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REVIEW ARTICLE

Shaky Feelings: Hypoglycemia and Cardiovascular Risk

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Abstract: Hypoglycemia is a very common side effect of insulin therapy and, to a lesser extent, of treatment with oral hypoglycemic agents. Severe hypoglycemia can precipitate adverse cardiovascular outcomes such as myocardial ischemia and cardiac arrhythmia. These are mainly secondary to autonomic activation which results in hemodynamic changes, vasoconstriction and rise in intravascular coagulability and viscosity. Although hypoglycemia is the most common side effect of insulin therapy in diabetes and its morbidity is well known, for many years, the potentially life-threatening effects of hypoglycemia on the cardiovascular (CV) system have either been overlooked or have been dismissed as inconsequential to people with insulin-treated type 2 diabetes. This scenario may possibly be a consequence of the persisting misconception that this population is seldom exposed to severe hypoglycemia, defined as any episode that requires external assistance for recovery, whereas self-treated events are classified as "mild". This review focuses on the importance of knowing about this condition and ways to tackle the same.

Introduction

There is a saying: "The best teachers teach from the *heart*, not from a book." Medicine is a profession in which one learns the most from patients. Their conditions are constantly teaching us things, and in this case the "heart" of the patient doing most of the talking. Patients communicate hypoglycemic symptoms as "feeling shaky," "racing heart," "out of energy," "pounding in the head," and hunger – all mediated by the sympathoadrenal system. Signs of hypoglycemia should be picked up and treated with proper control of diabetes to prevent further attacks of hypoglycemia. This is important as, apart from the effects of hypoglycemia on the brain, it can also affect the heart and cause cardiovascular morbidity and mortality. Thus diabetes is a double-edged sword, with both hyper- and hypoglycemia being detrimental and glucose control being balanced between these two entities.

Consequences of Hypoglycemia

The common consequences of hypoglycaemia are as follows:

- Seizures and coma
- Cognitive dysfunction and headaches
- Accidents and unemployment
- Fear
- Impaired quality of life
- Prevents desirable glucose targets
- Cardiovascular risk (*may be*)

Studies on Hypoglycemia and Cardiovascular Risk

Studies suggesting that hypoglycemia is associated with cardiovascular risk are many. Recently, several large randomized trials evaluating the effects of glycemic control on cardiovascular events have published their results.[1–3]

The ACCORD trial randomized 10,251 participants with a history of cardiovascular events or significant cardiovascular risk to a strategy of intensive glycemic control or standard glycemic control.[1] The ACCORD trial was halted because of a significant increase in all-cause mortality (22%) and cardiovascular mortality (35%) in the intensive treatment group. In both the intensive and standard treatment arms, participants with severe hypoglycemia had a higher mortality rate than those without severe hypoglycemia.[1] However, the association between hypoglycemia and mortality is much more complex in this study. The relative risk of death associated with severe hypoglycemia was 1.28 for the intensive arm versus 2.87 for the standard arm in spite of larger number of severe hypoglycemic episodes in the intensive arm. This suggests that severe hypoglycemia in a certain subset of patients may be associated with mortality rather than the strategy of treatment used (intensive vs. standard). However, these data are based on post-hoc analysis, and the true cause of the increased mortality in these patients may never become obvious. The subset of patients most prone to the detrimental effects of hypoglycemia had several of the following characteristics: they were likely to be women; African-American; older patients; or patients with a longer duration of diabetes and have higher A_{1C} and high albumin-to-creatinine ratio.

VADT randomized 1791 patients with type 2 diabetes mellitus (T2DM) to an intensive treatment group and a conventional treatment group.[3] At the end of the study, there was no significant difference in cardiovascular events between the two treatment arms. As expected, there was an increased incidence of severe hypoglycemia in the intensive treatment group. Predictors for hypoglycemia included increased duration of diabetes, insulin treatment at baseline, low BMI, previous cardiovascular events, and high albumin-to-creatinine ratio.

