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Metabolism and Target Organ Damage

Editorial

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Diabetes mellitus and heart disease

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ASSOCIATION OF DIABETES AND CARDIOVASCULAR DISEASE

Elevated quantities of blood glucose can lead to damage to blood vessels, resulting in complications associated with diabetes mellitus (DM). This damage ultimately leads to the development of cardiovascular issues. The microvascular and macrovascular complications linked to DM, including heart failure, coronary artery disease, peripheral vascular disease, and sudden cardiac death, are all factors contributing to disability and premature death caused by uncontrolled high blood sugar. Metabolic defects in the endothelium, liver, or β cells can be triggered by high caloric intake, smoking, and glucose toxicity. These defects affect cell-signaling pathways such as protein kinase B (PKB/Akt), AMP-activated protein kinase, and endothelial nitric oxide synthase, as well as oxidized lipids. Together, these factors potentiate the development of cardiovascular disease (CVD) in type 2 DM. Additionally, defects in epigenetic and post-translational modifications of vascular architecture, along with the release of proinflammatory cytokines, such as IL-6, IL-12, and IL-10, can trigger thrombosis. Dyslipidemia can also facilitate atherogenesis, while hypertension can be triggered by inflammatory signals. Collectively, these factors increase the risk of cardiovascular events and morbidity in individuals with DM. While the role of lipids as a major risk factor for CVD is well understood, the critical role of DM in CVD is less clear and only partially understood.

The significant impact of DM as a cardiovascular risk factor is concerning, attributed to the rise in urbanization, unhealthy lifestyles, and obesity in both developed and developing countries. CVDs play a significant role in the morbidity and mortality of individuals with type 2 DM, occurring approximately 15 years earlier than in those without the condition[1]. This highlights the increasing need to address and control DM in order to prevent complications and mortality associated with CVD. Recent literature studies have reported that cardiovascular events affect approximately 32.2% of patients with type 2 DM. Additionally, the reported death rate for type 2 DM patients without a prior history of heart disease is 15.5%, while the mortality rate is 42% for diabetic patients with a history of heart disease. Furthermore, the prevalence of DM and heart failure is 19% and 10%, respectively, in individuals over 65 years of age[2].

Multiple pathophysiological mechanisms underlie the relationship between DM and CVD. These include the direct effect of high blood glucose on endothelial function, which leads to the progression of atherosclerosis. Additionally, insulin resistance and hyperinsulinemia activate multiple inflammatory signaling pathways that promote atherosclerosis. Dyslipidemia also contributes to mitochondrial dysfunction[3]. This editorial provides valuable insights into the mechanisms responsible for cardiovascular injury and the development of microvascular and macrovascular cardiac complications associated with DM. It aims to summarize and explore the hypothesis and pathophysiological mechanisms that explain the increased prevalence of CVD in individuals with DM.

RISK FACTORS OF CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES

The onset of low-grade inflammation in smokers with type 2 DM creates a potential connection between smoking and cardiovascular events in individuals with DM. Smoking, through oxidative stress, diminishes nitric oxide production, resulting in endothelial dysfunction and reduced flow-mediated dilation in arteries, ultimately causing vascular injury. This, in turn, elevates the risk of CVD in smokers with type 2 DM[4].

Another important risk factor that amplifies the risk of CVD in DM is hypertension, which is characterized by vascular dysfunction and injury. Endothelial dysfunction, vascular inflammation, atherosclerosis, arterial remodeling, and dyslipidemia are key factors linking cardiovascular complications in DM with hypertension. The proinflammatory changes, adipocyte hypertrophy, and metabolic consequences of obesity and insulin resistance increase the risk of CVD in individuals with type 2 DM. It is interesting to note that the disruption of the intricate balance between vasoconstriction and vasodilation in hypertension impairs endothelium-dependent vasodilation, exacerbating insulin resistance and increasing the risk of CVD. Additionally, the imbalance between arterial wall scaffolding proteins and collagen content leads to vascular aging. Vascular stiffening results in increased arterial pulse pressure, which stimulates endothelial dysfunction and increases the risk of CVD in hypertensive diabetic individuals. Furthermore, hyperglycemia activates vasoinjurious pathways such as the polyol pathways, increasing oxidative stress, stimulating proinflammatory transcription factors, and activating immune responses. These pathways, induced by hypertension, subsequently increase the risk of major adverse cardiovascular adverse events (MACE) and glucose intolerance[5].

