cross-sectional (case-control)
Duan *et al*[34], 2018	China	Diabetic *vs* Control	251 *vs* 251	D: 58 ± 10; C: 51 ± 10	2016-2017	Cross-sectional (case-control)
Zhang *et al*[35], 2019	China	Pregnant women	1841 (167 GDM and 1674 Non-GDM)	GDM: 30.07 ± 4.11; non-GDM: 28.44 ± 3.14	2013-2015	Prospective study
Lee *et al*[36], 2019	Korea	Premenopausal adult women	459	20-48	2015-2016	Cross-sectional
Rancière *et al*[37], 2019	France	Diabetic *vs* Control	201 *vs* 584	30-65	1994-1996 + 3, 6 and 9 years	Longitudinal study
van der Meer *et al* [38], 2021	Netherlands	Subjects with impaired fasting glucose (*i.e.*, fasted glucose 6.1 mmol/L to 7.0 mmol/L)	500 (299 males and 201 females)	53.4 ± 10.3	2009-2013 and 2014-2015	Longitudinal study
Tang *et al*[39], 2023	China	GDM *vs* non-GDM pregnant women	100 *vs* 400	30.62 ± 6.46 *vs* 30.60 ± 6.41	From 2015	Cross-sectional (case-control)
Lee *et al*[40], 2021	USA	Diabetes-free women	1299	45-56	1999-2000, 2002-2003	Longitudinal study
Duan *et al*[41], 2021	China	Diabetic *vs* Control	60 *vs* 60	56 ± 7 *vs* 56 ± 7	2016-2017	Cross-sectional (case-control)
Moreno-Gómez-Toledano *et al*[43], 2022	USA	General population	3658 (641 diabetic)	Non-D: 41.11, D: 58.33	2013-2016	Cross-sectional
Zhu *et al*[44], 2022	USA	GDM *vs* non-GDM pregnant women	333	31.2 ± 4.6		Cross-sectional (case-control)

D: Diabetes; C: Control; GDM: Gestational diabetes mellitus.

based on the title and abstract eliminated 884 articles that did not meet the selection criteria, yielding a total of 44 articles. From them, 13 manuscripts that met the search criteria were selected for qualitative analysis, and six were finally included in the quantitative analysis. As can be seen in Figure 1, the rest of the academic papers corresponded to reviews or project reports (n = 12), studies of BPA or compounds not related to BPs (n = 12), pathologies other than diabetes (n = 6) and an *in vitro* study. The degree of novelty of the topic is reflected in the temporality of the 13 selected articles, published from 2017 to 2022.

Table 3 Quantitative data of bisphenols analyzed

Biological fluid	Bisphenol analyzed	Analysis method	Detection frequency (%)	GM (95%CI)/median (IQR)
Urine	BPS/BPF	HPLC-MS/MS	-	2.06 (1.56-2.69)/0.141 (0.141-0.141)
Urine	BPF/BPS/BPAP	HPLC-MS/MS	D: 81.5/15.9/0.0; C: 48.9/0.0/17.0	D: 3.6/0.10/0.05
Urine	BPS/BPAF/BPF	HPLC-MS/MS	D: 68.1/57.4/26.3; C: 47.8/39.4/37.1	D: 0.199 (ND-0.56)/0.093 (ND-0.84)/ND (ND-0.12); C: ND (ND-0.25)/ND (ND-0.05)/ND (ND-0.23)
Urine	BPS/BPAF/BPF	UHPLC-TQMS	90.06/42.59/94.72	0.36 (0.33, 0.38)/0.030 (0.028, 0.031)/2.01 (1.75, 2.32)
Urine	BPS/BPF/BPB/BPAP	HPLC-MS/MS	83.7/3.7/1.3/4.8	0.08 (0.03-0.24)/-/-/-
Urine	BPS-glucuronide	HPLC-MS/MS	Baseline: 14; year 3:9	< LOD (< LOD-< LOD)
Urine	BPS/BPF	LC-MS/MS	Baseline: 13/55; follow-up: 18/53	Baseline: < LOD (< LOD-< LOD)/0.29 (< LOD; 0.81); follow-up: < LOD (< LOD; < LOD)/0.25 (< LOD; 0.77)
Serum	BPS/BPF/BPB	UPLC-MS	82.2/67.2/88.8	0.097 (0.050-0.107)/0.605 (> LOD-0.609)/0.236 (0.233-0.269)
Urine	BPF	HPLC-MS/MS	Baseline: 73.7; follow-up: 80.6	Baseline: 0.99 (2.86); follow-up: 1.11 (2.64)
Urine	BPS/BPF/BPAF	HPLC-MS/MS	D: 66.7/31.7/45.0; C: 40.0/40.0/41.7	D: 0.21 (ND-0.35)/ND (ND-0.23)/ND (ND-0.15); C: ND (ND-0.23)/ND (ND-0.31)/ND (ND-0.05)
Urine	BPS/BPF	HPLC-MS/MS	88.4/57.1	D: 0.59 (0.53-0.64)/0.43 (0.38-0.48); C: 0.50 (0.48-0.52)/0.41 (0.39-0.43)
Urine	BPS/BPF	HPLC-MS/MS	75.1-90.0/-	0.497 (0.436-0.559)/not calculated[1]

[1]Not calculated because the proportion of results below limit of detection was too high to provide a valid result.

BPS: Bisphenol S; BPF: Bisphenol F; BPAF: Bisphenol AF; BPAP: Bisphenol AP; BPB: Bisphenol B; HPLC-MS/MS: High-performance liquid chromatography and tandem mass spectroscopy; UHPLC-TQMS: Ultra-high-performance liquid chromatography with triple quadrupole mass spectrometry; LC-MS/MS: Offline isotope dilution liquid chromatography tandem mass spectrometry; D: Diabetes; C: Control; ND: Not Detectable; LOD: Limit of detection.

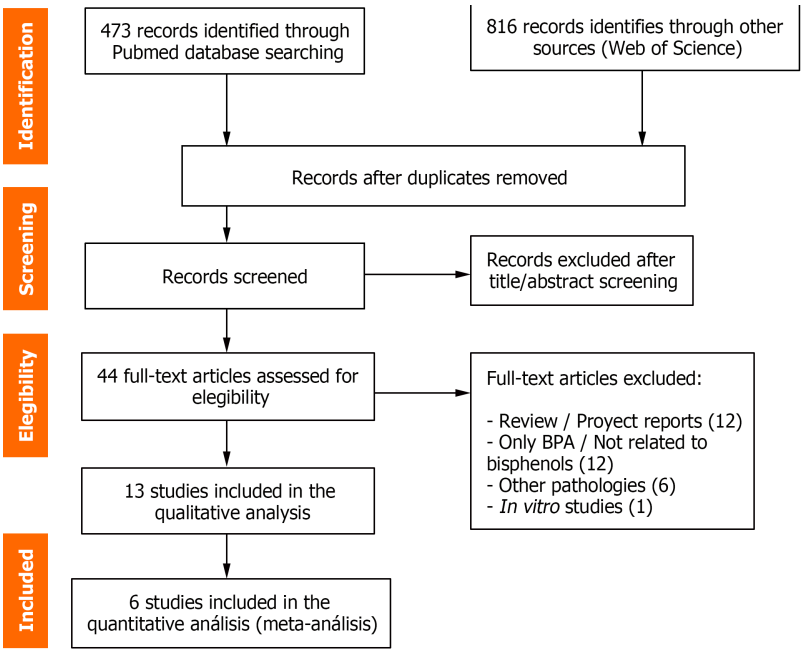

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Figure 1 Schematic representation of the methodology used based on The PRISMA Statement. BPA: Bisphenol A.

Qualitative analysis – genealogy of the paradigm

From a chronological point of view, the first work of interest was Kataria *et al*[32], published in 2017 (see Table 2 for qualitative manuscript details). The authors studied urinary BPs (BPA, BPS and BPF), and blood glucose and insulin levels in a small cohort of children aged 10–13 years. Subsequently, multivariate regression analysis of overweight, body mass index (BMI), insulin resistance, and albumin to creatinine ratio (ACR) showed only significant differences between BPS and ACR. In conclusion, the authors stated that BPS exposure was associated with renal function, but neither BPS nor BPF were related to DM.

In 2018, the first significant evidence between the new substitutes for BPA and DM in human populations appeared: Li *et al*[33] and Duan *et al*[34]. Li *et al*[33] observed a significant relationship between BPF and DM risk in an adult human cohort from Saudi Arabia. In the multinomial logistic regression model performed between quartile 4 (Q4) *versus* Q1 of BPF, corrected for creatinine, using age, gender, nationality, smoking status, and occupation as covariates, an OR (95%CI) of 8.02 (1.68–38.3) was observed. Due to the low presence of BPS and BPAF, they did not develop statistical association models with the BPA derivatives (Table 3). Duan *et al*[34] only observed statistically significant results for urinary BPS and BPAF. They performed binomial logistic regression analyzes for DM in a cohort of 251 DM patients *versus* 251 controls. After correcting for urinary creatinine and including the covariates sex, age, BMI, smoking and alcohol consumption, exercise status, education level, family history of DM, and blood pressure, an OR (95%CI) of 1.73 (1.37–2.18) for BPS and 4.95 (3.15–7.79) for BPAF was obtained.

In 2019, three articles relevant to the context of this manuscript were published: Zhang *et al*[35], Lee *et al*[36] and Ranciè re *et al*[37]. The studies were conducted in pregnant women, premenopausal adult women, and in the general population. Zhang *et al*[35] observed a significant association between BPAF and risk of gestational DM (GDM) in pregnant women with healthy BMI, determining an OR (95%CI) of 1.70 (1.03–2.72). The authors normalized the values of urinary metabolites correcting with specific gravity. Additionally, the logistic regression models performed in women with normal or high BMI, were corrected with the covariates maternal age, pre-pregnancy BMI, educational levels, parity, passive smoking and fetal sex. Lee *et al*[36] performed multipollutant models. The results showed a significant relationship between urinary BPS and the homeostasis model assessment for insulin resistance (HOMA-IR), reaffirming the possible relationship between BPS and DM. Finally, Rancière *et al*[37], in a 9-year longitudinal study carried out in the DESIR cohort, associated the glucuronidated form of BPS (BPS-G) with an increased risk of DM. Due to the small number of samples with the presence of BPS-G, they subdivided the population between the presence or absence of BPS-G, obtaining a hazard ratio value (95% CI) of 2.81 (1.74–4.53).