The ADVANCE study randomized 11,140 participants to an intensive glycemic control arm and a standard glycemic control arm.[2] Although there was an increased risk of hypoglycemia in the intensive treatment arm, there was no association between hypoglycemia and cardiovascular mortality.[2] One explanation for the discrepancy between this finding and that in the ACCORD study is the extremely low number of patients (<3%) who had severe hypoglycemia in the intensive treatment arm, during the course of the entire trial.

Patients in the ADVANCE trial had a 2–3-year shorter duration of diabetes as well as a lower baseline A_{1C} than patients in the ACCORD trial. The number of patients on insulin in the intensive arm versus the standard arm was 77% versus 55% in the ACCORD trail, 90% versus 74% in the VADT, and 41% versus 24% in the ADVANCE trial. Thus, the ADVANCE trial had a much smaller proportion of patients on insulin than ACCORD or VADT. This could in part account for the low level of hypoglycemia seen in the intensive arm of the ADVANCE trial (<3%) versus the ACCORD trail (16%) and VADT (21%).

The DCCT enrolled type 1 diabetic patients on insulin treatment. DCCT had a relatively high risk for severe hypoglycemia in the "conventional" treatment group (0.19 episodes/patient-year) and a threefold increased risk in the "intensive" group (0.62 episodes/patient-year). Interestingly, the more frequent severe hypoglycemia in the intensive group was not associated with increased cardiovascular mortality at later follow-up.[4] This indirectly highlights the different cardiovascular risk of hypoglycemia in type 2 versus type 1 diabetes.

The Physiology of Hypoglycemia

In health, a perfect balance is maintained between the levels of insulin and its antagonists so that glucose entry into the blood is precisely matched by the rates of glucose removal from the blood. In this way, a steady supply of glucose to the brain is assured. Hypoglycemia results when this balance is disturbed.

As blood glucose falls, a series of neurohumoral responses occur. In producing acute recovery from insulin-induced hypoglycemia, glucagon is probably the major hormone, but epinephrine alone can also produce near-normal recovery.[5] Stimulation of the sympathetic nervous system, reflected indirectly by rising norepinephrine levels, is also important, especially in the generation of warning symptoms of hypoglycemia. In more prolonged hypoglycemia, the actions of growth hormone and cortisol assume increasing importance, and clinical syndromes of hypoglycemia occur in their absence.[6–8]

This profound autonomic stimulus provokes hemodynamic changes, the important consequences of which are to maintain the supply of glucose to the brain and promote the hepatic production of glucose. Blood flow is, therefore, increased to the myocardium, the splanchnic circulation (to provide precursors of gluconeogenesis to the liver), and the brain. The hemodynamic changes associated with hypoglycemia include an increase in heart rate and peripheral systolic blood pressure, a fall in central blood pressure, reduced peripheral arterial resistance (causing a widening of pulse pressure), and increased myocardial contractility, stroke volume, and cardiac output.[9] The workload of the heart is, therefore, temporarily but markedly increased. This stress is especially important in patients with preexisting CVD.

Elasticity of Blood Vessels

In nondiabetic people, the arteries become more elastic during acute hypoglycemia with a decline in arterial wall stiffness, but in people with type 1 diabetes of >15 years' duration, arterial wall stiffness *per se* is greater and arteries are less elastic in response to hypoglycemia, manifesting in

a lesser fall in central arterial pressure.[10] Normal elasticity of the arterial wall ensures that the reflected pressure wave from the high-pressure arterioles, generated during each myocardial contraction, returns to the heart during early diastole, so enhancing coronary arterial perfusion, which occurs mainly during diastole (Figure 1). However, progressive stiffening of the arterial walls (as occurs in most people with long-standing diabetes) accelerates the return of the reflected wave causing its earlier arrival during late systole (Figure 2). This pathophysiological effect may interfere with coronary arterial perfusion and promote myocardial ischemia.