HIGH BLOOD GLUCOSE AND CHANGES IN INSULIN SENSITIVITY

Recent studies have shown that patients with type 2 DM often have epigenetic defects in their vascular architecture. For example, a mutation or dysfunction in leptin can lead to overfeeding, contributing to obesity, which in turn causes CVD[6]. Insulin resistance, along with free fatty acids and circulating proinflammatory cytokines, can result in the apoptosis of β-cells. This leads to consistently high postprandial glucose levels, causing glucose-related tissue toxicity, endothelial dysfunction, DNA methylation, and histone hyperacetylation. These factors affect both the microvessels and macrovessels,

resulting in harmful cardiovascular consequences[7]. Furthermore, having elevated serum levels of the soluble receptor for advanced glycation end products (RAGE), greater than 838.19 pg/mL, doubles the risk of cardiovascular complications, especially in diabetic patients with pre-existing CVD[8].

Insulin-stimulated glucose uptake into cardiomyocytes is reduced due to a decrease in liver GLUT4 expression and GLUT4 translocation from the cytoplasm to the cell membrane. An altered endogenous physiological mechanism in the heart, caused by impaired insulin sensitivity and downstream signaling via phosphatidylinositol 3-kinase (PI3K)α and AKT, is a significant characteristic of diabetic myocardium. Furthermore, defects in PI3K/AKT signaling worsen diabetic cardiomyopathy[9]. Most importantly, hyperglycemia that occurs in DM and insulin resistance has significant effects on numerous signaling pathways. When altered, it can trigger inflammation, oxidative stress, and dyslipidemia. These factors collectively impact vascular remodeling and contribute to diabetic CVD and atherosclerosis. Additionally, the resulting increase in myocardial fibrosis and cardiomyocyte death further influences heart physiology and function [Figure 1].

INFLAMMATION AND THROMBOSIS

When blood glucose is high, proinflammatory cytokines such as IL-6, IL-12, IL-10, and TNF-α are released. This synthesis of these mediators and their release is triggered by protein kinase c (PKC)-dependent NF-κB activation. Additionally, adipose tissue inflammation leads to the release of adipocytokines such as adiponectin, leptin, and adipsin. These inflammatory signals can transduce cellular signals in various tissues through toll-like receptor (TLR) signaling, ultimately activating NF-κB and leading to persistent chronic inflammation[10]. These circulating inflammatory signals activate thrombosis through platelet activation of classical and alternate pathways[11]. Platelet aggregation, especially in the coronaries and lower extremities, causes occlusion or subocclusion of these vessels, resulting in infarctions or necrosis of the heart and brain, subsequently increasing the risk of ischemic heart disease, myocardial infarction, and stroke. Other factors that can trigger thrombosis include plaque erosion, partial or total rupture, infiltration of immune cells that activate the release of chemoattractant chemokines, and components that worsen thrombosis. Additionally, plaque instability and necrosis further contribute to vascular lesions[12].

OXIDATIVE STRESS

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and their ability to be destroyed. In the case of DM, excessive ROS generation, increased mitochondrial respiration, and impaired antioxidant mechanisms cause direct oxidative damage to the heart or trigger inflammasome activation including the NLRP3/NALP3 inflammasome that detects stress signals, such as extracellular ATP released by damaged cells. Other signaling pathways activated by ROS include PKC, apoptosis signaling-regulating kinase 1 (ASK1), Jun- N terminal kinase (JNK), and compounds of the JAK-STAT signaling pathway, all of which can be implicated in DM-associated cardiac complications[13-15].

