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Review

The Role of Hypoglycemia in Cardiovascular Outcomes in Diabetes

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ABSTRACT

Intensive glucose management, targeting lower glycated hemoglobin (A1C) levels, has been shown to reduce the microvascular complications of diabetes, but the effect on cardiovascular (CV) outcomes is less clear. Observational follow-up of intensive glucose management studies suggest possible long-term CV benefits, but no clear reduction in CV events has been seen over 3 to 5 years. Intensive glucose management also increases the risk for hypoglycemia, particularly in patients with longstanding diabetes, cognitive impairment and hypoglycemia unawareness. Severe hypoglycemia has been linked to adverse consequences, including cardiac dysrhythmias, CV events and death, but the precise role of hypoglycemia in CV outcomes is uncertain. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was terminated early because of a higher rate of CV events in the intensive arm. Post hoc analyses of ACCORD and other trials suggest that cardiac autonomic neuropathy may be a predisposing factor to CV events. The Analyses of the Action in Diabetes and Vascular Disease (ADVANCE) trial and the Veterans Affairs Diabetes Trial (VADT) showed that subjects with severe hypoglycemia had more frequent adverse outcomes. However, rather than causing adverse events, it appears that severe hypoglycemia may be a marker of vulnerability for such events. This review focuses on the current understanding of the association between hypoglycemia and CV risk.

Mots clés :
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RÉSUMÉ

Il a été démontré que la prise en charge par un traitement intensif de la glycémie, qui cible des concentrations d'hémoglobine glyquée (A1c) plus faibles réduit les complications microvasculaires liées au diabète, mais l'effet sur les résultats cardiovasculaires (CV) s'avère moins évidente. Il est possible qu'il existe des avantages CV à long terme de la prise en charge par un traitement intensif de la glycémie, mais les études ne suggèrent aucune réduction évidente des événements CV sur une période de 3 à 5 ans. La prise en charge par un traitement intensif de la glycémie augmente également le risque d'hypoglycémie, particulièrement chez les patients ayant un diabète de longue date, des troubles cognitifs et une méconnaissance de l'hypoglycémie qui utilisent l'insuline. Une hypoglycémie grave a été associée à des conséquences défavorables, dont les dysrythmies cardiaques, les événements CV et la mort. Cependant, on ignore encore le rôle précis de l'hypoglycémie sur les résultats CV. L'essai ACCORD (Action to Control Cardiovascular Risk in Diabetes) a pris fin plus tôt en raison d'un taux plus élevé d'événements CV dans le volet de traitement intensif. Les analyses *post-hoc* de l'essai ACCORD et des autres essais suggèrent qu'il est possible que la neuropathie autonome cardiaque soit un facteur de prédisposition aux événements CV. Les analyses de l'essai ADVANCE (Action in Diabetes and Vascular Disease) et de l'essai VADT (Veterans Affairs Diabetes Trial) montraient que les sujets souffrant d'une hypoglycémie grave avaient une plus grande incidence de nombreux résultats indésirables. Cependant, il semble probable que l'hypoglycémie grave soit un marqueur de vulnérabilité plutôt que la cause d'événements indésirables. Cette revue porte sur la compréhension actuelle de l'association entre l'hypoglycémie et le risque CV.

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Introduction

Cardiovascular (CV) disease, including myocardial infarction, unstable angina, heart failure, or stroke causes significant mortality and morbidity in patients with type 2 diabetes (1). Preventing CV events is among the primary goals of diabetes management. The benefits of improved glycemic control in microvascular complications, such as diabetic retinopathy and nephropathy, have been demonstrated in several large randomized studies (2-4). Intensive mutifactorial interventions, including targeting hyperglycemia, hypertension, dyslipidemia and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin, have been shown to reduce CV events in patients with type 2 diabetes (5). Long-term observational follow up of intensive glucose trials targeting lower glycated hemoglobin (A1C) levels, such as the United Kingdom Prospective Diabetes Study (UKPDS) and the Veterans Affairs Diabetes Trial (VADT), suggest a potential reduction in CV events 10 years after randomization, termed the *legacy effect* (6,7). However, several clinical trials have demonstrated that intensive glucose management, in and of itself, does not improve CV outcomes over 3 to 5 years (4,8,9).

Because intensive glucose management is associated with an increased risk for hypoglycemia (low blood glucose), concerns surrounding the relationship between hypoglycemia and CV risk have emerged from the major glycemic trials, ACCORD, ADVANCE and VADT (4,8,9). In these trials, subjects who were randomized to intensive glucose management had higher incidences of hypoglycemia than those randomized to standard glucose control. In the ADVANCE and VADT studies, CV events were no different in intensively treated subjects than in those receiving standard treatment. In the ACCORD trial, the rate of CV mortality was greater in the intensive vs. the standard glycemic treatment groups. Post hoc analysis of the ACCORD data suggests that hypoglycemia was not the primary cause of increased CV mortality (10), but the relationship between hypoglycemia and the risk for CV events or death remains uncertain.