Electrocardiographic Changes

Hypoglycemia also causes prolongation of repolarization manifested as a prolongation of the corrected QT interval (QTc).[11–13] T-Wave changes in the form of flattening of T-wave and its prolongation are seen (Figure 3).[14] These changes may increase the risk of cardiac arrhythmia, various abnormal heart rhythms, including ventricular tachycardia and atrial fibrillation. It can also contribute to sudden cardiac death seen in hypoglycemia. These changes are due to sympathoadrenal stimulation and insulin action causing hypokalemia. Sympathetic system reduces the activity of K8 potassium channel and increases calcium influx. Insulin lowers the serum potassium, reduces the potassium efflux, and prolongs cardiac repolarization. These actions cause prolongation of repolarization.

Sudden Death

Sudden unexpected death of diabetic patients is linked to severe hypoglycemia and is termed as "death in bed syndrome"[15] denoting death in an undisturbed bed during sleep. In 1991, there was investigation of a series of deaths of young adults with type 1 diabetes.[16] The survey was commissioned by the British Diabetic Association after concern that insulin of human origin might cause fatal hypoglycemia. After deaths from definite causes were excluded, the authors identified 22 individuals with type 1 diabetes aged <50 years, who despite being previously well had a very similar manner of death. Sudden death in diabetes may be caused due to abnormal electrical activity of the heart (Figure 4).

Role of Autonomic Neuropathy

It is possible that an interaction between hypoglycemia-induced abnormalities of cardiac repolarization and autonomic neuropathy contributes to the risk of sudden death in individuals with diabetes. Diabetic autonomic neuropathy is known to be associated with an increased mortality, and resting QT intervals are generally longer in patients with autonomic neuropathy than in patients without.[17] The recent demonstration that brief periods of

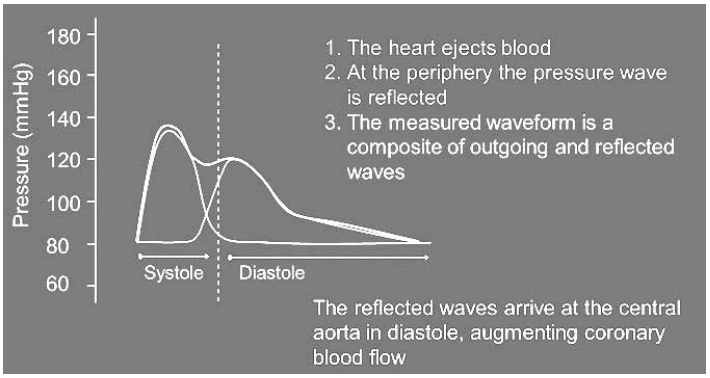

Figure 1 | The aortic pressure waveform (when large vessels are not stiff).
From: Brian Fryer European Association for the Study of Diabetes (EASD), 2012

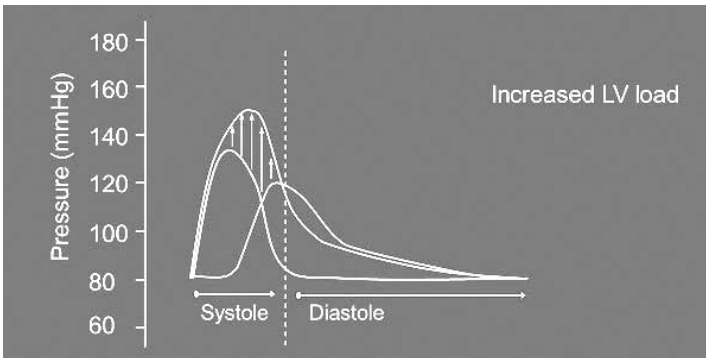

Figure 2 | The aortic pressure waveform – with increasing arterial stiffness.
From: Brian Fryer European Association for the Study of Diabetes (EASD), 2012

