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ISSN: 2329-6925
Journal of Vascular Medicine & Surgery

Review Article

Effects of Type 2 Diabetes Mellitus on Cardiovascular and Cerebrovascular Events and Management Strategies

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ABSTRACT

To revolve around glucose metabolism and CVD, this article summarized the impact of prediabetes and T2DM on CVD disease, the strategy of antidiabetic drug, and the management of stress hyperglycemia, provides a reference for early and comprehensive intervention of hyperglycemia. Under the combined effect of genetic and environmental factors, long-term hyperglycemia leads to metabolic dysregulation, inducing complications of large vessels, micro-vessels, and nerves, impairing vessels, kidneys, eyes, feet, and peripheral nerves, and consequently severely reducing the life quality of patients. Particularly, cardiovascular and Cerebrovascular Events (CVD) attack rapidly and devastatingly.

Keywords: Type 2 diabetes; Stroke; Antidiabetic drug; Stress hyperglycemia

Abbreviations: T2DM: Type 2 diabetes; T1DM: Type 1 Diabetes; CVD: Cerebrovascular Events; ADA: American Diabetes Association; FBG: Fasting Blood Glucose; OGTT: Oral Glucose Tolerance Test; MACE: Major Adverse Cardiovascular Events; ASCVD: Atherosclerotic Cardiovascular Disease; SGLT2i: Sodium-Glucose Cotransporter 2 inhibitor; GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist; DPP-4i: Dipeptidyl Peptidase-4-inhibitor; SHR: Stress Hyperglycemia Ratio

INTRODUCTION

Type 2 Diabetes (T2DM) mellitus is a prevalent worldwide lifelong multi-factorial and multi-system disease characterized by chronic hyperglycemia, with an increasing incidence year by year. Differed from Type 1 Diabetes (T1DM), which is caused by absolutely lacking of insulin, T2DM is mediated by insufficient insulin secretion and insulin resistance. In order to prevent potential CVD risk, early assessment and management of hyperglycemia are very important. In addition, due to stress and inflammatory response, some patients without confirmed history of hyperglycemia will experience transient elevation of blood glucose after CVD onset, described as stress hyperglycemia. Therefore, glucose regulation is involved in the whole process of CVD, and needs to be managed systematically. This paper will focus on the effects of diabetes and stress hyperglycemia on cardiovascular and cerebrovascular diseases and management strategies.

LITERATURE REVIEW

Effect of prediabetes on CVD

Prediabetes is screening window period: Prediabetes is a bidirectional transitional stage in which abnormal glucose metabolism occurs but has not yet progressed to diabetes, including impaired glucose tolerance and impaired fasting glucose. About 5-10% of prediabetes would develop diabetes mellitus, and 20-50% of patients could return to normal glucose metabolism after diet, exercise, or drug interventions. Notably, prediabetes also stays at a dangerous state, with endothelial cell damage due to hyperglycemia and inflammation, promoting the development of CVD. On this premise, prediabetes is the most important window period for early screening and intervention for those with high risk to reverse the abnormal glucose metabolism [1].

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Received: 24-Aug-2024, Manuscript No. JVMS-24-26787; **Editor assigned:** 26-Aug-2024, PreQC No. JVMS-24-26787 (PQ); **Reviewed:** 02-Sep-2024, QC No. JVMS-24-26787; **Revised:** 03-Feb-2026, Manuscript No. JVMS-24-26787 (R); **Published:** 10-Feb-2026, DOI: 10.350310/2329-6925.26.14.601

Citation: Chen S, Chen S, Mi D (2026) Effects of Type 2 Diabetes Mellitus on Cardiovascular and Cerebrovascular Events and Management Strategies. J Vasc Surg. 14:601.

Prediabetes promote CVD: Current mainstream criteria for prediabetes diagnosis are set by the American Diabetes Association (ADA). It can be diagnosed as prediabetes if met any of the following criteria: A1C 5.7-6.4%, Fasting Blood Glucose (FBG) 5.6-6.9 mmol/L, or 2 h glucose (2 h PG) value during a 75 g Oral Glucose Tolerance Test (OGTT) 7.8-11.0 mmol/L.

Compared with normoglycemic individuals, prediabetes increasing the risk of CVD regardless of previous CVD. A meta-analysis of 129 studies elucidated that after a median follow-up of 9.8 years, prediabetes was associated with an increased risk of all-cause mortality, composite cardiovascular disease, and coronary heart disease both in the general population and patients with atherosclerotic cardiovascular disease. Simultaneously, impaired glucose tolerance was associated with a higher risk of adverse outcomes than impaired fasting glucose. Another study found that prediabetes defined by A1C was significantly associated with a higher risk of CVD in patients with coronary artery disease. Thus, prediabetes defined by different criteria may have a different impact on CVD events [2-5].