In 2021 five articles relevant to the analysis were published: van der Meer *et al*[38], Tang *et al*[39], Lee *et al*[40], Duan *et al*[41] and An *et al*[42]. van der Meer *et al*[38] analyzed the presence of endocrine-disrupting metabolites in the urine of subjects with impaired fasting glucose levels (6.1–7.0 mmol/L). The authors collected two samples per individual in two different times (first sample 2009–2013; second sample 2014–2015) and investigated the BP metabolite excretion over time both within and between individuals. Interestingly, while BPA median concentrations decreased (50% reduction), BPF levels remained stable within individuals and over time. BPS was detected only in 18% of the samples, so it was excluded from subsequent analysis. Tang *et al*[39] performed a case–control study in pregnant women with and without GDM. Multinomial logistic regression models performed with serum BPS and BPF, corrected for pregnancy BMI, area of residence, passive smoking during pregnancy, gravity, parity, and exercise regularly, showed positive but nonsignificant results, with OR (95%CI) of 1.68 (0.95–2.99) for highest levels of BPS, and 1.18 (0.68–2.05) for BPF. Lee *et al*[40] analyzed urinary BPF in a longitudinal study with 1299 nondiabetic women (45–56 years) and were followed 3 years later. Individual phenols were examined using Cox regression, and the overall joint effects using quantile-based g-computation. The results showed no significant associations between BPF and DM in middle-aged women. Duan *et al*[41] published a new case–control study in 60 type 2 DM patients and 60 controls, matched by age, sex and BMI. They analyzed 19 serum metabolic biomarkers using multiple linear regression models, and observed a significant association between BPS, BPAF (but not BPF) with several serum metabolites (Pyridoxal, L-histidine and L-citrulline) that could be related to DM (and other pathologies related to endothelial dysfunction). Finally, An *et al*[42] used a different methodological approach. Published datasets related to the genes, proteins and metabolites disturbed by BPS were investigated through omics methods. An interesting conclusion revealed by this analysis was that high concentrations of BPS tended to downregulate biomolecules, while low BPS concentrations tended to enhance metabolic reactions. Furthermore, the authors found evidence of DM-related metabolic disturbances influenced by BPS exposure, such as vitamin or glutathione metabolism.

Finally, Moreno-Gómez-Toledano *et al*[43] and Zhu *et al*[44] published two retrospective cohort studies, in the general population and pregnant women, respectively. In the Moreno-Gómez-Toledano *et al*[43] study, urinary BPS and BPF, corrected with creatinine, were analyzed using binomial and multinomial logistic regression models, corrected by age, sex, BMI, smoking, hypertension, and DM. For the urinary BPS, the results were 1.099 (1.016–1.188), OR (95%CI) in the binomial, and 1.28 (0.99–1.67) in the multinomial analysis. Urinary BPF showed OR of 0.991 (0.928–1.059) and 0.92 (0.70–1.20), respectively. Zhu *et al*[44] did not analyze BPF because the proportion of results below the limit of detection (LOD) was too high to provide a valid result. Urinary BPS was analyzed through multinomial logistic regression models, adjusted for urinary creatinine levels, age, pre-pregnancy BMI, and race/ethnicity (White, Black, Hispanic, and other). The results showed an OR (95% CI) in Asian/Pacific Islanders (A/PIs) of 2.12 (1.0–4.5) and 4.60 (1.55–13.7) in non-A/PIs.

Meta-analysis

As previously detailed, the BPA substitutes–diabetes paradigm comprises a small number of heterogeneous but potentially significant publications.

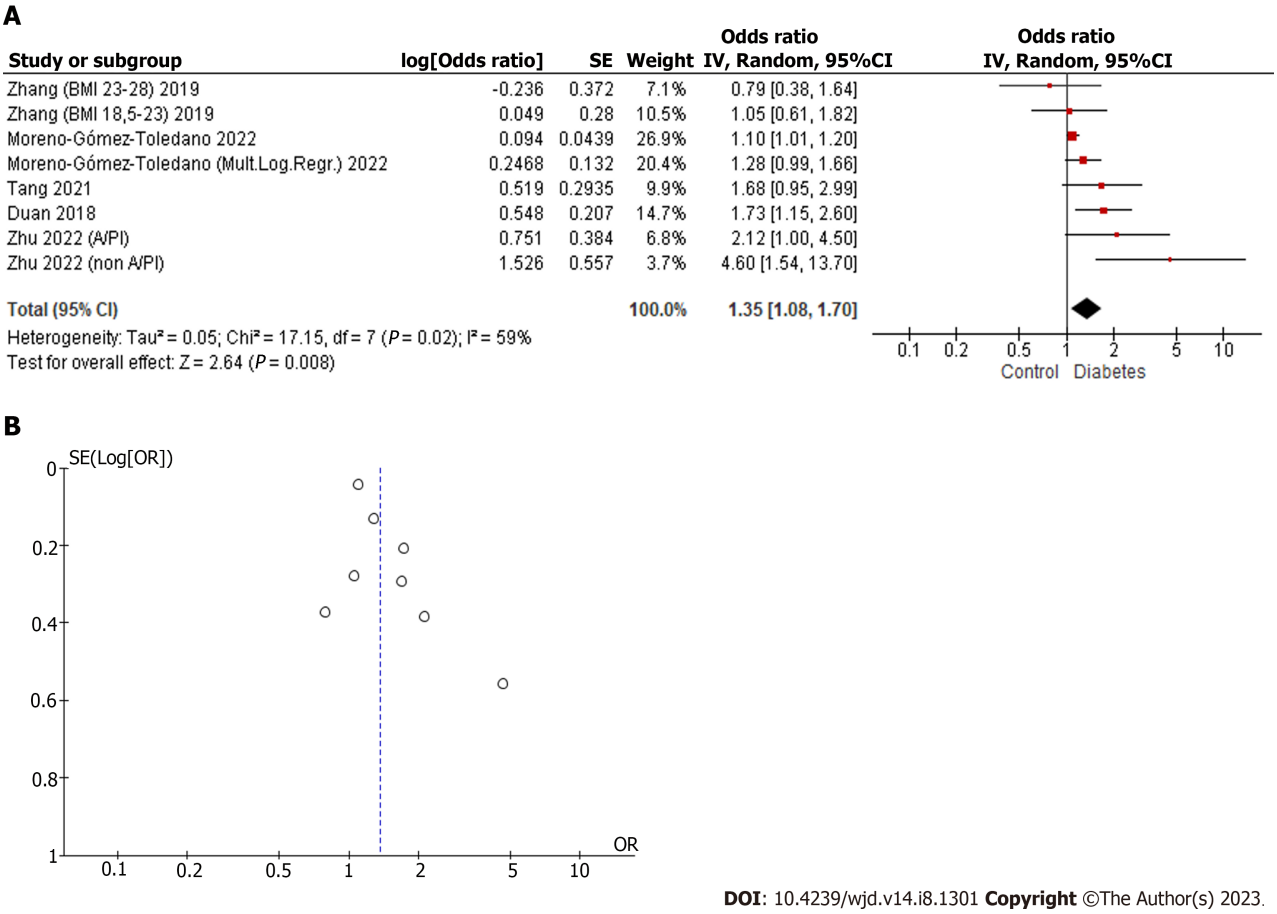

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Figure 2 Meta-analysis. A and B: Meta-analysis (inverse variance method) of the publications that studied bisphenol S and diabetes in humans (A), and funnel plot (for publication bias) (B). 95%CI: 95% confidence interval; BMI: Body mass index.

BPS

For the BPS meta-analysis, the works of Duan *et al*[34], Zhang *et al*[35], Tang *et al*[39], Zhu *et al*[44] and Moreno-Gómez-Toledano *et al*[43] were used. For the combined analysis, binomial and multinomial logistic regression analyses of the different population groups were selected, including a total of eight elements in the meta-analysis. In the work of Zhu *et al*[44], the population was subdivided into two differentiated groups: A/PIs and non-A/PIs. In Zhang *et al*[35], pregnant women with normal pre-pregnancy BMI (18.5–23.0) and high pre-pregnancy BMI (23–28) were included. Finally, in the work of Moreno-Gómez-Toledano *et al*[43], binomial and multinomial logistic regression model analyses were performed with a multiethnic American cohort of adult individuals.

The results of the combined analysis, as can be seen in Figure 2, showed a moderate heterogeneity, (I^2 = 59%). The combined odds ratio was 1.35 (1.08–1.70), with a highly significant P = 0.008. The positive and significant results increased the strength of the evidence that BPS could be an environmental factor that could be related to DM.

BPF

Articles with relevant data for qualitative analysis were Zhang *et al*[35], Tang *et al*[39], Moreno-Gómez-Toledano *et al*[43] and Li *et al*[33]. The same subgroups used in the quantitative analysis of the BPS were included, in addition to the multinomial logistic regression performed in the case–control study by Li *et al*[33]. The results did not show a significant combined result, although they showed a positive trend with DM (Figure 3). Except for the work of Li *et al*[33], none of the other study models showed a significant relationship between BPF and DM, which agrees with the result of the combined model. The I^2 of 51% and combined odds ratio of 1.10 (0.85–1.41), with P = 0.47, showed the moderate heterogeneity of the studies and confirmed that there was no evidence to connect BPF with DM.

BPAF

The third most widely used BP is the one with the least amount of evidence in the literature. As can be seen in Figure 4, three population groups from Duan *et al*[34] and Zhang *et al*[35] were included. I^2 showed a high degree of heterogeneity (89%). The combined result (2.06; 0.83–5.15) showed a positive trend with DM, but due to the small amount of evidence and the absence of a significant result, it was concluded that it is necessary to increase the number of studies to explore the possible implications of BPAF for the risk of development or progression of DM.