IMPAIRED MITOCHONDRIAL FUNCTION

As previously discussed, in type 2 DM, mitochondrial dynamics are impaired and ROS generation exceeds degradation capacity[16]. The characteristic features include a reduction in mitochondrial size, fragmentation, decreased expression of mitochondrial proteins, imbalance in fusion/fission control, increased cardiac oxidative stress, and altered myocardial substrate utilization. Increased blood glucose levels and cardiac lipid load cause excess ROS production. Furthermore, hyperglycemia increases the glycosylation of several proteins critical to mitochondrial respiration, oxidative phosphorylation, and electron carrier function. This leads to cardiac dysfunction and impairment of overall cardiac function[17].

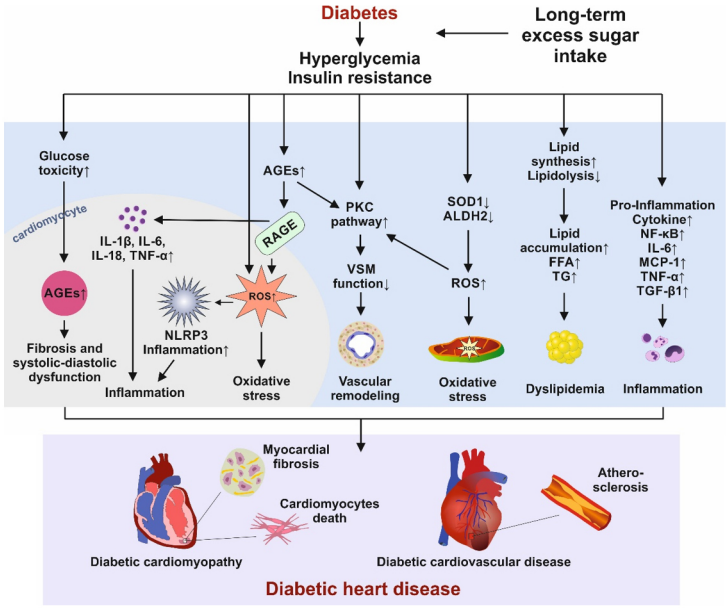

Figure 1. Pathogenesis of diabetic heart disease. Chronic hyperglycemia, diabetes, and insulin resistance are contributing factors that lead to complex processes, ultimately resulting in diabetic heart disease. These factors impact lipid homeostasis, increase the expression and secretion of proinflammatory cytokines, and trigger the formation of oxidative stress. The consequences of these processes include modified vascular remodeling, cardiomyocyte death, and myocardial fibrosis, ultimately leading to diabetic cardiomyopathy, cardiovascular disease, and atherosclerosis. AGEs: advanced glycation endproducts; ALDH2: aldehyde dehydrogenase 2; FFA: free fatty acid(s); NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; PKC: protein kinase C; RAGE: receptor for advanced glycation end products; ROS: reactive oxygen species; SOD1: superoxide dismutase 1; TG: triglyceride(s); VSM: vascular smooth muscle. This figure was redrawn in a modified form from[10].

ACTIVATION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

In individuals suffering from DM, the renin-angiotensin-aldosterone system (RAAS) becomes activated, which is a critical regulator of blood pressure. This activation contributes to cardiac overload and DM-induced remodeling[18]. The stimulation of RAAS causes widespread vascular damage and endothelial dysfunction, ultimately leading to the development of diabetic cardiomyopathy and other cardiac complications.

ENDOTHELIAL AND VASCULAR DYSFUNCTION

The vasculature is made up of endothelial cells, smooth muscle cells, pericytes, and fibroblasts. An imbalance in homeostasis resulting from abnormal glucose and lipid metabolism causes changes in vascular structure and function, such as macro or microangiopathy, increased endothelial shear stress and arterial stiffness[19]. Chronic hyperglycemia can lead to the buildup of advanced glycation products, resulting in atherosclerosis[20]. Interestingly, in individuals with DM, the cross-sectional area of the media intima of small vessels is increased. This suggests that chronic sugar overload results in hypertrophic remodeling due to increased wall stress and decreased myogenic response of the small arteries[21].

