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Hypoglycemia, Arrythmia and Mortality in Diabetes, an underestimated risk?

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Abstract

Introduction and purpose
Hypoglycemia, characterized by a decrease in blood glucose levels below 70mg/dl, is a dangerous condition, especially in individuals with diabetes mellitus. This condition can trigger a variety of symptoms such as changes in mental status, activation of the sympathetic nervous system and, in severe cases, life-threatening arrhythmias. The aim of the study was to provide an overview of literature linking hypoglycemia with cardiac arrhythmias and increased mortality. A search of the PubMed and Google Schoolar databases was carried out using key words: ‘hypoglycemia’, ‘arrhythmia’, ‘Type 1 diabetes’, ‘Type 2 diabetes’ in order to find the latest publications.

Description
The harmful effects of hypoglycemia on the cardiovascular system are well-documented, with recent studies indicating an association between recurrent hypoglycemic episodes and increased mortality, particularly in individuals with type 1 and type 2 diabetes. Hypoglycemia may contribute to cardiac arrhythmias through multiple mechanisms, including dysregulation of ion channels, catecholamine release, and electrolyte imbalances. Notably, the impact of hypoglycemia on heart rhythm appears to differ between daytime and nighttime episodes, with nocturnal hypoglycemia often leading to bradycardia, while daytime hypoglycemia is more commonly associated with tachycardia.

Summary
Despite advancements in understanding the correlation between hypoglycemia and arrythmias the underling mechanisms remain unclear. With the increasing number of diabetes patients treated with insulin, further research is required.

Keywords: hypoglycemia; arrhythmia; Type 1 diabetes; Type 2 diabetes.

Introduction

Hypoglycemia is characterized by a decrease in blood glucose levels to a point where symptoms such as changes in mental status or activation of the sympathetic nervous system (sweating, palpitations, tremors, anxiety, and hunger) may occur. It is often defined as a blood glucose levels below 70 mg/dL, although the threshold at which symptoms appear is variable [1].

The American Diabetes Association (ADA) and the International Hypoglycemia Study Group define it clinically as a blood glucose level <54 mg/dL. A level <70 mg/dL is considered a warning value and indicates the need for rapid treatment with carbohydrates and adjustment of diabetes medications [2, 3]. Glucose is a primary energy source for the brain, which requires a constant supply, leading to the development of physiological responses aimed at protecting against hypoglycemia by increasing blood glucose levels [1,4,5]. When glucose levels fall below 80–85 mg/dL, insulin secretion and glucose uptake in peripheral tissues decrease, and when blood glucose levels drop below 65–70 mg/dL, the release of counterregulatory hormones such as glucagon, growth hormone, adrenaline, noradrenaline, and cortisol is activated.

Clinically, a blood glucose level below 70 mg/dL initiates neuroendocrine responses to hypoglycemia in individuals without diabetes, whereas in those with type 1 or long-standing type 2 diabetes and unawareness of hypoglycemia, these responses occur at a lower glycemic threshold. This is due to impaired glucagon secretion and a blunted sympatho-adrenal response [4,6,7].

Hypoglycemia rarely occurs in patients without diabetes, but when it does, it is often associated with alcohol, critical illness, counter-regulatory hormone deficiencies, non-islet tumors, and malnutrition. However, it is most commonly related to diabetes and treatment with insulin, meglitinides, or sulfonylureas. Metformin, GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP-4 inhibitors typically do not cause hypoglycemia [2,8].

It is now recognized that both type 1 and type 2 diabetes are associated with an increased cardiovascular mortality [9] and the harmful effects of hypoglycemia on the cardiovascular system are arguably mediated by multiple pathways, including coagulation abnormalities, inflammation, endothelial dysfunction, and cardiac arrhythmias [10]. The aim of this study is to review the existing literature on the relationship between hypoglycemia, cardiac arrhythmias, and mortality, emphasizing the need for further studies to explore the underlying mechanisms and to better understand the role of glycemic variability in cardiovascular complications.