Prediabetes need early intervention: Lifestyle change is the primary intervention for reversing prediabetes, including diet control and appropriate exercise. The DPP trial found that the 3-year incidence of diabetes was significantly lower in the lifestyle intervention group (4.8/100) compared to the control group (10.8/100). This effect persisted in most patients after cessation of the lifestyle intervention, which may be mediated through weight loss, improving overall metabolic status. Currently it has been proved that there is a potential benefit of newly oral hypoglycemic agents, and so it may bring new protective function against CVD in prediabetes.

The role of T2DM in promoting CVD events

T2DM promote atherosclerosis: According to ADA, it can be diagnosed as T2DM if met any of the following criteria: A1C ≥ 6.5%, FBG ≥ 7.0mmol/L, 2 h PG value during OGTT ≥ 11.1mmol/L or random plasma glucose ≥ 11.1 mmol/L with classic symptoms of hyperglycemia or hyperglycemic crisis [6-9].

In diabetic patients, the risk of atherosclerosis increases and the progress accelerates, probably provoked by the imbalance between damaging factors and endogenous protective factors. Damaging factors mainly include oxidative stress and inflammatory response, inducing plaque adhesion and accumulation. Endogenous protective factors can neutralize the toxic effects of hyperglycemia and protect the endothelium, which is a potential target for future vascular protection in diabetic patients.

T2DM and CVD incidence: Diabetes is an established risk factor of CVD, particularly, with a 1.8-fold increase in the relative risk of stroke in men with diabetes and a 2.3-fold increase in women. However, there is no recognized standard for the specific value of glucose control. Two classic studies, ACCORD and ADVANCE, both failed to prove the superiority of intensive glucose control in reducing large vessels events and mortality. Thus, the most suitable glucose control target in T2DM for the primary prevention of CVD still desired to be further explored.

T2DM and CVD recurrence: Patients with T2DM are facing high risk of recurrence after CVD. The median risk of Major Adverse Cardiovascular Events (MACE) of T2DM patients with acute cardiac infarction was found to be significantly higher (20.1% *vs.* 13.5%, OR=1.94). In addition, stroke patients with diabetes had an increased risk of death and a higher risk of ischemic stroke recurrence. In general, management of diabetes management should be a priority for secondary prevention in patients with CVD, but lacking comprehensive evidence compared with lipid and blood pressure intervention, calling more exploration.

Options for cardiovascular events associated with novel hypoglycemic drugs

Effects of novel hypoglycemic agents on cardiovascular events: With the advent of new hypoglycemic agents with cardiovascular protective effects, they are included as an extension of these essential therapies for people with T2D or at high risk for ASCVD.

Currently, in terms of cardiovascular events, Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors and Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA) reduce the risk of major CV events in patients with diabetes, whereas Dipeptidyl Peptidase-4 (DPP-4) inhibitors do not appear to provide any CV advantage. GLP-1 RAs reduces the risk of major CV events through a variety of mechanisms, including lowering glycosylated hemoglobin, LDL cholesterol levels, blood pressure, body weight, urinary albumin/creatinine ratio, and highly sensitive C-reactive protein levels. SGLT-2 is also having the ability to reduce mean HbA1c, BMI, and systolic blood pressure.

Effect of novel hypoglycemic agents on cerebrovascular events: For cerebrovascular events, we performed a network meta-analysis. The final meta-analysis consisted of 38 RCTs with 228839 participants. For stroke occurrence, comparing with placebo GLP-1RA and thiazolidinedione can reduce the risk of stroke events, DPP-4i and SGLT2i did not show an advantage in reducing stroke events. However, in our other study, SGLT2i was found to reduce the occurrence of hemorrhagic stroke events.