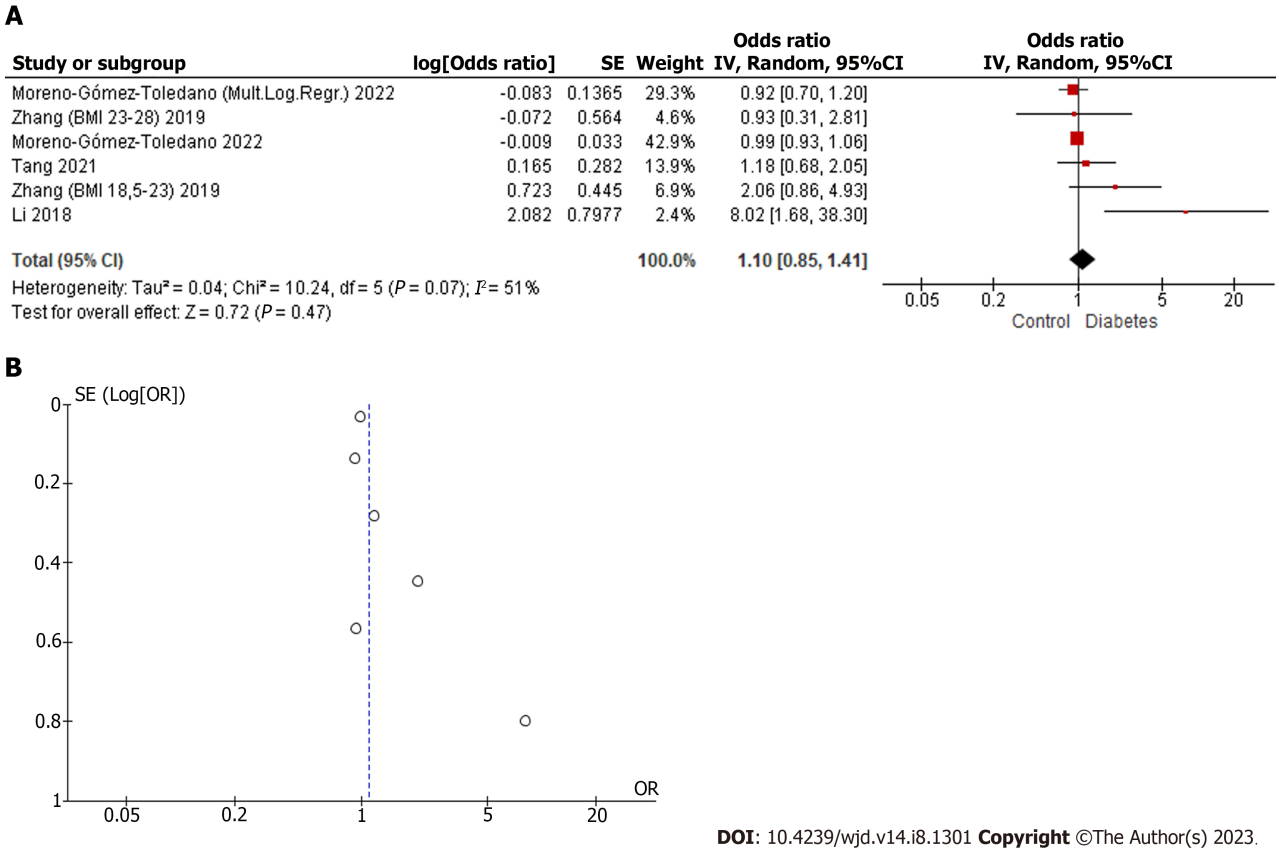

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Figure 3 Meta-analysis. A and B: Meta-analysis (inverse variance method) of the publications that studied bisphenol F and diabetes in humans (A), and funnel plot (for publication bias) (B). 95%CI: 95% confidence interval; BMI: Body mass index.

Publication bias

Despite the moderate degree of heterogeneity of the studies included in the quantitative analyzes of BPS and BPF, the funnel plots showed symmetry, as can be seen in Figures 2 and 3. In the case of the BPAF, there was insufficient evidence. As can be seen in Figure 4, it is essential to increase the number of studies related to the BPAF–diabetes paradigm.

DISCUSSION

The present study was the first systematic review and meta-analysis of the new emerging bisphenols–diabetes paradigm. The systematic analysis of the literature has identified 13 studies with evidence for the context of the study in humans. The detailed analysis of the genealogy of the paradigm provided qualitative and quantitative data, which were used for the subsequent meta-analysis for each of the three most widely used BPA substitutes used in the plastic industry.

The new BPA substitute molecules retain a similar structure, with the presence of two phenolic rings. The monomers only differ in their interphenolic linker, characterized by the presence of sulfur in BPS, fluorine in BPAF, and the absence of methyl groups (CH3) in BPF[25,45]. Possibly due to their structural homology, there is evidence that suggests similarities in the hormonal activity of the new BPs[22]. In wild-type mice, Marroqui *et al*[46] observed that treatment with BPS and BPF rapidly increased insulin release and decreased ATP-sensitive K^+ channel activity. In contrast, treatment in beta estrogen receptor knockout (BERKO) mice did not cause DM-related changes. For BPAF, Wei *et al*[47] demonstrated an important relationship with the development of DM in zebrafish (*Danio rerio*) exposed to environmentally relevant concentrations of the phenolic molecule. Animals exposed to μg/L doses suffered a significant increase in fasting blood glucose levels, hepatic glycogen content, and hepatosomatic indexes, and decreased muscular glycogen content. In addition, they observed alterations in insulin regulation, and quantitative PCR revealed alteration of genes involved in glycometabolic networks, which might promote hepatic gluconeogenesis and inhibit glycogenesis and glycolysis in the muscle and/or liver.

The quantitative results of the meta-analysis showed that the evidence analyzed in the literature related to BPS and DM showed a positive and significant relationship. There was a moderate degree of heterogeneity between studies and the symmetrical pattern observed in the funnel plot added robustness to the combined analysis. The OR (95% CI) of 1.35 (1.08–1.70), with a *P* value of 0.008 confirmed the qualitative evidence described in the qualitative analysis. However, BPF showed a positive trend, but did not show a significant result. Similarly, in the case of the BPAF, probably due to the small amount of evidence available, a significant result (although markedly positive) was not obtained either.

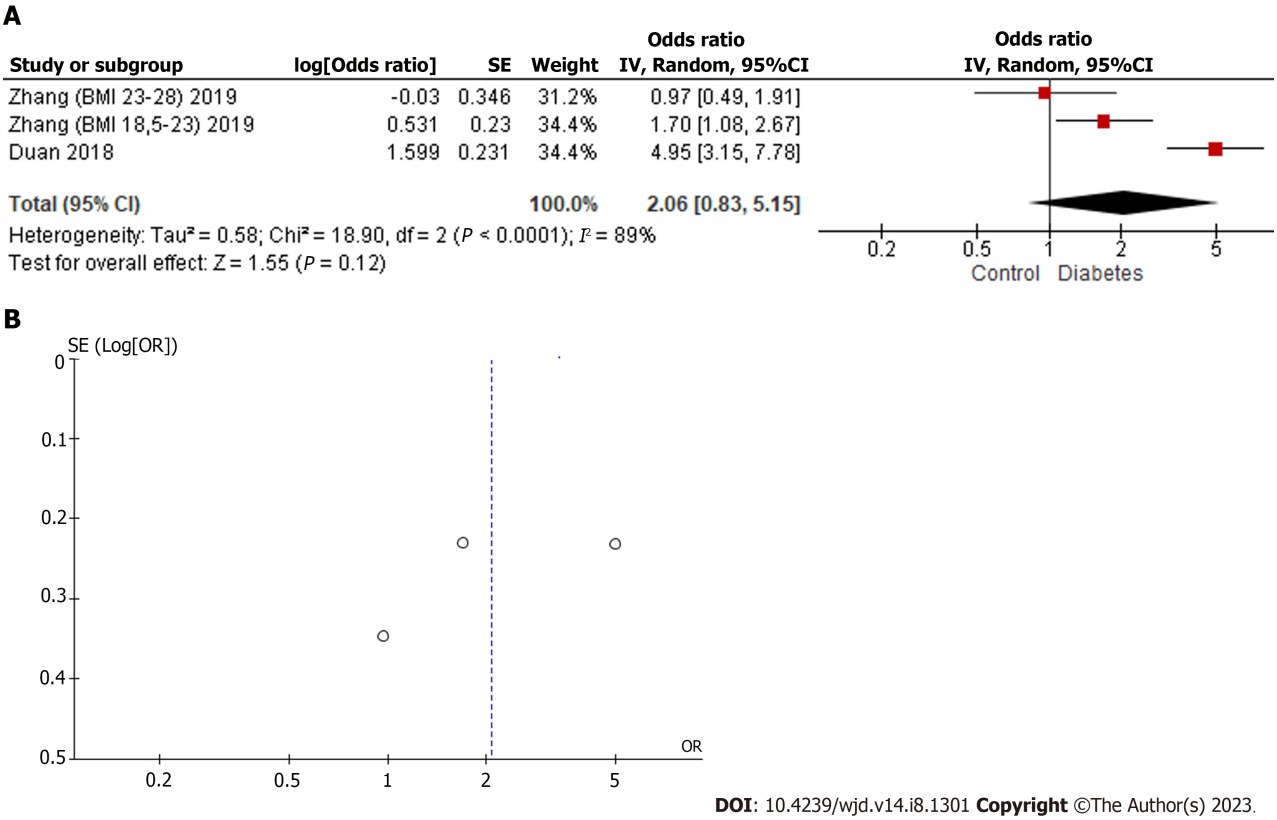

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Figure 4 Meta-analysis. A and B: Meta-analysis (inverse variance method) of the publications that studied bisphenol AF and diabetes in humans (A), and funnel plot (for publication bias) (B). 95%CI: 95% confidence interval; BMI: Body mass index.

There were two examples in the literature that pointed to BPS as a potentially more dangerous monomer than BPA, because there was alarming evidence related to the pharmacokinetics and biodegradability of BPS. Gayrard *et al*[48] observed that the bioavailability of BPS was 250 times greater than BPA in a porcine study model, and Danzl *et al*[49] demonstrated that BPA and BPF were biodegradable in the marine environment; a phenomenon that does not occur with BPS.