Material and methods of research

The review takes into account articles published in electronic databases such as PubMed and Google Scholar to search for the most recent publications. Key words included ‘hypoglycemia’, ‘arrhythmia’, ‘Type 1 diabetes’, ‘Type 2 diabetes’ and variation of the terms. The literature review considered clinical trials, double-blind randomized controlled trials, metanalysis, reviews and systematic review articles published between 2010-2024,

paying particular attention to articles published in the last eight years. Following a preliminary analysis, relevant peer reviewed articles on the topic were included in the review.

State of knowledge

Hypoglycemia and mortality

There is evidence to indicate a correlation between hypoglycemia and sudden nocturnal death, particularly in young patients, this manifests itself as 'dead in bed syndrome' in which people with insulin-treated diabetes experience severe nocturnal hypoglycemia and are unable to seek life-saving treatment to correct the hypoglycemia [11,12].

In a cohort study conducted in Taiwan involving 10,411 patients with type 1 diabetes, it was demonstrated that repeated exposure to severe hypoglycemic events significantly increases the risk of mortality and cardiovascular diseases. History of severe hypoglycemia was analyzed over three time periods: within 1 year, 1–3 years, and 3–5 years prior to the study outcomes. Severe hypoglycemic events occurring during the year preceding the outcomes were strongly associated with an elevated risk of all-cause mortality and cardiovascular diseases. Events occurring 1-3 years and 3-5 years prior were also linked to increased risk, though to a lesser extent (odds ratios of 1.94 and 1.68). Individuals who experienced severe hypoglycemia were more likely to develop cardiovascular diseases or die prematurely. Patients with a history of severe hypoglycemia within the preceding year exhibited a 2.74-fold increased likelihood of death and a 2.02-fold increased risk of developing cardiovascular diseases. Notably, the heightened risk of mortality and cardiovascular complications was mainly associated with severe hypoglycemic episodes occurring within the year prior to these adverse outcomes [13].

The potential association between hypoglycemia and increased mortality is also highlighted by findings of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. This study demonstrated that intensive glycemic control in patients with type 2 diabetes resulted in a significant increase in all-cause mortality, primarily due to a 35% increase in cardiovascular-related deaths compared to patients receiving standard therapy. These findings led to the premature termination of the trial. Among patients assigned to intensive glycemic control, the incidence of severe hypoglycemia increased three-fold, which may partially account for the observed increase in cardiovascular mortality [14,15,16].

The study by Rozalina G. McCoy also demonstrated a similar association. A total of 1,013 patients with type 1 (21.3%) and type 2 (78.7%) diabetes were evaluated, who had been treated at a specialized diabetes clinic between August 2005 and July 2006. Patients were asked about the frequency of hypoglycemia during an interview prior to their visit. Mild hypoglycemia was defined as symptoms treated without assistance, while severe hypoglycemia was defined as symptoms requiring external help. Among them, 625 (61.7%) reported experiencing hypoglycemia, and 76 (7.5%) reported severe hypoglycemia. After five years, patients who reported severe hypoglycemia had a mortality rate 3.4 times higher than those who reported mild or no hypoglycemia [17].

The exact mechanisms underlying hypoglycemia-induced mortality remain unclear, but dysregulation of electrical signals in the heart is thought to play a role, potentially increasing susceptibility to cardiac arrhythmias and sudden cardiac death [11, 12, 13, 16, 18, 19, 20, 21, 22]. Other hypotheses suggest that sympathetic-adrenal activation, increased thrombogenesis, and inflammation may serve as potential mechanisms linking these factors [12, 13]. The likely process explaining the relationship between inflammation, endothelial dysfunction, and

increased mortality involves the intensification of intravascular coagulation and thrombosis, which promotes tissue ischemia [13].