DYSLIPIDEMIA

Dyslipidemia associated with obesity in type 2 DM significantly contributes to the development of atherosclerosis[22]. The progression of atherosclerosis is worsened by chronic high levels of atherogenic low-density lipoprotein (LDL), lipoprotein C, and apolipoprotein B. High levels of oxidized LDL are also linked to coronary artery disease[23,24]. Chronic hyperglycemia, in conjunction with dyslipidemia, damages the endothelium and promotes plaque progression.

The hyperacetylation of histones H3K9/K14 in the endothelium leads to increased expression of metalloproteinases that regulate genes and glucose metabolism. Interleukins, along with metalloproteinases, play a role in vascular remodeling, causing plaque instability and progression, ultimately resulting in heart failure, sudden cardiac death, and coronary artery disease[25].

CLINICAL STUDIES

Despite advances in the prevention and/or treatment of CVD in diabetic individuals, the effects of type 2 DM on CVD remain high and are increasing at an alarming rate. This section discusses some noteworthy clinical studies. Metformin is considered a first-line drug for the treatment of type 2 DM, showing a significant decrease in macrovascular events and DM-related mortality. Several observational studies have shown that metformin alone or in combination with other orally administered agents decreases cardiovascular events and mortality[26,27].

There are already several important and encouraging randomized controlled multicenter trials available with different drugs, involving large patient groups. In these phase III studies, several drugs are being tested. These drugs either selectively stimulate the nuclear receptor peroxisome proliferation-activated receptor-γ (PPAR-γ) and, to a lesser extent, PPAR-α (such as pioglitazone), belong to the glucagon-like peptide 1 (GLP-1) receptor agonists (like liraglutide or semaglutide), or are sodium-glucose co-transporter 2 (SGLT2) inhibitors [Figure 2].

The cardiovascular effects of pioglitazone are promising and were examined in the Insulin Resistance Intervention after Stroke (IRIS) trial. It was demonstrated that the risk of myocardial infarction was reduced in diabetic patients receiving pioglitazone. Interestingly, several meta-analyses of retrospective studies have shown that dipeptidyl peptidase-4 (DPP-4) inhibitors are associated with reduced cardiovascular events[28,29].

The LEADER trial revealed that liraglutide significantly decreased major cardiovascular events by 13% and cardiovascular death by 22%[30,31]. Similarly, the SUSTAIN-6 trial found that semaglutide in type 2 DM reduced the primary composite endpoint of cardiovascular death[32-34]. Recent evidence suggests that SGLT2 inhibitors provide cardiovascular protection in patients with type 2 DM. The EMPA-REG OUTCOME trial demonstrated that after a median observation period of 3.1 years, empagliflozin significantly reduced the primary composite outcome of cardiovascular death and non-fatal myocardial infarction[35-36]. The cardiorenal benefits reported in SGLT2 trials have shed light on the characterization of their mechanism of action. The main feature of these drugs is to directly inhibit SGLT2, which is predominantly present in the small intestine, resulting in the delay of glucose uptake and a reduced concentration in postprandial glycemia. They also inhibit SGLT2, which is found in the initial part of the proximal tubules. Interestingly, the lowering in glucose reabsorption in the kidneys causes a variety of direct and indirect changes in hemodynamics. This includes less sodium and water reabsorption, a decrease in plasma volume, and the generation of a diuretic effect. As a result, there is a reduction in systolic and diastolic blood pressure, as well as a decrease in preload and afterload without compromising heart rate. These combined effects help to explain the therapeutic benefits of SGLT2 in reducing heart failure and cardiovascular events in individuals with DM[37].