Duan *et al*[41] (described in the qualitative analysis), observed metabolome alterations in a cohort of 60 patients with DM and 60 control subjects. Cohort analysis revealed a significant association (linear regression models) between BPS and pyridoxal 5′-phosphate (PLP). PLP deregulation has been linked to DM and blood glucose regulation. In addition, PLP may improve insulin sensitivity by controlling expression of the gene related to adipogenesis[41]. Metabolome analysis also revealed a significant association between BPAF and pyridoxal, L-histidine and L-citrulline. Histidine supplementation has been shown to be effective for insulin resistance, plasma lipid levels, and inflammatory markers, and delayed the development of atherosclerosis in several rodent models of diaDMbetes and metabolic syndrome[50]. Furthermore, citrulline is involved in the production of nitric oxide by nitric oxide synthase, and it plays a crucial role in DM[51], since it is a strong vasodilatory and anti-inflammatory signaling molecule that plays diverse roles in maintaining vascular homeostasis[52].

CONCLUSION

The body of evidence analyzed in this study revealed interesting relationships between the new BPA substitute molecules and DM. The quantitative results showed a positive relationship with BPS, BPF and BPAF, which was only significant with BPS. The present work revealed the small amount of scientific evidence related to the paradigm in the human context, as well as the need to deepen the study of the emerging BPA substitute molecules. Our results suggest the need to apply the precautionary principle, regulating the use of new BPs. In conclusion, replacing BPA with molecules such as BPS, BPF or BPAF is unlikely to protect the population from potential health risks, such as DM.

ARTICLE HIGHLIGHTS

Research background

Diabetes mellitus (DM) is one of the largest global health emergencies of the 21st century. The prevalence of DM has

increased substantially, from 108 million adults in 1980 to 536 million. In parallel, the consumption of plastic products has increased substantially in recent decades, which implies chronic exposure to monomers, such as bisphenol (BP)A, or its new substitute molecules, BPS, BPF and BPAF.

Research motivation

In recent years, the relationship between BPA and DM has been demonstrated. The new BPA substitute molecules have high structural homology with BPA, as well as similar hormonal activity. Therefore, the study of new BPs is potentially linked to population health.

Research objectives

The present systematic review of the literature allowed a coherent evaluation of the state of the art of the new bisphenols–diabetes paradigm. Subsequently, a meta-analysis was performed to unify the existing quantitative data in human cohorts.

Research methods

Using the PRISMA guidelines as a reference, a systematic review of the literature was carried out. Using the qualitative data, a chronological review was performed, and all quantitative data of interest were identified. Subsequently, a meta-analysis was performed for each BP identified using the RevMan software, and a funnel plot was also performed for risk of bias.

Research results

Qualitative analysis identified 13 recently published articles (2017–2022) that contextualized the new evidence between emerging BPs and DM. The subsequent meta-analysis showed positive results with the three BPs, but only BPS was significant.

Research conclusions

The present study was the first systematic review and meta-analysis of the new BPA substitute molecules and DM. The results support the possible positive relationship between the new BPs and the risk of DM, especially with BPS. Consequently, the substitution of BPA may not improve population health, and government institutions should consider applying the precautionary principle.

Research perspectives

The results support the need to deepen the paradigm, increasing the evidence in basic and translational research, to determine the real risk to which the human population is exposed.

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FOOTNOTES

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META-ANALYSIS

Sodium-glucose Cotransporter-2 Inhibitors induced euglycemic diabetic ketoacidosis: A meta summary of case reports

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Abstract

BACKGROUND

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are commonly prescribed to manage patients with diabetes mellitus. These agents may rarely lead to the development of euglycemic diabetic ketoacidosis (EDKA), which may complicate the disease course of these patients.

AIM

To analyze the demographic profile, predisposing factors, symptomology, clinical interventions and outcomes of patients presenting with EDKA secondary to SGLT2i use by reviewing the published case reports and series.

METHODS

We performed a systematic search of PubMed, Science Direct, Google Scholar and Reference Citation Analysis databases using the terms "canagliflozin" OR "empagliflozin" OR "dapagliflozin" OR "SGLT2 inhibitors" OR "Sodium-glucose cotransporter-2" AND "euglycemia" OR "euglycemic diabetic ketoacidosis" OR "metabolic acidosis". The inclusion criteria were: (1) Case reports or case series with individual patient details; and (2) Reported EDKA secondary to SGLT2i. Furthermore, the data were filtered from the literature published in the English language and on adults (> 18 years). We excluded: (1) Conference abstracts; and (2) Case reports or series which did not have individual biochemical data. All the case reports and case series were evaluated. The data extracted included patient

demographics, clinical symptomatology, clinical interventions, intensive care unit course, need for organ support and outcomes.

RESULTS

Overall, 108 case reports and 17 cases series with 169 unique patients that met all the inclusion criteria were included. The majority of patients were females (54.4%, *n* = 92), and the commonly reported symptoms were gastrointestinal (nausea/vomiting 65.1%, abdominal pain 37.3%) and respiratory (breathlessness 30.8%). One hundred and forty-nine (88.2%) patients had underlying type II diabetes, and the most commonly involved SGLT-2 inhibitor reported was empagliflozin (46.8%). A triggering factor was reported in most patients (78.7%), the commonest being acute severe infection (37.9%), which included patients with sepsis, coronavirus disease 2019, other viral illnesses, and acute pancreatitis. 61.5% were reported to require intensive unit care, but only a minority of patients required organ support in the form of invasive mechanical ventilation (13%), vasopressors (6.5%) or renal replacement therapy (5.9%). The overall mortality rate was only 2.4%.

CONCLUSION

Patients on SGLT2i may rarely develop EDKA, especially in the presence of certain predisposing factors, including severe acute infections and following major surgery. The signs and symptoms of EDKA may be similar to that of DKA but with normal blood sugar levels, which may make the diagnosis challenging. Outcomes of EDKA are good if recognized early and corrective actions are taken. Hence, physicians managing such patients must be aware of this potential complication and must educate their patients accordingly to ensure early diagnosis and management.

Key Words: Canagliflozin; Empagliflozin; Euglycemia; Diabetes mellitus; Diabetic ketoacidosis; Sodium-glucose cotransporter-2 inhibitors; Sodium-glucose cotransporter-2

Core Tip: Sodium-glucose cotransporter-2 inhibitors are a newer class of oral hypoglycemic drugs commonly prescribed for managing patients with diabetes mellitus. Even though these drugs are effective in controlling blood glucose and have favorable cardiac effects, they may rarely lead to the development of euglycemic diabetic ketoacidosis (EDKA), which may complicate the disease course of these patients. Certain risk factors, such as severe acute illness and major surgery, may predispose these patients to develop EDKA. The signs and symptoms of EDKA are similar to classic symptoms of diabetic ketoacidosis, but these patients have normal blood glucose levels, making the diagnosis difficult. Hence, a higher index of suspicion is warranted in such patients, as delay in diagnosis may lead to higher morbidity and mortality.

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INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are relatively new oral hypoglycemic agents (OHAs), which are increasingly being used to manage patients with diabetes mellitus (DM). The current American Diabetes Association (ADA) guidelines recommend using SGLT2i as one of the second-line agents, along with metformin, in managing patients with type II diabetes mellitus (T2DM). They may also be used as the primary agent in patients with heart failure, chronic kidney disease, risk of atherosclerotic cardiovascular disease, and those who are metformin intolerant or in whom metformin is contraindicated[1].

The mechanism of action of SGLT2i is independent of insulin secretion, making them an appealing choice for combination therapy. By inhibiting the SGLT2 receptors in the proximal tubules of the kidneys, this reduces glucose reabsorption and the renal threshold for glucose, thereby increasing renal excretion and reducing serum glucose levels[2].

SGLT2i have several clinical advantages, including reduced risk of hypoglycemic episodes, improved blood pressure control, weight reduction and positive cardiovascular outcomes[2,3]. However, the use of SGLT2i is also associated with an increased incidence of genitourinary infections and hypovolemia[4]. Within months of Food and Drug Administration (FDA) approval, cases of diabetic ketoacidosis (DKA) were reported among those using SGLT2i. In earlier reports, the incidence of DKA was 0.522 per 1000 patient-years in patients taking canagliflozin 100 mg/d. A higher incidence of 0.763 per 1000 patient-years was reported in patients taking higher doses of 300 mg/d. However, most patients had blood glucose levels higher than 300 mg/dL, and EDKA has been even more rarely reported[5].

DKA is a well-documented complication in patients with T1DM that is often recognized at the time of a new diagnosis of diabetes and is generally precipitated by poor adherence to treatment or acute infection[6]. EDKA is a rare, but mostly

missed and under-reported complication of DM management. It is arbitrarily defined as DKA without marked hyperglycemia. The ADA has defined EDKA as the presence of high anion-gap metabolic acidosis and increased plasma ketones in the presence of blood glucose levels below 250 mg/dL (13.9 mmol/L)[7].

The main aim of this meta-summary was to identify the predisposing factors, symptomatology, clinical course and outcomes of the patients on SGLT2i presenting with EDKA. This may aid physicians involved in managing such patients to make an early diagnosis and prevent future events.

MATERIALS AND METHODS

For this meta summary, a systematic search of PubMed, Science Direct, Reference Citation Analysis (https://www.referencecitationanalysis.com/), and Google Scholar databases was conducted from January 1, 2015, to January 31, 2023. The search terms used were "canagliflozin" OR "empagliflozin" OR "dapagliflozin" OR "SGLT2 inhibitors" OR "Sodium-glucose cotransporter 2" AND "euglycemia" OR "euglycemic diabetic ketoacidosis" OR "metabolic acidosis". The inclusion criteria were: (1) Case reports or case series with individual patient details; and (2) Reported EDKA secondary to SGLT2i. Furthermore, data were filtered from the literature published in the English language and on adult (> 18 years) humans. We excluded: (1) Conference abstracts; and (2) Case reports or series which did not have individual biochemical data. The authors screened all the search results to include only the relevant literature. Duplicate articles from different search databases were excluded.

All the case reports, and case series were evaluated. The data extracted included patient demographics, clinical symptomatology, clinical interventions, intensive care unit (ICU) course, need for organ support and outcomes. A datasheet for evaluation was also prepared.

Statistical analysis

The prepared datasheet was analyzed using Excel and Microsoft Office 2019. Categorical variables were presented as frequency and percentage. Mean (SD) or median [interquartile range (IQR)] was used to describe the continuous variables. The statistical analyses were performed using SPSS (version 25.0, IBM SPSS Inc., Chicago, IL, United States). MS Office software (MS Office 2019, Microsoft Corp., WA, United States) was used for tabulation and final documentation.

