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HOW DIABETES AND CARDIOVASCULAR DISEASE (CVD) ARE STRONGLY INTERCONNECTED?

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ABSTRACT

Diabetes and cardiovascular disease (CVD) are strongly interconnected. Over time, high blood sugar can damage blood vessels and the nerves that control the heart. People with diabetes are more likely to have other conditions that raise the risk for heart disease. Insulin resistance (IR) and cardiovascular disease (CVD) represent two universal public health hazards, especially in advanced countries. A causal-effect relationship has been established that links IR with CVD. Diabetes is a non-communicable disease that occurs when the body cannot produce enough insulin and/or cannot use insulin effectively, and is diagnosed by observing raised levels of glucose in the blood. Over time, high levels of glucose in the blood (known as hyperglycaemia) can lead to the development of disabling and life-threatening health complications. Individuals with type 2 diabetes (T2D) have a twofold increased risk for cardiovascular disease (CVD) (myocardial infarction, stroke, peripheral vascular disease), and CVD is the principal cause of death in T2D patients. Clinical trials consistently have demonstrated that lowering HbA1c in T2D patients has no or only a modest effect on reducing cardiovascular (CV) risk. Insulin exerts many effects on the human body, including the cardiac tissue.

KEYWORDS: Cardiovascular disease (CVD), Peripheral artery disease (PAD), Insulin Resistance Intervention After Stroke Trial (IRIS).

The prevalence of individuals with an elevated body weight has markedly increased since the 80s, to the point that a new diagnosis category has emerged, “severe obesity,” defined by a body mass index (BMI) of 40 kg/m2 and more. Indeed, whereas more than 40 % of the US population now reaches the criterion for the diagnosis of obesity, more than 9 % are considered as being characterized by severe obesity.[1]

A close link exists between DM and cardiovascular disease (CVD). CVD is the most prevalent cause of mortality and morbidity in diabetic populations.[2]

CVD death rates in the United States are 1.7 times higher among adults (> 18 years) with DM than those without diagnosed DM, largely due to an increased risk of stroke and myocardial infarction (MI).[3]

This increased risk of CVD mortality in diabetic patients is found in both men and women. The relative risk for CVD morbidity and mortality in adults with diabetes ranges from 1 to 3 in men and from 2 to 5 in women compared to those without DM.[4]

In addition, enhanced recognition and improved management of patients with T2DM increases longevity, further increasing the diabetes population.[5]

Different pathophysiological mechanisms underlie the relationship between diabetes and CVD. Abundant epidemiological data support the pathophysiological role of hyperglycaemia, as it exerts a direct effect on endothelial function and on the induction and progression of atherosclerosis, but other pathophysiologic factors such as hyperinsulinaemia, insulin resistance, and dyslipidaemia are involved.[6]

A substantial portion of the diabetes health burden can be attributed to diabetes related macrovascular and microvascular complications, such as coronary heart disease (CHD), stroke, peripheral artery disease (PAD), heart failure (HF), diabetic retinopathy (DR), renal disease, and cardiac autonomic neuropathy (CAN) . Cardiovascular disease (CVD) represents the main cause of morbidity and mortality in subjects with T2DM3, in whom it occurs approximately 15 years earlier than in people without diabetes.[7]

It is more common in women, who show a mortality rate from CVD higher than that of men when compared with their counterparts without diabetes.[8]

Individuals with type 2 diabetes (T2D) have a twofold increased risk for cardiovascular disease (CVD) (myocardial infarction, stroke, peripheral vascular disease), and CVD is the principal cause of death in T2D patients.[9]

The “dawn phenomenon” refers to periodic episodes of hyperglycemia occurring in the early morning hours. Originally described in the early 1980s by Schmidt et al.[10]

The dawn phenomenon differs from the Somogyi effect in that an episode of hypoglycemia does not precede it. Understanding and differentiating between these two clinical entities becomes critical in the optimal management of diabetes.[11]