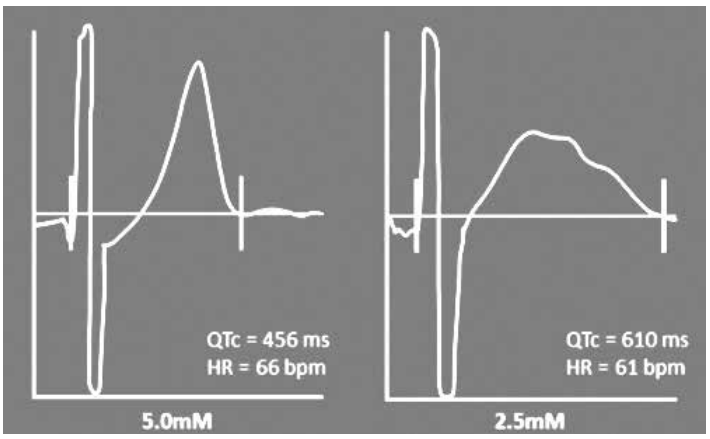

Figure 3 | Electrocardioraphic changes during hypoglycemia.
(From Marques JL, George E, Peacey SR, *et al*. Altered ventricular repolarization during hypoglycaemia in patients with diabetes. *Diabetic Med*. 1997;14:648–54.)

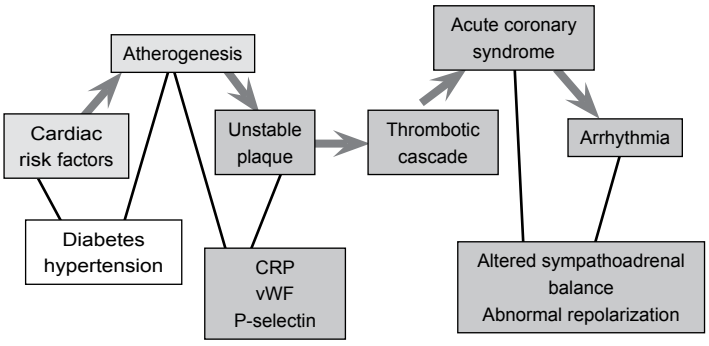

Figure 4 | Pathophysiology of sudden death in hypoglycemia.

experimental hypoglycemia impair CV autonomic function for up to 16 hours is an additional evidence for a clinically relevant interaction.[18] However, some studies show that QT prolongation is less in patients with autonomic neuropathy[19] than in those without hypoglycemia due to impaired sympathoadrenal stimulation.

Inflammation and Rheology

Inflammation has been associated with cardiovascular disease and diabetes. Several inflammatory markers including C-reactive protein (CRP), interleukin (IL)-6, IL-8, tumor necrosis factor alpha (TNF-α), and endothelin-1 have been shown to be increasing during hypoglycemia.[20,21] This increase in inflammatory cytokines could result in endothelial injury and abnormalities in coagulation, resulting in increased risk for cardiovascular events. Certain growth factor levels such as vascular endothelial growth factor are also increased locally and in circulation after an episode of hypoglycemia.[22] Furthermore, some cytokines such as IL-1 have been shown to increase the severity of hypoglycemia, thus perpetuating a positive feedback cycle.[23]

Hypoglycemia induces abnormalities in platelet function and activation of the fibrinolytic system.[24,25] Increased epinephrine levels lead to an increase in platelet activation, leukocyte mobilization, and blood coagulability. Many of these changes can be reversed by α- or β-blockade.

Recent studies suggest that endothelial function may be compromised during acute hypoglycemia.

Inflammation, blood component, and functional abnormalities and endothelial dysfunction are closely interdependent. These abnormalities could potentially be aggravating the factors that contribute to increased cardiovascular risk with severe hypoglycemia, especially when applied to the subset of patients with preexisting cardiovascular disease, longer duration of diabetes, and severe autonomic neuropathy.