RESULTS

The present review was carried out using the preferred reporting items for systematic reviews and meta-analyses 2009 checklist (Figure 1). Ultimately, 108 case reports and 17 cases series with 169 unique patients meeting the predefined inclusion criteria were included (Supplementary material). The majority of included patients were from the United States of America (74, 43.8%) and Canada (23, 13.6%) (Figure 2). Most of the patients reported were females (54.4%, n = 92), and the commonly reported symptoms were gastrointestinal (nausea/vomiting 65.1%, abdominal pain 37.3%) and respiratory (breathlessness 30.8%). One hundred and forty-nine (88.2%) patients had underlying type II diabetes; the most commonly involved SGLT2i was empagliflozin, 46.8% (Table 1). Most patients (78.7%) reported a triggering factor, the commonest being acute severe infection (37.9%), which included patients with sepsis, coronavirus disease 2019, other viral illnesses, and acute pancreatitis. The second most common triggering factor was a perioperative period (24.3%), which included patients undergoing bariatric surgery, coronary artery bypass grafting, orthopedic surgeries, pancreatectomy and cranial nervous system surgeries. Multiple triggering factors were reported in several patients (Table 1). The median time on SGLT2i before developing EDKA was 30 d (interquartile range 6.5-165 d).

The median blood glucose level at presentation was 184.5 mg/dL. Most patients had severe metabolic acidosis with a median serum pH of 7.14 and bicarbonate levels of 8.6 mmol/L. Hyperlactatemia was uncommon, with median lactate levels being 1.3 mmol/L (Table 2). The overall mortality rate was only 2.4%.

DISCUSSION

In the present meta-summary, data from 169 individual case reports were analyzed. Most patients (88.2%) were suffering from T2DM. Common presenting symptoms included nausea, vomiting, and abdominal pain. Empagliflozin was the commonest SGLT2i involved in 46.8% of cases. At presentation, the median blood glucose levels were 184.5 mg/dL, and the median blood pH was 7.14. Nearly 62% of patients were reported to require ICU admission. Even though patients presented with severe metabolic acidosis, the overall mortality rate was only 2.4%.

DKA is a medical emergency which is diagnosed with hyperglycemia (blood glucose > 250 mg/dL), metabolic acidosis (arterial pH < 7.3, serum bicarbonate < 15 mEq/L), and ketonemia. However, between 2.6% to 3.2% of DKA admissions may present with normal to near-normal blood glucose levels (blood glucose < 250 mg/dL)[8,9]. Even though the association of EDKA with SGLTi is well established, the cause for EDKA secondary to SGLT2i is not well recognized. Several mechanisms have been proposed, including independent action on pancreatic alpha cells, which increases plasma glucagon levels, stimulates hepatic ketogenesis, and reduces renal clearance of ketone bodies (especially beta-hydroxybutyrate and acetoacetate)[2,10]. SGLT2i increase renal excretion and block glucose reabsorption from the proximal

Table 1 Baseline patient parameters

Parameter	Number of patients, *n* = 169
Age (± SD), yr	51.7 (13.8)
Gender, *n* (%)	Females, 92 (54.4)
	Males, 77 (45.6)
Type of diabetes, *n* (%)	Type I, 18 (10.7)
	Type II, 149 (88.2)
	Not mentioned, 2 (1.1)
Body mass index (± SD)	29.6 (6.4)
Clinical presentation, *n* (%)	Nausea/Vomiting, 110 (65.1)
	Abdominal pain, 63 (37.3)
	Breathlessness, 52 (30.8)
	Fatigue, 46 (27.2)
	Altered mental status, 34 (20.1)
	Loss of consciousness, 11 (6.5)
	Chest pain, 5 (3)
	Shock, 4 (2.4)
	Fever, 4 (2.4)
	Others, 12 (7.1)
Comorbidities, *n* (%)	Diabetes, 166 (98.2)
	Hypertension, 45 (26.6)
	Coronary artery disease, 20 (11.8)
	Dyslipidemia, 13 (7.7)
	Cancer, 4 (2.4)
	Others, 24 (14.4)
SGLT-2 inhibitor involved, *n* (%)	Empagliflozin, 79 (46.8)
	Canagliflozin, 50 (29.6)
	Dapagliflozin, 39 (23.1)
	Ipragliflozin, 1 (0.6)
	Tofogliflozin, 1 (0.6)
Other OHAs prescribed, *n* (%)	Yes, 135 (79.9)
	No, 25 (14.8)
	Not mentioned, 9 (5.1)
Other diabetes medications involved, *n* (%)	Metformin, 119 (70.4)
	Dipeptidyl peptidase 4 inhibitors, 42 (24.9)
	Sulfonylureas, 26 (15.4)
	Thiazolidinediones, 10 (5.9)
	Meglitinides, 3 (1.8)
	α-Glucosidase inhibitors, 2 (1.2)
	Insulins, 57 (33.7)
	Glucagon-like peptide-1 receptor agonist, 21 (12.4)
	Not mentioned, 11 (6.5)
History of alcohol use, *n* (%)	6 (3.6)

Identifiable triggering factor, *n* (%)	Present, 133 (78.7)
Triggering factor, *n* (%)	Infection, 64 (37.9)
	Major surgery, 41 (24.3)
	Reduced food intake, 32 (18.9)
	Any major illness, 17 (10.1)
	Reduced carbohydrate/ketogenic diet 14 (8.3)
	Dehydration, 14 (8.3)
	Reduced insulin dosages, 10 (5.9)
	Prolonged fasting, 9 (5.3)
	Trauma, 2 (1.2)
Ketones for diagnosis, *n* (%)	Only urine, 62 (36.7)
	Only plasma, 36 (21.3)
	Both, 60 (35.5)
	Not mentioned, 11 (6.5)
Organ failure, *n* (%)	Respiratory, 20 (11.8)
	Cardiac, 11 (6.5)
	Renal, 8 (4.7)
Need for organ support, *n* (%)	Invasive mechanical ventilation, 22 (13)
	Vasopressors, 11 (6.5)
	RRT, 10 (5.9)
Other treatments given, *n* (%)	Sodium bicarbonate, 21 (12.4)
Need for ICU, *n* (%)	104 (61.5)
Days in ICU (± SD)	3.4 (5.4) d
Days in hospital (± SD)	9.3 (10.4) d
Outcome, *n* (%)	Alive, 164 (97)
	Death, 4 (2.4)
	Not mentioned, 1 (0.6)

SGLT: Sodium-glucose-cotransporter; OHA: Oral hypoglycemic agent; RRT: Renal replacement therapy; IMV: Invasive mechanical ventilation; ICU: Intensive care unit.

Table 2 Baseline laboratory parameters

Parameter	Median values
Blood glucose (IQR)	184.5 (151.8-219.3) mg/dL
Serum osmolality (IQR)	297 (290.8-312.8) mmol/kg
pH (IQR)	7.14 (7.05-7.24)
Bicarbonate (IQR)	8.6 (6-11) mmol/L
Lactates (IQR)	1.3 (1.1-1.8) mmol/L
Anion gap (IQR)	22.50 (19-28) mmol/L

IQR: Interquartile range.

convoluted tubule, thereby reducing serum glucose levels[11]. The combined effect of these mechanisms may lead to ketonemia and ketoacidosis without much of an increase in serum glucose levels.

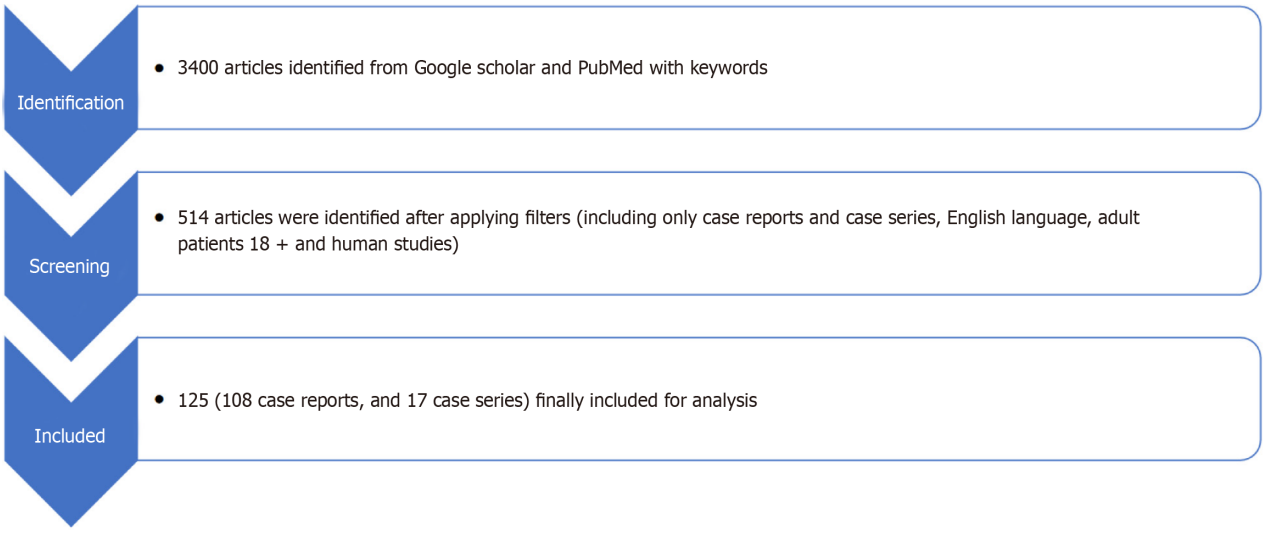

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Figure 1 The preferred reporting items for systematic reviews and meta-analyses flow diagram for the selected literature.