Individuals with type 2 diabetes (T2D) have a twofold increased risk for cardiovascular disease (CVD) (myocardial infarction, stroke, peripheral vascular disease), and CVD is the principal cause of death in T2D patients.[12]

Clinical trials consistently have demonstrated that lowering HbA_{1c} in T2D patients has no or only a modest effect on reducing cardiovascular (CV) risk. In contrast, the correction of traditional CVD risk factors.[13,14]

The recently published LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) trials provide evidence that glucagon-like peptide 1 receptor agonists (GLP-1 RAs) (liraglutide and semaglutide) reduce CVD risk beyond their glucose-lowering effect and improvement in other CVD risk factors in T2D patients with established CVD.[15,16]

Together with EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), IRIS (Insulin Resistance Intervention After Stroke Trial).[17]

A recent study in subjects with normal glucose tolerance demonstrated that GLP-1 infusion augments blood flow in small vessels in skeletal muscle and heart.[18]

and increased blood flow in small coronary vessels after myocardial ischemia has been shown to predict increased survival and reduced infarct size after MI.[19]

Studies in animals have demonstrated that the postischemic beneficial effects of GLP-1 on the heart are preserved in animals lacking the GLP-1 receptor, suggesting a GLP-1 receptor–independent mechanism.[20]

Pancreas – Anatomy

The pancreas is a retroperitoneal organ located in the upper abdomen, spanning from the duodenum to the spleen. It is divided anatomically into the head, neck, body, and tail.[21]

The islets are composed of multiple cell types with distinct roles: alpha (α) cells secrete glucagon; beta (β) cells produce insulin; delta (δ) cells release somatostatin; PP cells produce pancreatic polypeptide; and epsilon (ε) cells secrete ghrelin Beta cells are located centrally in the islets and are the main regulators of glucose homeostasis via insulin production.[22]

Insulin Structure Insulin is a peptide hormone composed of two chains: the A chain (21 amino acids) and the B chain (30 amino acids), connected by disulfide bonds. It is initially synthesized as preproinsulin, which is converted into proinsulin in the endoplasmic reticulum, and finally cleaved into insulin and C-peptide in the Golgi apparatus. The mature insulin molecule is stored in secretory granules within pancreatic beta cells.[23,24]

The β-Cell

The β-cells are the principal component of the pancreatic islets in all species. They are polygonal cells, with an average diameter of 13–18 μm that possess ~10,000 secretory granules, each containing up to 8–9 fg insulin (1.6–1.8 amol insulin).[25]

Insulin is stored in crystalline form in the secretory vesicles as a Zn_2-$insulin_6$ complex, and accounts for 5–10% of the total protein content of the β-cell, more than any other protein. It is released by regulated exocytosis. Only a small fraction of the secretory granules (<1%/h) undergo exocytosis even at high glucose concentrations.[26]

Whereas the insulin granules in mouse β-cells typically have a "fried egg" appearance, the insulin core/crystal is more irregular in human β-cells. Human β-cells also contain lipofuscin bodies (wear-and-tear pigments) that can be used to estimate the age of the β-cell.[27]

Beta-cell Preservation: Myth or Fact?

Prolonged hyperglycemia leads to oxidative stress, endoplasmic reticulum (ER) stress, hypoxic stress, and cytokine induction leading to β-cell compensation, stress, and later failure and de-differentiation.

Beta-cell identity is fragile, but islet identity is stable: islet cells share chromatin structure and methylome. Other than hormone genes, they represent flexibility and plasticity states rather than stable subtypes.

FoxO1 plays an important role in the de-differentiation and re-differentiation of β cells. Reprogramming of other cell types to β cells is a possibility and can be a potential treatment option for diabetes in the future.

Glucagon-like peptide 1 (GLP-1), sodium-glucose Cotransporter-2 (SGLT2) inhibitors, thiazolidinediones, metformin, and intensive insulin therapy offer β-cell protection and preservation.