Additionally, a broader cardiometabolic activity is reported for SGLT2 inhibitors[38,39]. Constant glycosuria leads to weight loss and promotes free fatty acid oxidation, increasing β-hydroxybutyrate consumption by the heart. This, in turn, improves cardiac function by optimizing mitochondrial function in the heart. Furthermore, the benefits of SGLT2 inhibitors include slowing chronic kidney disease progression and improving renal performance. The nephroprotective effects are attributed to a decrease in preload due to

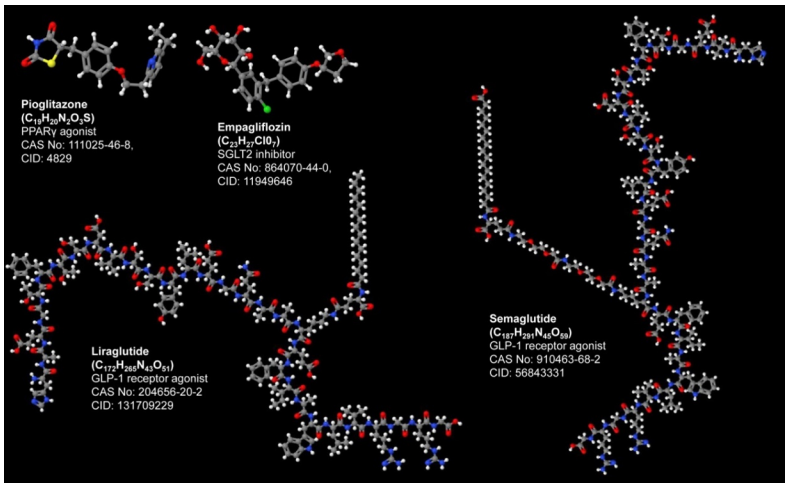

Figure 2. Examples of effective drugs in type 2 diabetes. Pioglitazone is a 1,3-thiazolidine-2,4-dione that carries a benzyl group at position 5, further substituted by a 2-(5-ethylpyridin-2-yl)ethoxy group at position 4 of the phenyl ring. It exerts its pharmacological effects by acting as a PPARγ agonist that promotes insulin sensitivity. Empagliflozin inhibits the SGLT2 transporter, primarily responsible for the reabsorption of glucose in the kidney. Liraglutide is similar to human GLP-1. The lysine at position 29 is replaced by an arginine and the remaining lysine carries a hexadecanoyl group attached to it via a glutamic acid spacer. Similarly, semaglutide is a GLP-1 analog containing amino acids 7-37 of GLP-1 with amino acids 8 and 34 replaced by α-aminobutyric acid. Moreover, the lysine at position 26 is acylated with stearic diacid. These structures were generated using Jmol (version 14.2._2015.07.09), and chemical depiction information sourced from the PubChem Compound Database that is available at: https://www.ncbi.nlm.nih.gov/pccompound/ (last accessed 28.3.2024).

the diuretic effect, which prevents an increase in intraglomerular pressure. The increase in sodium in the glomerular fluid also encourages tubuloglomerular feedback, resulting in vasodilation of the efferent glomerular arteriole, resulting in reduced intraglomerular pressure.

It is worth mentioning a few other clinical trials on patients with type 2 DM and cardiovascular events. The outcomes of the HARMONY trial aimed to determine the effects of albiglutide on patients with type 2 DM and coronary heart disease. It reported that albiglutide was superior to placebo with respect to MACE[40]. Another interesting trial, known as the EXSCEL trial, tested exenatide once weekly in 14,752 patients with type 2 DM, with or without previous cardiovascular events. It reported that the incidence of MACE did not differ significantly in patients who received exenatide compared to those who received a placebo[41].