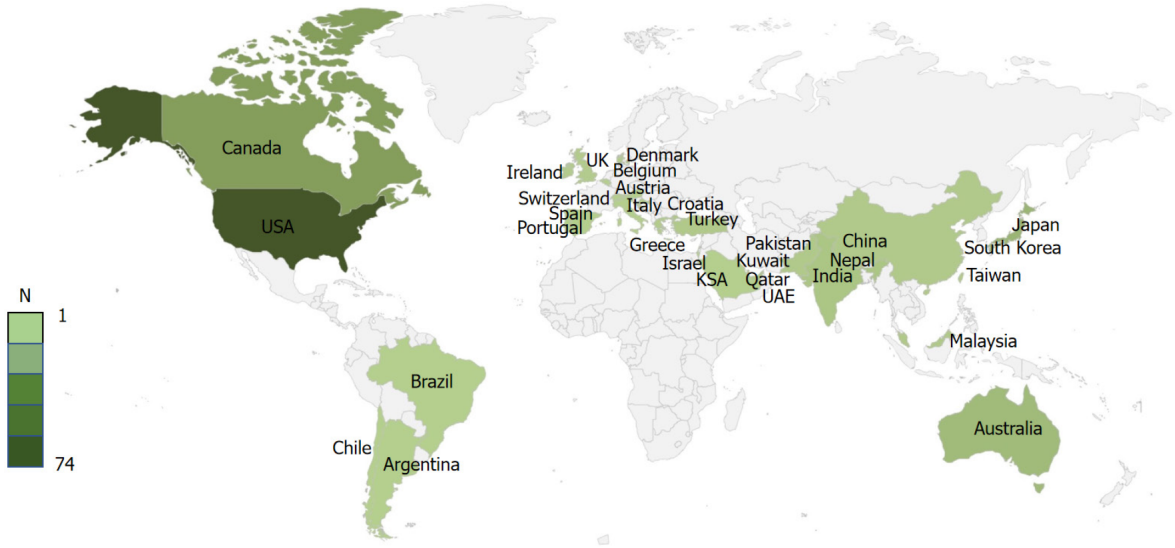

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Figure 2 Geographical distribution of the patients reported with Sodium-glucose cotransporter-2 inhibitors associated euglycemic diabetic ketoacidosis.

In the present meta-summary, most (88.2%) patients had type II diabetes. This could be explained by the fact that type II diabetes is much more common in adults accounting for almost 90% of cases[12]. SGLT2i are primarily recommended for treating type II diabetes, but they increase the risk of developing DKA 7-fold in these patients[13]. SGLT2i are now being prescribed for type I diabetes also, especially in those who failed to achieve glycemic targets with insulin alone, because their use is associated with improved HbA1c levels, reduction in body weight and better blood pressure control in these patients[14-16]. However, because of their increased potential to precipitate EDKA in TIDM, SGLT2i are generally discouraged in these patients[7,10,17].

A previous meta-summary analyzing data from 77 patients with EDKA associated with SGLT2i also reported a higher incidence among females (67.5%) but reported canagliflozin (44.2%) as the commonest SGLT2 inhibitor involved. However, as our meta-summary shows, empagliflozin (46.8%) was the most commonly implicated agent, followed by canagliflozin (29.6%). This could be explained by the fact that canagliflozin was the first SGLT2 inhibitor commercially available; hence it was more widely prescribed earlier. With changing prescription practices, newer SGLT2i are more widely prescribed, explaining the increase in reporting of side effects. Other findings in the previous meta-summary were similar to our findings, including the age at presentation (51.3 years), presenting symptoms and preponderance of type II diabetics (83.1%)[18]. The risk of developing EDKA is unrelated to the duration of exposure[13,18,19]. In the present study, the median duration of therapy with SGLT2i before the patients developed EDKA was 30 d, but patients developed EDKA even after one day or one dose of therapy[20,21].

The symptoms of EDKA are often non-specific and missed or ignored by patients and even their physicians due to misleadingly normal or near-normal blood glucose levels. This may lead them to maintain or reduce their insulin dose, further exacerbating ketosis and metabolic acidosis.

Testing for urinary ketone bodies remains a standard test for the diagnosis of DKA. However, urine screening of ketones by nitroprusside agents only measures acetone and acetoacetate and does not detect beta-hydroxybutyrate, resulting in missing ketonuria. Hence, testing for blood ketones (b-hydroxybutyrate) is generally recommended[7]. However, urinary ketones remained a standard test in the present meta-summary and was solely relied upon in 36.7% of cases.

Identifying precipitating factors can have significant clinical implications in preventing and managing EDKA. In the present study, acute infection and perioperative stress were found to be common triggering factors. Any major illness, trauma or surgery may result in a stress response associated with an increased release of catecholamines, heightened production of cortisol and reduced secretion and utilization of insulin[22]. If patients continue their SGLT2i, reduced plasma glucose levels may mask the precise insulin requirements, increasing the risk of developing DKA.

As major surgery is an important factor that may precipitate EDKA, taking due precautions before surgery is imperative. Even the current recommendation by FDA and International Consensus Review on SGLT2i is to stop these drugs three days before surgery[23,24]. As these drugs are primarily excreted through the kidneys, it may be prudent to stop them even earlier in patients with renal dysfunction[25].

Other common factors which may predispose patients to develop EDKA include prolonged fasting, low carbohydrate or ketogenic diet, excessive alcohol intake, dehydration and reduction in insulin dosage[18,19,26]. High protein and low carbohydrate diets may increase serum glucagon and reduce serum insulin levels. They may also cause an increase in counterregulatory hormones (epinephrine and cortisol), leading to increased free fatty acids and increased production of ketone bodies. As the reduction in insulin dosage may also precipitate DKA, stopping or drastically reducing the dose abruptly is not recommended. Moreover, the stress response due to a systemic illness or major surgery is a common trigger; hence, timely discontinuation of SGLT2i should be considered in acute stressful conditions such as a major illness or post-operatively[23]. Patient education and pre-operative discontinuation of SGLT2i and switching to insulin may aid in curtailing the risk of EDKA. Furthermore, the European Medicines Agency suggests stopping SGLT2i immediately if symptoms or signs of DKA are suspected and not starting them until EDKA is excluded and an apparent precipitating factor has been identified and resolved[27].

Strength and limitations

The present meta-analysis compiled 125 global studies involving 169 unique patients who had developed EDKA secondary to the use of SGLT2i. Additionally, we included only those studies which had individual patient details to compare patient demographics, precipitating factors and clinical outcomes. This is the largest such analysis, which adds strength to this review. However, the included studies were only case reports and case series which had no control arm. The studies were heterogeneous, and had a high risk of bias and missing data, which may affect the generalizability of the results. Additionally, because we did not include the case reports or series which did not report individual biochemical data, we may have missed some relevant reports.

CONCLUSION

Patients on SGLT2i may rarely develop EDKA, primarily due to certain predisposing factors, including severe acute infections and following major surgery. The signs and symptoms may be similar to DKA but with normal blood sugar levels, making the diagnosis challenging. EDKA outcomes are good if recognized timely and corrective actions are taken. Hence, physicians managing such patients must be aware of this potential complication and educate patients accordingly to ensure early diagnosis and management.

ARTICLE HIGHLIGHTS

Research background

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are commonly prescribed drugs in managing patients with diabetes mellitus (DM). These agents may rarely lead to the development of euglycemic diabetic ketoacidosis (EDKA), which may complicate the disease course of these patients.

Research motivation

EDKA is a rare, but mostly missed and under-reported complication of DM management. The use of SGLT2i may increase the risk of developing EDKA.

Research objectives

The main aim of this meta-summary was to identify the predisposing factors, symptomatology, clinical course and outcomes of the patients on SGLT2i presenting with EDKA.

Research methods

We performed a systematic search of PubMed, Science Direct, Google Scholar and Reference Citation Analysis (https://www.referencecitationanalysis.com/) databases using the terms "canagliflozin" OR "empagliflozin" OR "dapagliflozin" OR "SGLT2 inhibitors" OR "Sodium-glucose cotransporter-2" AND "euglycemia" OR "euglycemic diabetic ketoacidosis" OR "metabolic acidosis".

Research results

Overall, 108 case reports and 17 cases series with 169 unique patients were included. One hundred and forty-nine (88.2%) patients had underlying type II diabetes, and the most commonly involved SGLT2 inhibitor reported was empagliflozin (46.8%). A triggering factor was reported in most patients (78.7%), the commonest being acute severe infection (37.9%). Sixty-one-point-five percent were reported to require intensive unit care, but only a minority of patients required organ support. The overall mortality rate was only 2.4%.

Research conclusions

Patients on SGLT2i may rarely develop EDKA, especially in the presence of certain predisposing factors. The signs and symptoms of EDKA may be similar to those of DKA but with normal blood sugar levels. Outcomes of EDKA are good if recognized early and corrective actions are taken.

Research perspectives

Large scale studies must be conducted to find out the true incidence and clinical impact of EDKA in patients using SGLT2i.

FOOTNOTES

Author contributions: Juneja D acquisition of data, analysis and interpretation of data, drafting the article, final approval; Nasa P acquisition of data, analysis and interpretation of data, drafting the article, final approval; Jain R interpretation of data, revising the article, final approval; Singh O designing the study, drafting the article, final approval.

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CASE REPORT

Sequential treatment for diabetic foot ulcers in dialysis patients: A case report

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Abstract

BACKGROUND

Diabetic foot ulcers (DFUs) are common in patients with diabetes, especially those undergoing hemodialysis. In severe cases, these ulcers can cause damage to the lower extremities and lead to amputation. Traditional treatments such as flap transposition and transfemoral amputation are not always applicable in all cases. Therefore, there is a need for alternative treatment methods.

CASE SUMMARY

This report describes a 62-year-old female patient who was admitted to the hospital with plantar and heel ulcers on her left foot. The patient had a history of renal failure and was undergoing regular hemodialysis. Digital subtraction angiography showed extensive stenosis and occlusion in the left superficial femoral artery, left peroneal artery and left posterior tibial artery. Following evaluation by a multidisciplinary team, the patient was diagnosed with type 2 DFUs (TEXAS 4D). Traditional treatments were deemed unsuitable, and the patient was treated with endovascular surgery in the affected area, in addition to supportive medical treatment, local debridement, and sequential repair using split-thickness skin and tissue-engineered skin grafts combined with negative pressure treatment. After four months, the wound had completely healed, and the patient was able to walk with a walking aid.

CONCLUSION

This study demonstrates a new treatment method for DFUs was successful, using angioplasty, skin grafts, and negative pressure.

Key Words: Diabetic foot; Dialysis; Plantar and heel ulcers; Percutaneous transluminal

angioplasty; Tissue-engineered skin; Wound repair; Case report

Core Tip: Diabetic foot ulcers can be a serious and common complication of diabetes. In severe cases, they can lead to lower extremity damage and amputation. Traditional treatments such as flap transposition and transfemoral amputation are not always applicable in all cases. This report describes the successful treatment of ischemic diabetic plantar and heel ulcers in a patient undergoing hemodialysis using sequential treatment involving percutaneous transluminal angioplasty, tissue-engineered skin grafts, and negative pressure wound therapy. This treatment method may be a viable alternative for patients who are unsuitable for traditional treatments and could help prevent the need for amputation.