Diabetes and cardiovascular disease (CVD) are strongly interconnected

Here's how diabetes impacts CVD

Increased Risk

1. *Atherosclerosis*: Diabetes accelerates atherosclerosis (plaque buildup in arteries), increasing the risk of heart attacks and strokes.
2. *High blood pressure*: Diabetes often co-exists with high blood pressure, further increasing CVD risk.
3. *Dyslipidemia*: Diabetes can lead to abnormal lipid profiles, contributing to CVD.

Mechanisms

1. *Inflammation*: Diabetes promotes chronic inflammation, damaging blood vessels and increasing CVD risk.
2. *Oxidative stress*: High blood sugar levels lead to oxidative stress, further damaging blood vessels.
3. *Endothelial dysfunction*: Diabetes impairs endothelial function, reducing blood vessel flexibility and increasing CVD risk.

Cardiovascular Complications

1. *Coronary artery disease*: Diabetes increases the risk of heart attacks and coronary artery disease.
2. *Stroke*: Diabetes increases the risk of stroke, particularly ischemic stroke.
3. *Peripheral artery disease*: Diabetes can lead to peripheral artery disease, reducing blood flow to limbs.

Management Strategies

1. *Tight blood sugar control*: Maintaining good blood sugar control can help reduce CVD risk.
2. *Blood pressure management*: Controlling high blood pressure is crucial for reducing CVD risk.
3. *Lipid management*: Managing lipid profiles through diet, exercise, and medication can help reduce CVD risk.
4. *Lifestyle modifications*: Regular exercise, healthy diet, weight management, and stress reduction can benefit both diabetes and CVD.

By managing diabetes and CVD risk factors, individuals can reduce their risk of complications and improve overall health!

Discover Breakthroughs in Diabetic Cardiomyopathy

Insulin exerts many effects on the human body, including the cardiac tissue. The pathways implicated include the PKB/Akt signaling pathway, the Janus kinase, and the mitogen-activated protein kinase pathway, and lead to normal cardiac growth, vascular smooth muscle regulation, and cardiac contractility.[28]

The development of diabetic cardiomyopathy constitutes the leading cause of mortality in diabetic patients. Diabetic cardiomyopathy is a heart disease independent of hypertension or coronary atherosclerosis. There is a large body of evidence implicating insulin deficiency/resistance in the pathogenesis of these disorders. Other than diabetic cardiomyopathy, cardiovascular autonomic neuropathy is also a risk factor for patients with DM, as it leads to increased mortality and left ventricular diastolic and systolic dysfunction.[29]

As a matter of fact, research has proven that DM type 1 patients with diabetic autonomic neuropathy have a reduced left ventricular filling pattern, with a more intense LV working load and systolic function, while DM type 2 patients with diabetic autonomic neuropathy appeared to have an increased working LV workload, as well as diastolic dysfunction and an increased A/V index.[30]

Insulin resistance and cardiovascular disease

Insulin resistance (IR) and cardiovascular disease (CVD) represent two universal public health hazards, especially in advanced countries. A causal-effect relationship has been established that links IR with CVD.

Cardiovascular disease (CVD) was responsible for 17.9 million lives lost in 2019; by 2030, this number is expected to increase to >22.2 million, making CVD the leading cause of death globally.[31]

The vast majority of cardiovascular events are attributed to atherosclerosis, in which lipid plaques form in the vessel walls.[32]

CVD has been extensively associated with chronic low-grade inflammation and involvement of both innate and adaptive immunity, with macrophages being the primary protagonists of this process.[33]

Thus, it becomes clear that the pathogenesis of CVD has an immunoinflammatory background. During the initial phase of atherosclerosis, endothelial injury triggers the production of proinflammatory cytokines like MCP-1, ILs, TNF-α, and adhesion molecules, thus laying the foundation for increased production of CRP.[34]

As mentioned earlier, these same events occur in the setting of IR. Impaired insulin cellular signaling in IR alters glucose metabolism and endothelial dysfunction and may contribute to the acceleration of atherosclerosis.[35]

Moreover, numerous studies link IR with other health conditions, including obesity, non-alcoholic fatty liver disease (NAFLD), hypertension, polycystic ovary syndrome (PCOS), and heart failure (HF).[36]