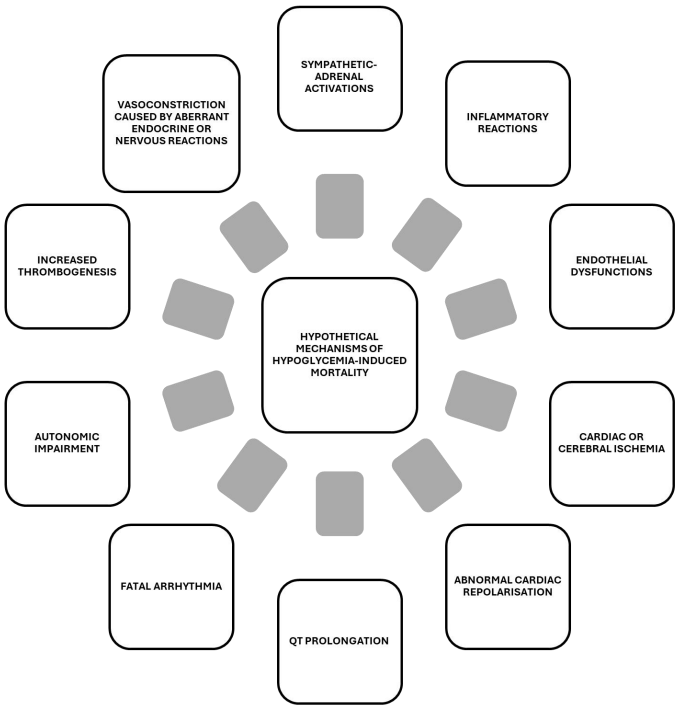

Figure 1. Hypothetical mechanisms of hypoglycemia-induced mortality. [12,13]

The relationship between inflammation, hypoglycemia, and mortality was supported in a study where insulin-deficient rats were divided into two groups: a control group and a group treated with vitamin E (administered as four doses of α-tocopherol at 400 mg/kg). Compared to the control group, rats treated with vitamin E exhibited a threefold reduction in cardiac oxidative stress, a sixfold decrease in mortality due to severe hypoglycemia, and a sevenfold reduction in the incidence of heart block. In summary, vitamin E treatment and the associated reduction in cardiac oxidative stress in diabetic rats significantly reduced fatal cardiac arrhythmias induced by hypoglycemia [22].

Alternatively, some older studies suggest that severe hypoglycemia may not be a direct cause of mortality but rather a marker of vulnerability to these events, which may be due to a higher burden of disease, such as advanced age or longer duration of diabetes [12, 14, 23, 24].

For instance, in the 2010 study by Sophia Zoungas, the relationship between severe hypoglycemia and the risk of macrovascular and microvascular events, as well as mortality, was analyzed in a cohort of 11,140 patients with type 2 diabetes. Over approximately 5-year follow-up period, at least one severe hypoglycemic episode occurred in 231 patients (2.1%), with 150 patients from the intensive glycemic control group (2.7% of 5,571 patients) and 81 from the standard glycemic control group (1.5% of 5,569 patients). Severe hypoglycemia was significantly associated with an increased adjusted risk of major macrovascular events (hazard ratio [HR] 2.88), microvascular events (HR 1.81), cardiovascular mortality (HR 2.68), and all-cause mortality (HR 2.69). Severe

hypoglycemia demonstrated a strong correlation with adverse clinical outcomes, potentially contributing to their occurrence; however, analyses also suggest that it may serve as a marker of patient vulnerability to such events. [23].

Similar conclusions were reached by Laura Boucai et al. in a retrospective cohort analysis of patients hospitalized in 2007. They compared mortality risk among individuals with hypoglycemia (glucose ≤70 mg/dl) and normoglycemia, considering the distinction between spontaneous and medication-induced hypoglycemia. Among 31,970 patients, hypoglycemic episodes occurred in 3,349 individuals (10.5%), who were older, had more comorbidities, and more frequently received antidiabetic medications. Hypoglycemia was associated with increased hospital mortality (HR: 1.67, $p<0.001$); however, this risk applied only to patients with spontaneous hypoglycemia (HR: 2.62, $p<0.001$), not those where it was induced by treatment (HR: 1.06, $p=0.749$). After adjusting for comorbidities, the association between spontaneous hypoglycemia and mortality was no longer significant (HR: 1.11, $p=0.582$). This suggests that hypoglycemia may be a marker of a severe clinical condition rather than a direct cause of death [24].