Hypoglycemia in Diabetes

Hypoglycemia is considered to be a major limiting factor in the management of diabetes (11). Fear of hypoglycemia is often a barrier to achieving optimal glycemia control. Mild hypoglycemia (blood glucose between 3.0 and 3.9 mmol/L) is associated with neurogenic symptoms, such as tremor, palpitations and perspiration. These episodes are usually recognized easily and may be treated with oral carbohydrates (12). Severe hypoglycemia, defined as any low blood glucose requiring assistance from another person (13), is characterized by neuroglycopenic (reduced glucose to the brain) symptoms, such as weakness, poor concentration, slurred speech, confusion or even seizure or coma (14). In type 1 diabetes, the risk for severe hypoglycemia is associated with lower target A1C levels (15). However, in type 2 diabetes, the incidence of severe hypoglycemia has been linked to higher A1C levels (16,17). Other risk factors include age, cognitive impairment, poor health literacy, food insecurity, use and duration of insulin or sulfonylurea therapy, renal impairment, presence of diabetic neuropathy and prior episodes of hypoglycemia (13). In longstanding diabetes, the risk for hypoglycemia is greater in the setting of hypoglycemia unawareness (reduced awareness of symptoms of low blood glucose) (17). The mechanism of hypoglycemia unawareness is not entirely clear, but it appears to be linked with attenuated sympathoadrenal responses to hypoglycemia and loss of glucose counterregulation, including glucagon and epinephrine, which has been termed hypoglycemia-associated autonomic failure (18).

Hypoglycemia has a number of other adverse pathologic effects, including activation of proinflammatory mediators (ICAM, VCAM, E-selectin, VEGF, IL-6), increase in platelet activation (P-selectin) and decrease in systemic fibrinolysis (increase in PAI-1), leading to a prothrombotic state, which may promote cardiac ischemia (19-21). Hypoglycemia is associated with increased heart rate, systolic blood pressure, myocardial contractility, stroke volume and cardiac output, as well as reduced central blood pressure and peripheral arterial resistance (22). ST- and T-wave changes with the lengthening of the QT interval and cardiac repolarization have been observed in patients with diabetes, which may be induced by hypoglycemia or may occur spontaneously (23-25). Hypoglycemia may also increase the risk for potentially fatal cardiac arrhythmias, including torsade de pointes and atrial fibrillation (26,27).

Hypoglycemia has also been linked to an increased risk for mortality, especially in type 1 diabetes (28). Studies suggest that 2% to 4% and possibly up to 10% of people with type 1 diabetes die from hypoglycemia, presumably linked to cardiac causes, although the underlying mechanisms are not clear (29-30). In type 2 diabetes, a retrospective study of United States Medicare supplemental insurance claims (n=860,845) showed that patients with hypoglycemic events had a 79% higher regression-adjusted odds ratio of acute cardiovascular events (1.79; 95% CI 1.69 to 1.89) than patients without hypoglycemia (31).

Intensive Glycemic Therapy in Critically Ill Patients

The effect of intensive glucose management on short-term outcomes in the critical care setting has been mixed. In an early study of intensive glucose control in critically ill patients (n=1548) admitted to a surgical intensive care unit, subjects were randomly assigned to intensive insulin therapy (maintenance of blood glucose between 4.4 and 6.1 mmol/L) or conventional treatment (maintenance of glucose between 10.1 and 11.1 mmol/L) (32). The intensively treated group had significantly reduced mortality (4.6% in the intensive arm vs. 8.0% with conventional treatment, $p<0.04$). Intensive insulin therapy appeared to be most beneficial in patients who remained in the intensive care unit for more than 5 days. However, a similar study in patients (n=1200) admitted to a medical intensive care unit did not significantly reduce in-hospital mortality (40.0% in the conventional-treatment group vs. 37.3% in the intensive-treatment group; $p=0.33$) (33). Hypoglycemia occurred more commonly in the intensive-treatment group, but the severity of hypoglycemia was similar between the 2 groups. In patients who had hypoglycemia, the mortality rate was higher in the conventional-treatment group (66.7%) compared to the intensive-treatment group (46.4%), suggesting that hypoglycemia did not play a causal role in mortality.

In the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, subjects (n=6104) were randomized to either intensive glucose control (targeting a blood glucose range of 4.5 to 6.0 mmol/L) or to conventional glucose management (targeting a glucose level less than 10.0 mmol/L), and higher mortality rates occurred in the intensively treated group (34). A total of 829 patients (27.5%) in the intensive group and 751 (24.9%) in the standard group died (odds ratio for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; $p=0.02$). Post hoc analysis found an adjusted hazard ratio of death among patients with moderate to severe hypoglycemia of 1.41 (95% CI, 1.21 to 1.62; $p<0.001$), as compared to 2.10 (95% CI, 1.59 to 2.77; $p<0.001$) in those without hypoglycemia (35). More frequent episodes of hypoglycemia and severe hypoglycemia were also associated with a higher risk for death in the absence of insulin therapy, raising the possibility that, rather than being a direct cause of mortality, hypoglycemia may be a marker of vulnerability in critically ill patients (36).