IR and HF form a vicious cycle; IR is an independent risk factor for HF development, while HF may exacerbate whole-body IR.[37]

Semaglutide reduces risk of cardiovascular events in patients with type 2 diabetes, finds study

Semaglutide, used as an anti-diabetic and anti-obesity medication, can cut the risks of heart attacks, strokes, and cardiovascular disease by 14%, the international study, of which India was a part, found. Diabetes management shouldn't be focused narrowly on blood sugar levels, but must concurrently work at protecting cardiac and renal health too, states a recent study that found daily oral semaglutide (an anti-diabetic medication used for the treatment of type 2 diabetes and an anti-obesity medication used for long-term weight management) could cut the risk of heart attacks, strokes and cardiovascular death by 14%.[38]

How diabetes increases heart disease risk

Patient with diabetes can experience damaged arteries, which become easy targets for hardening, called atherosclerosis, that can cause high blood pressure. If not treated on time, it can lead to trouble, including blood vessel damage, a heart attack, and kidney failure. Diabetes is considered as a catalyst for Coronary Heart Disease (CHD), the leading cause of death globally. As younger Indians are now being detected with Type 2 diabetes mellitus (T2DM), their risk of developing cardiovascular disease is almost two to four-fold higher than those without diabetes.[39]

People with diabetes are nearly twice as likely to develop heart disease, and managing risk factors such as high blood pressure, high cholesterol, obesity, and smoking is crucial to protecting your heart. You can lower your risk by controlling your blood glucose, eating a healthy diet, engaging in regular exercise, and taking prescribed medications.

Can you predict your risk of diabetes and a heart attack?

Triglyceride and glucose are important indices independently, but if divided the triglyceride by glucose, produce a very good indicator of insulin resistance. The Triglyceride-Glucose Index (TyG) has now been tested across 22 countries over 13 years,' says Dr V Mohan. A large study across 22 countries has shown that a relatively new index, called the Triglyceride-Glucose Index (TyG), is a good predictor of insulin resistance and can help in identifying people who are at a **higher risk of developing type-2 diabetes**, heart disease, **heart attack,** and stroke. The cohort study of over 1.4 lakh people, followed up over a period of 13 years, shows that those with a high TyG at a starting point were much more likely to suffer from these ailments later on, with the effect being more pronounced in people from low and middle-income countries.[40]

Prevention and Management of Diabetes

This study highlights the crucial role of food choices in both the prevention and management of diabetes, as dietary habits exert a direct influence on blood glucose regulation and long-term health outcomes. A balanced intake of whole grains, legumes, fruits, and vegetables consistently demonstrates protective effects, whereas processed foods and refined sugars are strongly associated with glycemic variability and complications. Culturally sensitive dietary guidance enhances patient adherence, particularly when traditional diets are integrated with modern nutritional science, offering a promising path for sustainable lifestyle modification. Personalized nutrition plans further optimize glycemic control and reduce risks, while awareness campaigns and structured education remain indispensable for empowering patients. At the community level, targeted programs can bridge knowledge gaps among vulnerable groups, reinforcing the message that food plays a central role in disease control. In clinical practice, there is a pressing need to move beyond pharmacotherapy and prioritize dietary interventions as evidence continues to support food as a first-line therapy. Multidisciplinary care involving physicians, dietitians, and allied health professionals has been shown to strengthen outcomes, and continued research into regional food patterns will add depth to existing guidelines.

Ultimately, healthier food choices empower individuals to take control of their condition, underscoring that a food-centered approach serves as both a preventive and therapeutic cornerstone in diabetes care.

CONCLUSION

Diabetes significantly increases your risk of heart disease because high blood sugar damages blood vessels and nerves, which can lead to conditions like coronary disease, heart failure, and stroke. People with diabetes are nearly twice as likely to develop heart disease, and managing risk factors such as high blood pressure, high cholesterol, obesity, and smoking is crucial to protecting your heart. One can lower their risk by controlling their blood glucose, eating a healthy diet, engaging in regular exercise, and taking prescribed medications.

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