One hypothesis explaining the increased mortality in diabetic patients experiencing hypoglycemia involves the dysregulation of the heart's electrical signals, thereby increasing susceptibility to cardiac arrhythmias. A direct causal relationship between hypoglycemia and fatal arrhythmias is difficult to establish, as it requires simultaneous monitoring of both heart rhythm and glucose levels, which is not a routine practice in clinical settings [15]. However, such monitoring was used in a cohort study conducted by F. Pistrosch and colleagues, where 94 patients with type 2 diabetes and established cardiovascular disease underwent simultaneous continuous glucose monitoring and Holter monitoring for five days. It was found that in patients experiencing hypoglycemic episodes, the incidence of serious ventricular arrhythmias (VT) was significantly higher than in patients without hypoglycemia [25].

Hypoglycemia and Arrhythmias

Numerous studies have shown that patients with type 1 or type 2 diabetes are at increased risk of developing cardiovascular complications, including arrhythmias, caused by hypoglycemia [4,10,15].

Hypoglycemia may increase the risk of cardiac arrhythmias by a number of mechanisms, including inhibition of the cardiac ion channel, altered electrolyte and hormone levels, as well as those related to the patient's underlying medical conditions [15, 19]. The release of catecholamines and hypokalemia prolong cardiac repolarization, increasing the risk of early subsequent depolarizations and ventricular arrhythmias [19]. Reno et al., in studies involving rats, demonstrated that potassium supplementation during severe hypoglycemia reduces the occurrence of cardiac arrhythmias and that infusion of Glibenclamide to block ATP-sensitive potassium ion channels during severe hypoglycemia also reduces the incidence of fatal cardiac arrhythmias [20, 26]. Furthermore, both the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) influence the heart during hypoglycemia. A measure of SNS and PNS activity is heart rate variability (HRV). In most cases of hypoglycemia, when the SNS is activated, there is a reduction in HRV. In contrast, at night, SNS withdrawal and PNS activation leads to bradycardia and ectopic ventricular beats [6], with no observed changes in HRV [27].

Hypoglycemia can affect cardiac repolarization and electrophysiology, leading to various types of arrhythmias [15]. It has been observed that a decrease in blood glucose levels leads to electrocardiographic changes such as ST-segment depression, reduction in T-wave height and width, shortening of the PR interval, and prolongation of the QT interval, with more severe hypoglycemia being associated with greater QT interval prolongation. QT

interval prolongation increases the risk of ventricular arrhythmias and is a strong predictor of cardiovascular mortality in patients with diabetes [4, 6].

Andersen et al. conducted an experimental study in which they observed a significant prolongation of the QTc interval during acute insulin-induced hypoglycemia in both insulin-treated type 2 diabetic patients and matched controls, with no difference between groups [18]. In addition, an experimental study by Fitzpatrick et al demonstrated an association between hypoglycemia and QTc interval prolongation in both type 1 and type 2 diabetes patients [28]. Clinically, the prolongation of the QT interval during hypoglycemia can be reduced by the use of selective beta-blockers, leading to the conclusion that the main cause of QT prolongation during hypoglycemia is sympathoadrenal stimulation [6].