Recently, the PIONEER6 trial tested oral semaglutide in 3,183 patients with type 2 DM[42]. Oral semaglutide failed to induce a significant reduction in MACE. Another notable trial, known as the ELIXA trial, tested lixisenatide, a GLP-1 receptor agonist, in type 2 DM patients who had recently experienced a coronary event. It was reported that lixisenatide did not significantly alter the rate of major cardiovascular events[43]. Of particular interest, the REWIND trial evaluated the effects of dulaglutide on cardiovascular outcomes in 9,901 patients suffering from type 2 DM and reported a 22% relative reduction in MACE after a median follow-up of 5.4 years[44].

The DECLARE-TIMI 58 trial investigated the therapeutic effects of dapagliflozin on cardiovascular events in patients with type 2 DM. After a median follow-up of 4.2 years, it was found that dapagliflozin did not lead to a significant reduction in MACE[45]. Similarly, in 2020, the VERTIS CV trial examined the effects of ertugliflozin on cardiovascular events in patients with type 2 DM and concluded that after a median follow-up of 3.5 years, there was no decrease in MACE[46].

A holistic therapeutic approach is necessary for the management of type 2 DM, given the rise of cardiovascular events and other complications associated with the disease. One trial showed improved glycemic control and a decreased risk of cardiovascular events after a 5-year follow-up with a combination therapy of metformin and a DPP-4 inhibitor. Similarly, a few studies demonstrated increased glycemic control, weight loss, and optimal blood pressure management in individuals treated with metformin and canagliflozin as an SGLT2 inhibitor combination therapy. It is worth noting that the combination of exenatide and metformin is beneficial in preventing adverse cardiovascular events, reducing inflammation, and preventing weight gain. In addition to these, several comprehensive approaches have been reported and are currently under investigation, but are beyond the scope of our discussion[47]. Table 1 illustrates recent randomized controlled trials with glucose-lowering drugs showing improvements in cardiovascular events. Most importantly, recent evaluations have shown that these drugs not only impact CVD, but also reduce the risk of worsening nephropathy in patients suffering from type 2 DM[33,34].

CONCLUSION

DM, a multifactorial condition, significantly increases the risk for the development of myocardial infarction, ischemic heart disease, and sudden cardiac death. Understanding the complex mechanisms involved in the pathophysiology linking DM and CVDs will open new horizons for patients to prevent the potentially devastating complications of DM-associated CVD. Several drugs including pioglitazone, liraglutide, semaglutide, empagliflozin, canagliflozin, or drug combinations such as metformin/canagliflozin or metformin/exenatide hold promise for patients suffering from DM and associated CVDs. These drugs are currently under close investigation.

Table 1. Recent randomized controlled trials conducted with glucose-lowering drugs and their impact on cardiovascular events

TRIAL	ClinicalTrials.gov identifier	Phase	Enrollment (actual)	Intervention	Primary outcome	HR for primary outcome (95%CI)	Cardiovascular mortality (95%CI around HR)
IRIS	NCT00091949	3	3,876	Pioglitazone *vs.* placebo	Recurrent stroke or myocardial infarction	0.76	NN*
LEADER	NCT01179048	3	9,340	Liraglutide *vs.* placebo	The time it takes for a heart attack or stroke	0.73-1.05	0.78 (P = 0.001)
SUSTAIN-6	NCT01720446	3	3,297	Semaglutide *vs.* placebo	The time between the randomization phase and the onset of a major adverse cardiovascular event, defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke	0.74	0.58-0.95 (P < 0.001 for noninferiority; P = 0.02 for superiority)
EMPA-REG OUTCOME	NCT01131676	3	7,064	Empagliflozin *vs.* placebo	Time to the onset of any of the following components: cardiovascular death, non-fatal myocardial infarction, or stroke	0.57-0.82	0.62 (P < 0.001)

* In this study, the authors found no significant between-group difference in all-cause mortality. CI: Confidence interval; HR: Hazard ratio; IRIS: Insulin Resistance Intervention after Stroke; More details and references for the listed trials are given in the text.

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Made substantial contributions to the writing of this editorial: Chandrasekaran P, Weiskirchen R
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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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