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INTRODUCTION

Diabetic foot is one of the most serious and painful chronic complications in diabetic patients, especially in elderly patients, with an annual incidence of 8.1% in China[1]. Although the rate of major amputation caused by diabetic foot has been reduced to 2.14% nationwide, China still lags far behind the developed countries in Europe and America in this respect[2]. The increased complications of diabetic nephropathy and advanced renal replacement therapies have significantly enhanced the proportion of diabetic patients treated with dialysis for end-stage renal diseases, leading to an increasing number of hemodialysis patients with diabetic foot ulcers (DFUs). These patients cannot always be cured and usually have a poor prognosis, particularly when they have complications such as arterial occlusion of the lower limbs, which, to a certain extent, explains the high amputation and mortality rates of diabetic foot patients in China[3]. Therefore, it is essential to formulate affordable and effective treatment schemes in clinical practice to reduce the amputation and mortality rates among hemodialysis patients with diabetic foot.

The patient described in this report is the first to undergo open debridement, percutaneous transluminal angioplasty (PTA), split-thickness skin graft, tissue-engineered skin graft, and negative pressure wound therapy to treat ischemic diabetic plantar and heel ulcers, with no relapses during the 6-mo follow-up period.

CASE PRESENTATION

Chief complaints

The 62-year-old female was admitted to hospital in February 2021 due to left foot ulcer for one month, aggravated and painful for one week.

History of present illness

The patient had a left foot ulcer for one month, aggravated and painful for one week.

History of past illness

The patient had a history of chronic renal failure, uremia, and hemodialysis for 5 years. Four years ago, she underwent left forearm arteriovenous fistula formation. In July 2019, the patient underwent balloon angioplasty and stenting for lower extremity arterial sclerosis with ulceration in the left leg. In November 2019, she underwent balloon angioplasty and stenting for lower extremity arterial sclerosis with ulceration in the right leg.

Personal and family history

The patient denied any family history of diseases.

Physical examination

Physical examination at admission showed a body temperature of 38.3°C, pulse rate of 103 bpm, a respiratory rate of 21 breaths/min, and blood pressure of 162/83 mmHg. According to a specialized medical check-up, the left foot, with toenail hypertrophy, was dark in color, with the fourth toe absent, and fine hair had fallen out. An ulcer 4 cm × 2 cm in size was observed in the middle of the planta pedis, and the base was yellow and rotten, with the plantar fascia exposed. In addition, the peripheral skin showed wound undermining, which had spread to the heel ulcer. There was a large area of absent skin on the heel, exposing the calcaneus, and the base was yellow and rotten. A dark scab was found on part of

the wound, and around the area where the pus percolated, the skin was red and swollen, with a blurry boundary and symptoms of wound undermining. The vascular lacuna had spread towards the lower leg *via* the proximal end.

Laboratory examinations

Laboratory examinations were performed at admission. As shown by routine blood examination, the red blood cell and white blood cell counts were 3.12×10^{12}/L and 18.23×10^{9}/L, respectively, and the hemoglobin concentration was 83 g/L. The following blood biochemistry indices were obtained: K^+ mmol/L, serum albumin 24.0 g/L, serum creatinine 468.0 μmol/L, plasma brain natriuretic peptide > 35 000 pg/mL, erythrocyte sedimentation rate 65.0 mm/h, interleukin-6 89.5 pg/mL, C-reactive protein 83.7 mg/L, procalcitonin 6.6 ng/mL, and glycosylated hemoglobin 8.1.

Imaging examinations

Echocardiography showed an ejection fraction of 34%; the ankle-brachial index (ABI) was 0.6 on the left side and 0.7 on the right side. According to digital subtraction angiography, the patient suffered from severe stenosis of the left superficial femoral artery at the proximal and distal ends of the stent, extensive stenosis and occlusion of the left peroneal artery, and occlusion of the left posterior tibial artery.

Further diagnostic work-up

Based on clinical symptoms, physical signs, as well as laboratory and auxiliary examinations, the patient was diagnosed with: (1) Type 2 diabetic foot combined with peripheral vascular disease, peripheral neuropathy, and retinopathy; (2) Chronic renal failure treated with dialysis for uremia; (3) Hypertension (Grade 3) defined as a very high risk; (4) Coronary atherosclerotic heart disease with cardiac function Level III; (5) Anemia; (6) Hypoproteinemia; (7) Arteriosclerosis obliterans of the upper limbs with gangrene; and (8) Hyperkalemia. In addition, this patient had undergone PTA of both lower limbs and resection of toes on both feet.

FINAL DIAGNOSIS

The final diagnosis was type 2 DFU.

TREATMENT

On admission, the patient underwent debridement in addition to routine treatment (including control of blood glucose, blood pressure, and blood lipids, systemic antibiotic treatment, vascular dilation, pain relief, neurotrophic supplement, *etc*.).

PTA was performed in the first week. Restenosis of the superficial femoral arterial stent as well as the occlusion of peroneal and posterior tibial arteries were alleviated by endovascular drug-coated balloon dilatation to ensure that the blood could flow from the main artery to the affected foot. In the second week, the necrotic tissues on the patient's planta pedis and heel were removed by surgery, during which the area of debridement was expanded on the back of the lower leg to resect part of the tendo calcaneus. Negative pressure treatment was then initiated. In the fourth week, a split-thickness skin graft combined with negative pressure treatment was performed on the back of the lower leg, and the patient also underwent tissue-engineered skin graft and negative pressure treatment for the heel ulcer. During surgery, the tissue-engineered skin was soaked in sterile normal saline for 3-4 min, and then trimmed to fit the shape of the wound. The stent was sutured along the edge of the wound under tension-free conditions, with the collagen layer appressed to the wound. The silica gel layer was then covered by sterile Vaseline gauze, which was followed by negative pressure treatment and regular postoperative dressing changes. Following adequate vascularization in the collagen layer, the silica gel layer was removed using tweezers[4]. The wound bed was kept moist with the application of artificial dermis, and regular dressing changes were performed to evaluate the extent of epithelialization. The decision to perform a secondary graft using split-thickness skin or reapply artificial skin was made, particularly in cases involving exposed tendons or areas subjected to mechanical stress. Following split-thickness skin grafting, an optimal level of moisture was maintained, and the need for additional grafting, or even multiple grafting procedures, was determined based on the viability of the skin grafts. The tissue-engineered skin was then grafted repeatedly until the wound healed (Figure 1).

OUTCOME AND FOLLOW-UP

The patient was successfully cured of ischemic diabetic plantar heel ulcer.

DISCUSSION

It is reported that 39.3% of diabetic foot patients also have chronic renal diseases[5]. As the glomerular filtration rate reduces, there is a fold increase in nonhealing ulcers, major amputation, and mortality risk[6]. Massive proteinuria is not

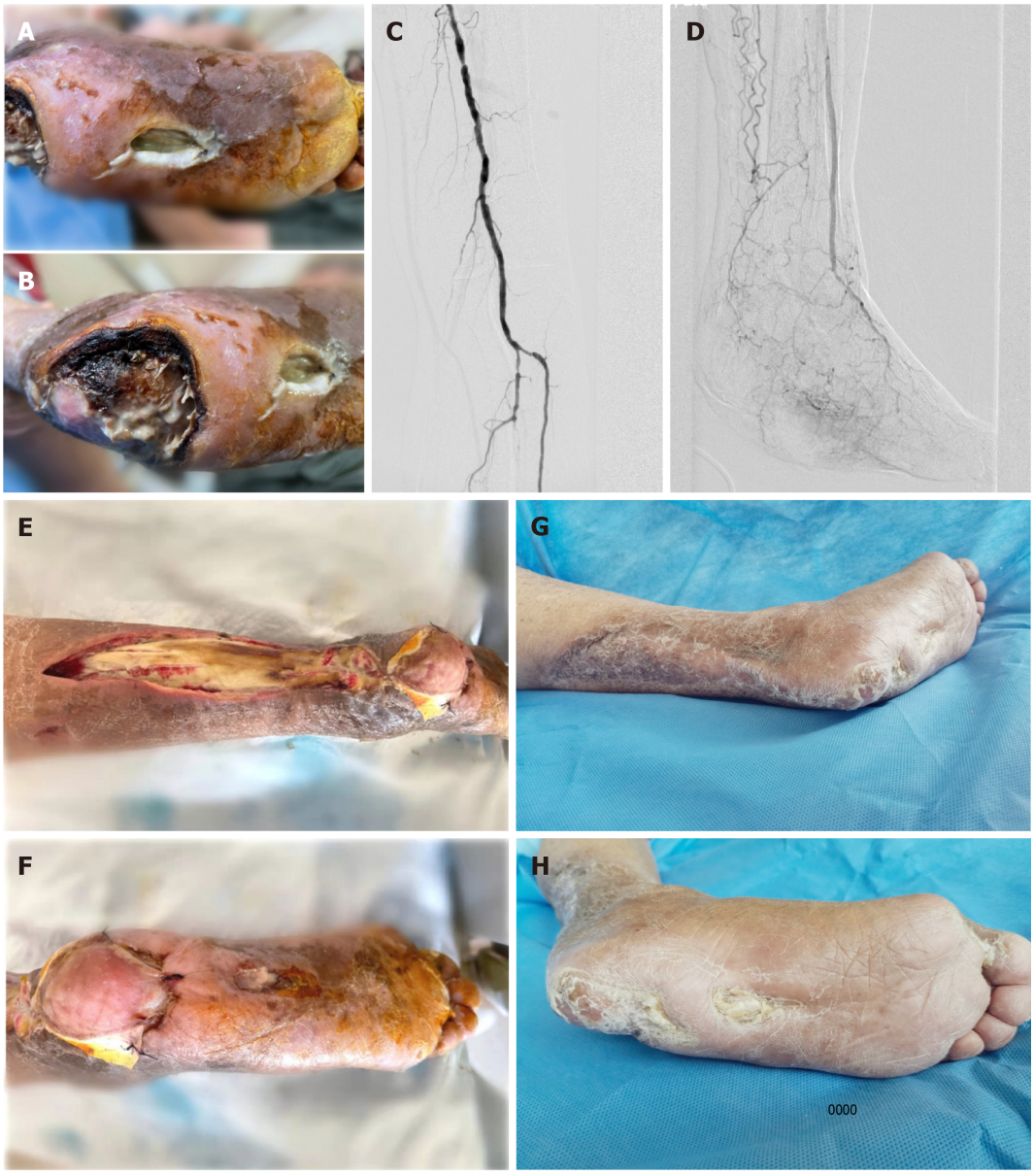

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Figure 1 Management of lower limb ulcer and arterial stenosis. A: Wound in the middle of the planta pedis, with plantar fascia exposed; B: Heel ulcer, which is connected to the wound in the middle of the planta pedis; C: Extensive arterial stenosis and occlusion in the left lower limb shown by digital subtraction angiography; D: Blood flow of the foot after percutaneous transluminal angioplasty; E: The ulcer spreading to the lower leg, and the wound reconstruction on the back of the lower leg; F: Application of tissue-engineered skin to the heel wound; G: Wound healing on the back of the lower leg; H: Wound healing on the planta pedis.