Some prospects for new hypoglycemic drugs: Although the cardiovascular protective effect of new hypoglycemic agents has been fully recognized, a Swedish study found that the use of new hypoglycemic agents was lower in people with low cardiovascular risk and was usually associated with poor prognosis. Therefore, according to the review, we believe that the application of new hypoglycemic drugs needs to be popularized, and we expect more studies to pay attention to the effects of new hypoglycemic drugs on cerebrovascular events

Management of stress hyperglycemia

Stress hyperglycemia has a high incidence in severe patients: Stress hyperglycemia generally refers to transient hyperglycemia during illness and is usually restricted to patients without previous evidence of diabetes. According to ADA consensus

definition there are currently two diagnostic criteria the first is fasting glucose >6.9 mmol/L or random glucose >11.1 mmol/L without evidence of previous diabetes, the second is pre-existing diabetes with deterioration of pre-illness glycemia control. Stress hyperglycemia does not only occur in people with diabetes. The incidence of stress hyperglycemia is approximately 11-12% in hospitalized patients and as high as 80% in patients undergoing heart surgery, and the incidence increases linearly with age.

Stress hyperglycemia is associated with poor prognosis: The effects of diabetes on endothelial cells involve a variety of changes, including hyperglycemia, oxidative stress, inflammatory activation, and changes in barrier function, etc. However, stress hyperglycemia is caused by greater inflammatory activation and neuroendocrine disorders, and often has a worse prognosis. Several studies have been conducted on the effect of stress hyperglycemia on the prognosis of cardiovascular and cerebrovascular events, and the conclusion has been almost unanimous: A higher Stress Hyperglycemia Ratio (SHR) is associated with a worse prognosis and prolonged stress hyperglycemia was also associated with a poor prognosis. Here SHR is defined as blood glucose on admission/[(28.7 × HbA1c %)-46.7]. A recent NHANES study analysis showed that SHR was independently associated with all-cause mortality and cardiovascular mortality in people with diabetes or prediabetes. Its association with all-cause death was U-shaped and its HRs increased significantly when SHR>0.87. It is associated with L-shaped cardiovascular disease mortality, and when SHR>0.93, its HRs changes.

Routine insulin hypoglycemia is the most appropriate intervention at present: Based on this study and the calculation formula of SHR, it can be seen that the control of stress hyperglycemia has a great effect on improving the prognosis of cardiovascular and cerebrovascular events. In diabetescare in the hospital: Standards of medical care in diabetes 2020 has pointed out that persistent hyperglycemia should be treated with insulin, starting at 180 mg/dL (10.0 mmol/L). Once insulin therapy is started, a target glucose ranges of 140-180 mg/dL (7.8-10.0 mmol/L) is recommended. In our team's previous meta-analysis, we found that intensive glycemic control (4.44-7.22 mmol/L) was associated with a significantly increased risk of hypoglycemic events compared with conventional glycemic control (7.22-11.1 mmol/L). When a hypoglycemic event occurs, the brain alters the areas of blood supply within its brain, resulting in decreased blood sugar in some nerve areas, which in turn results in transient focal neurological signs. In case of severe hypoglycemia, secondary brain damage or infarction may be caused. According to the summary, we have reason to think that for patients with stress hyperglycemia, the use of insulin to regularly control blood sugar and maintain the stability of blood sugar to avoid large fluctuations in blood sugar can effectively improve the prognosis of patients with cardiovascular and cerebrovascular diseases.

More prospects for the research of stress hyperglycemia: At present, studies have indicated that stress hyperglycemia at admission is closely related to the increased risk of new-onset diabetes 3 months after discharge. However, this study also indicates that the strength of this association is still uncertain due to the presence of large clinical heterogeneity, and no studies have shown that hypoglycemic intervention can reduce the transition from stress hyperglycemia to diabetes. Therefore, we are very much looking forward to the emergence of relevant studies, which will be a new target for global diabetes prevalence control. And we also believe that with the popularity of real-time continuous blood glucose monitoring, it has more theoretical advantages for research in this field.

DISCUSSION

We found that although the influence of diabetes on the occurrence and recurrence of cardiovascular and cerebrovascular diseases has been clearly defined, whether the mechanism is consistent remains unclear. The cause of stress hyperglycemia is not clear, and there is no relevant research on how long to complete hypoglycemia after stress hyperglycemia can improve the prognosis of cardiovascular and cerebrovascular events. Finally, the effect of new hypoglycemic drugs on cardiovascular improvement has been recognized by everyone, but whether there is any effect on the recurrence of cerebrovascular events is still unknown.

CONCLUSION

Prediabetes and type 2 diabetes increase the risk of cardiovascular and cerebrovascular events and recurrence, and early intervention is needed. GLP-1RA in new hypoglycemic agents has a beneficial effect on reducing the occurrence of cardiovascular and cerebrovascular events. Finally, for stress hyperglycemia caused by cardiovascular and cerebrovascular events, early use of insulin for routine glucose control can improve the prognosis of patients.

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