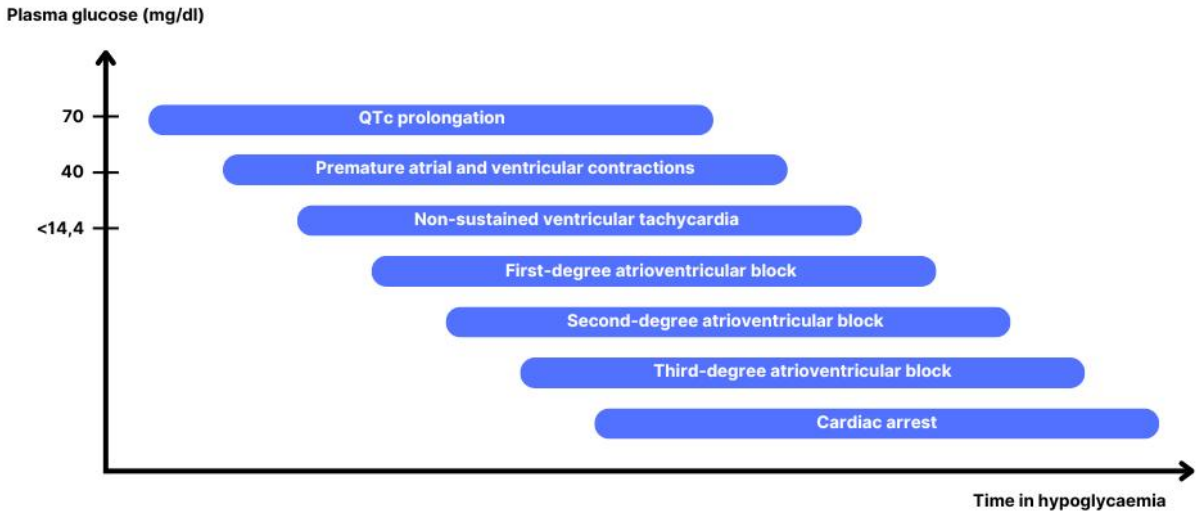

Figure 2. Characterization of ECG Changes During Severe Hypoglycemia Induced by Insulin in Rats. [14,20]

Hypoglycemia-induced ventricular arrhythmias also include ventricular premature beat (VPB), ventricular tachycardia (VT), ventricular fibrillation (VF) and sudden cardiac death (SCD) [15, 18, 29].

Hypoglycemia contributes to both ventricular and supraventricular arrhythmias, such as sinus tachycardia, atrial premature beats and atrial fibrillation (AF) [15, 19, 20, 21, 30]. In a retrospective study of patients with type 2 diabetes aged between 30 to 75 years, Ko et al. found that the incidence of AF was significantly higher in patients with severe hypoglycemia than in patients without hypoglycemia. They concluded that previous hypoglycemic events were associated with a higher risk of new onset AF [30]. In contrast, Humos et al. conducted a study in which they assessed the impact of hypoglycemia on ST-segment elevation myocardial infarction (STEMI). They showed that hypoglycemia in patients hospitalized for STEMI was associated with increased mortality, atrial fibrillation and ventricular fibrillation, regardless of the presence of diabetes at the start of the study [29].

Clinical studies have shown that daytime hypoglycemia and nocturnal hypoglycemia have opposite effects on cardiac rhythm. The observed differences in the occurrence of cardiac arrhythmias between daytime and nocturnal hypoglycemia may be related to an inadequate counterregulatory response to hypoglycemia during sleep [4,6].

There have been a number of studies using simultaneous continuous glucose monitoring (CGM) and ECG monitoring. Novodvorsky et al. conducted a study in people with type 1 diabetes under the age of 50, in which they identified differences in the risk of arrhythmia and repolarization during night and daytime hypoglycemia. They observed that nocturnal hypoglycemia is associated with an increased risk of bradycardia, whereas daytime hypoglycemia is linked to a higher risk of tachycardia. Factors influencing these responses include diurnal variability in autonomic tone, differing sympathoadrenal responses to hypoglycemia during wakefulness and sleep, and the impact of body position [27]. A similar relationship was shown by Chow et al. in a study involving people with type 2 diabetes. They observed that during nocturnal hypoglycemia, the risk of bradycardia, atrial ectopy, and ventricular premature beats (VPB) is significantly increased. They hypothesized that the occurrence of bradycardia during nocturnal hypoglycemia may be related to an increased vagus nerve response following sympathetic nervous system activation [19].

Furthermore, Novodvorsky et al confirmed the proarrhythmogenic effect of hypoglycemia by demonstrating a significant prolongation of the QTc interval and the T-peak T-end interval (TpTend) both during the day and at night. TpTend is a measure of left ventricular repolarization dispersion, and its prolongation represents a period of potential vulnerability to recurrent ventricular arrhythmias and is associated with an increased risk of sudden cardiac death [27].

Summary

Diabetes is a major health problem, affects the quality of life of patients and their families, leading to long-term complications and shortened life expectancy. As the number of diagnosed cases increases around the world, so does the number of people who develop episodes of hypoglycemia. There is a large body of evidence that recurrent episodes of hypoglycemia may result in increased risk of death, arrhythmias and cardiovascular complications. Despite the presented studies, the exact mechanisms of the influence of decreased glucose levels are not known. The differing effects of glucose drops during the day and night on heart rhythm also deserve attention of scientist. Therefore, further research is needed to clarify the relationship between glycemic variability and cardiac arrhythmias.

DISCLOSURES

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