Hypoglycemia in In-patient Glucose Control

The role of hypoglycemia in cardiovascular mortality in the in-patient setting is still controversial. Much of the variability in results is due to the different protocols used, differences in definition of hypoglycemia, as well as methodology of its detection and report, presence or absence of safeguards against hypoglycemia in the protocols, local training level of the personnel administering the protocols, and selected patient population. Hence, carefully constructed clinical trails to research this question are required.

Hyperglycemia is common in acutely ill patients and is associated with an increased morbidity and mortality.[26] This has subsequently led to a large number of trials using various intensive insulin protocols to control in-patient blood glucose. However, results from these trials have increased the controversy over the risks-versus-benefit of tight in-patient glycemic control. Van den Berghe *et al*.[27] demonstrated that intensive insulin therapy in critically ill patients reduced morbidity and mortality. The DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study found that insulin–glucose infusion followed by intensive subcutaneous insulin in diabetic patients with acute myocardial infarction improved long-term survival.[28] Conversely, the DIGAMI 2 study did not confirm superiority of insulin versus conventional treatment, but reaffirmed the importance of good glycemic control in prevention of cardiovascular events.[29] The recently published NICE-SUGAR (Normoglycemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation) study found that intensive glucose control increased mortality among adults in the ICU.[30] The Glucose Insulin in Stroke Trial (GIST)-UK looked at tight control of glucose in patients with acute stroke using an intensive insulin infusion protocol and found no benefit.[31] The GIST-UK trial was underpowered to draw any firm conclusions. However, the subanalysis of the mean change in glucose at 24 hours showed that patients who had a decrease in plasma glucose of ≥2 mmol/L had a mortality rate of 34% versus 22% for those who had a <2 mmol/L decrease.[32] This raises the question of hypoglycemia having a role in increased mortality in the in-patient setting.

Some recent studies looking at using intensive insulin infusions such as the volume and insulin therapy in severe sepsis and septic shock (VISEP) showed that the incidence of hypoglycemia was higher in the intensively treated group.[33] A study by Kosiborod *et al*.,[34] looking at 16,871 patients admitted with myocardial infarction, found that a J-shaped relationship existed between glucose and mortality. Incremental increases above 120 mg/dL and incremental declines below 70 mg/dL were found to be strongly associated with increased mortality. The slopes of these relationships were even steeper in patients with diabetes, suggesting that hypoglycemia could contribute to increased mortality, especially in diabetic patients. In another study, a pooled analysis of over 4200 patients from various myocardial infarction intervention studies, death occurred in 4.6% of the patients with hypoglycemia versus 1% of those who were considered euglycemic (81–199 mg/dL).[35] In contrast, a subanalysis of the DIGAMI 2 data did not show hypoglycemia to be an independent risk factor for future morbidity or mortality in patients with T2DM and myocardial infarction.[36] It is prudent to conclude from the available data that severe hypoglycemia should be avoided as much as possible in the in-patient setting.

Management

Hypoglycemia is blood glucose less than 70 mg/dL. It should be treated with 50% dextrose using the following formula:

$$D50 = (100 - BG) \times 0.4 \text{ mL IV}$$

For example, if blood glucose (BG) is 60 mg/dL, 100 – 60 × 0.4 = 16 mL 50% D. The blood glucose is rechecked in 15 minutes and treatment repeated if needed. If the patient can take orally, 15 g of rapid-acting carbohydrate is given. Insulin should be continued if blood glucose is normal.

Long-term management of diabetes is prudent to prevent hypo- or hyperglycemia. Insulin and drug regimens should be changed if needed to maintain euglycemia.

Final Word

Hyper- and hypoglycemia form the two cliffs of a plateau and diabetes management should be such as to form a proper balance between the two. Hypoglycemia can lead to sudden death, arrhythmias, vascular abnormalities, and can worsen coronary heart disease. Further studies are required for guidelines on sugar control of ICU patients. However, hypoglycemia is more detrimental. Prompt treatment of hypoglycemia and proper long-term management will improve the morbidity and mortality of diabetic patients.

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