only a crucial risk factor causing nonhealing ulcers and amputation, but also an independent risk factor for cardiovascular events and death, as well as all-cause mortality[7]. Both hemodialysis and peritoneal dialysis can increase the risk of DFU by more than four times among patients with uremia. On average it takes diabetic patients 7 mo (2-40 mo) to progress from hemodialysis to amputation[8,9]. Since 2017, our department has received and cured 115 dialysis patients with DFUs, with the limb salvage rate reaching 83.1%.

This report describes a female patient with multiple complications and comorbidities, who had undergone hemodialysis treatment for 3 years. Although the blood supply in both lower limbs seemed sufficient according to the ABI which was measured to be 0.6 on the left side and 0.7 on the right side, the results of X-ray, color Doppler ultrasound and computed tomography angiography indicated that the patient had severe arterial calcification in her lower limbs. Therefore, the ABI was considered to be too "impractically high" to evaluate the degree of foot ischemia accurately. Under such circumstances, endovascular drug-coated balloon dilatation was performed to improve the blood supply to the distal end of the left lower limb.

Considering that the heel ulcer was located in the weight-bearing area, a sural neurovascular flap or free flap can be used to repair the wound to ensure that the healed skin is extremely hard-wearing. However, our patient who had a large area of ulcer in the flap donor site on the back of her lower leg, was intolerant to the anesthesia used during the free flap operation, and the therapeutic effect could not be guaranteed. Therefore, the tissue-engineered skin containing an artificial dermal matrix was grafted. After treatment, the heel ulcer healed with good abrasive resistance, and the patient

was able to walk with the help of a walking aid.

The artificial composite dermis prepared by Yannas *et al*[10] in 1982 using collagen matrix and a medical silicone rubber membrane was successfully used as a dermal regeneration template to repair a deep burn wound. In 2017, China developed the first double-layer tissue-engineered skin[4], which achieved good results in various departments, such as the Department of Burn, Department of Plastic Surgery, Department of Hand and Foot Surgery, *etc*. The tissue-engineered skin has now been widely applied to deep burns, traumatic skin defects, chronic skin ulcers, wound repair after tumor resection, and scar plastic surgery, with the therapeutic effect highly recognized by clinicians at home and abroad[11].

In domestic and foreign literature, the dermal substitute is also known as tissue-engineered skin, tissue-engineered skin matrix, artificial skin, and artificial dermis in accordance with different structures, materials, and preparation methods. However, in essence, it is used to induce the regeneration of dermis through a dermal stent template, thus substituting the defective dermal tissues and optimizing the appearance and function of the healed wound. The primary methods for wound repair involve skin grafting and flap procedures. For patients with lower limb chronic ischemia, both pedicle flaps and free flaps can result in significant trauma. Pure split-thickness skin grafts, especially in weight-bearing areas, have poor durability. Mid-thickness skin grafts pose challenges in terms of graft survival, particularly in this patient population. The use of artificial dermis alone is associated with high costs and increased patient burden. Therefore, a combination of split-thickness skin grafting and artificial dermis is employed for such patients.

In this report, the double-layer tissue-engineered skin was adopted. The upper layer was a semipermeable silicone rubber membrane, which acted like the epidermis to control the evaporation of water and inhibit the invasion of microorganisms; the lower layer, namely the spongy dermal stent layer constructed by collagen-chondroitin sulfate, has high biocompatibility and low immunogenicity, and acts as a cell proliferation stent to promote the intrusive growth of vascular endothelial cells and fibroblasts in the graft site, thus forming a composite constituted by the stent, new capillaries, and cells. After adequate vascularization for 2-3 wk, the autologous split-thickness skin can be grafted[12]. The dermal stent is then gradually degraded and substituted by new dermal tissues.

National and international research has shown that the tissue-engineered skin, which can promote and accelerate wound healing of chronic ulcers[13], has been successfully used to treat diabetic, vascular and pressure ulcers. When the wound caused by chronic ulcers is repaired with tissue-engineered skin, the debridement must be repeated to avoid infection, and the graft cannot be performed until the wound is clean and the basal blood supply is sufficient. It may take two or more weeks to realize adequate vascularization of tissue-engineered skin on the chronic ulcer wound, so the autologous skin should be grafted according to the vascularization status.

In the case of deep wounds, the tissue-engineered skin can be overlaid repeatedly to thicken the new dermis, which was the method used in this case, in which the tissue-engineered skin was repeatedly grafted to the heel, and the wound healed before skin grafting. There are many clinical reports on the treatment of DFUs using tissue-engineered skin[14,15], but the application to weight-bearing areas and dialysis patients with ischemic DFUs has not previously been reported (Table 1).

Additionally, Blood glucose levels play a critical role in diabetes management and can affect wound healing and susceptibility to infection. In diabetic patients with ischemic ulcers, maintaining optimal glycemic control is vital for successful wound healing. Similarly, creatinine levels reflect renal function and can provide insight into the patient's overall health status and the potential impact of hemodialysis on wound healing. In future studies, we recommend the inclusion of these parameters to provide a more comprehensive assessment of treatment outcomes. By examining the relationship between blood glucose levels, renal function, and wound healing in similar patient populations, researchers can gain further insights into the effectiveness of the sequential treatment approach described in our case report.

CONCLUSION

Diabetic nephropathy is a high-risk factor leading to DFU and amputation. Diabetic foot patients who have undergone amputation usually have a poor prognosis, with the median survival time being 3.12 years (minor amputation: 5.5 years; major amputation: 1.9 years) and the 5-year postoperative survival rate is approximately 40%. The independent risk factors for postoperative death include age and major amputation. Therefore, whether to perform amputation should be thoroughly discussed in clinical practice, especially in diabetic foot patients.

Ischemia is another tough issue for dialysis patients. Although endovascular surgery is preferred to bypass surgery during revascularization in these patients, they still face significant challenges. First, abnormal calcium-phosphorus metabolism and severe vascular calcification cause considerable difficulties during endovascular revascularization. Second, dialysis patients are less tolerant to anticoagulants and contrast agents, which will prolong the process of endovascular revascularization. Third, dialysis patients with diabetes, in poor physical condition, are usually complicated by hypoproteinemia and renal anemia.

The tissue-engineered skin, containing natural extracellular matrices, protogenous growth factors and living cells, can transfer growth and cell factors to the wound to accelerate the healing process. This will promote dermal regeneration and inhibit scar hyperplasia, thus restoring wound elasticity and flexibility and improving the appearance and function of the skin. Furthermore, traditional flap transposition can be replaced by this skin graft technique as the exposed bones and tendons can be directly covered using the tissue-engineered skin during wound repair.

Research indicates that tissue-engineered skin substitutes can promote the healing of refractory foot ulcers with high safety. According to a network meta-analysis, these substitutes have a low failure rate, but there are few relevant studies and the overall sample size is small. Therefore, more studies are needed to verify the safety, effectiveness, and failure rate

Table 1 Literature review of similar case reports on the treatment of diabetic foot ulcers

No.	TEXA grade	Complication	Diseased region	Application method	Outcome	Healing time
1	2B	Peripheral neuropathy	Heel	Sural neurovascular flap transposition under epidural anesthesia	Partly healed	4 wk
2	2B	Peripheral neuropathy; hypertension	Heel	Sural neurovascular flap transposition under epidural anesthesia	Healed	6 wk
3	2A	Peripheral neuropathy; coronary heart disease	Non-weight-bearing area	Tissue-engineered skin	Healed	2 mo
3	2A	Hypertension	Non-weight-bearing area	Tissue-engineered skin	Healed	2 mo
4	2A	Peripheral neuropathy	Non-weight-bearing area	Tissue-engineered skin	Healed	3 mo
5	4D	Peripheral neuropathy; peripheral vascular disease; retinopathy; dialysis for uremia; hypertension; coronary heart disease; anemia; hypoproteinemia; arteriosclerosis obliterans of upper limbs with gangrene	Planta pedis, heel, and back of the lower leg	PTA, negative pressure treatment, autologous split-thickness skin graft, and tissue-engineered skin	Healed	4 mo

PTA: Percutaneous transluminal angioplasty; TEXA: Toe-Flow-Deep Extent-Infection-Neuropathy Assessment Scheme grade.

of these substitutes in the treatment of DFUs. Based on the existing evidence, the tissue-engineered skin graft can be used as an auxiliary therapy for treating refractory DFUs.

At present, there are few domestic and foreign clinical reports on the repair of nonhealing diabetic foot wounds, especially in hemodialysis patients or in weight-bearing areas such as the planta pedis and heel, and the combination of tissue-engineered skin graft with negative pressure treatment and autologous split-thickness skin graft is not mentioned in the available literature. Therefore, it is necessary to conduct further clinical research based on this case report to explore the proper use and amount of tissue-engineered skin in weight-bearing areas of dialysis patients with ischemic diabetic foot.

FOOTNOTES

Author contributions: Wang JJ contributed to the guarantor of integrity of the entire study; Wang JJ, Chen XG, and Huang XM contributed to clinical study and experimental study; Wang PY and Yu YY contributed to data analysis; Wang JJ and Yu YY contributed to manuscript writing and editing; all authors have read and approved the final manuscript.

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