Cardiovascular Effects of Hypoglycaemia in Type 2 Diabetes Mellitus

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Abstract

Diabetes management should endeavour to achieve HbA1c target levels, which, however, may be associated with an increased risk of hypoglycaemia. In patients with type 2 diabetes mellitus, the incidence of asymptomatic hypoglycaemic episodes may be as high as 46.6%. Very tight glycaemic control, due to the higher frequency of hypoglycaemic episodes, increases cardiovascular mortality, as demonstrated in the ACCORD study. The increase in sympathetic activity and hypokalaemia resulting from the counter-regulation during hypoglycaemia play a role in the development of unfavourable cardiovascular consequences. Hypoglycaemia may lead to QT prolongation and increased QT dispersion, and may precipitate malignant ventricular arrhythmias. Hypoglycaemia may also trigger ischaemic episodes in patients with coronary heart disease. With regard to cardiovascular protection, it is important in type 2 diabetes to achieve adequate glycaemic control by avoiding the risk of hypoglycaemia.

Keywords — hypoglycaemia, cardiovascular risk, QT interval

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I. INTRODUCTION

It is common knowledge that diabetes is a condition associated with a very high cardiovascular risk1, and thus, unsurprisingly, cardiovascular events account for 60% of overall mortality in diabetic patients. In patients with diabetes, the risk of cardiovascular events is two to three times higher than for non-diabetics2, while their prognosis is also significantly poorer3.

A number of epidemiological studies confirmed that a correlation exists between blood glucose levels and the risk of cardiovascular diseases in diabetic patients, even prior to the establishment of a diagnosis of diabetes4, since higher blood glucose levels increase cardiovascular risk4.

In the UKPDS (United Kingdom Prospective Diabetes Study), it has been shown that intensive glycaemic control reduce the microvascular consequences of diabetes. However, each decrease of 1% in the HbA1c level through intensive glycaemic treatment decreases the risk of fatal and non-fatal myocardial infarctions by 14%-5. 6. Intensive treatment of patients with newly diagnosed type 2 diabetes results in the decrease of relative risk of myocardial infarction by 16% (p=0.52, NS) compared to conventional therapy6. The UKPDS study confirmed the hypothesis that a direct correlation exists between the level of glycaemic control and the incidence of diabetic complications.

By retrospective analysis of the results of the UKPDS study, Currie et al have demonstrated that overall mortality and the risk of cardiovascular events was the lowest at a HbA1c value of 7.5%. By contrast, the risk was found to be 1.52 times higher at a HbA1c value of 6.4% (lowest decile), and 1.79 times higher at a HbA1c value of 10.5% (uppermost decile) in the pooled analysis of cohorts. This means that a U-shaped correlation can be shown between HbA1c and overall mortality and cardiovascular events; that is, both very low and very high HbA1c levels result in an increased risk7. A subsequent analysis of the UKPDS study found poorer glycaemic control in patients who were returned to GP care over the past 10 years; however, the risk reduction for macrovascular complications was still significant. The latter finding drew attention to the importance of cardiometabolic legacy8.

II. HYPOGLYCEMIA

Frequency of hypoglycaemia in type 2 diabetes

The frequency of severe hypoglycaemic episodes observed in type 2 diabetes mellitus with tight control of HbA1c values and the administration of hypoglycaemic antidiabetics (insulin, sulfonylureas, glinides) is comparable in magnitude to that observed in type 1 diabetes9. According to data from the UKPDS study, hypoglycaemic episodes in long-standing type 2 diabetes already exacerbated by multiple complications can significantly compromise the achievement of appropriate glycaemic control10. It is perhaps less known that hypoglycaemia can also frequently occur during the treatment of type 2 diabetes mellitus using orally administered...
preparations. Previously, this risk has been greatly underestimated because the incidence of mild hypoglycaemia was ignored in the various studies. In fact, the real frequency of hypoglycaemic episodes can only be accurately determined through continuous glucose monitoring (CGM). Chico et al confirmed using CGM that 46.6% of patients with type 2 diabetes had asymptomatic hypoglycaemic episodes occurring in equal proportions either in daytime or night-time periods (42.8 and 42.8%, respectively), and occurring at both times of day in a minority of patients (14.4%) (Fig. 1)\(^{11}\).

**Hypoglycaemia and counter-regulatory mechanisms**

During hypoglycaemia, the body defends itself using a number of the counterregulatory mechanisms to elevate blood glucose levels. First, at a low-to-normal blood glucose level of 4.4 mmol/L, insulin secretion decreases and hepatic and renal glucose production increases.

Next, a secondary line of defence is formed by the activation of the neuroendocrine system. In mild hypoglycaemia (at 3.6 to 3.8 mmol/L), pancreatic alpha cells and adrenal glands discharge glucagon and epinephrine, respectively. Glucagon stimulates hepatic gluconeogenesis and glycolysis, while epinephrine increases the production of glucose in the liver and kidneys and simultaneously reduces peripheral glucose uptake.

During hypoglycaemia, tachycardia and increased cardiac contractility, and increased oxygen demand occur due to the increased activity of the sympatho-adrenergic system. Systolic blood pressure rises and circulatory redistribution causes vasoconstriction in certain organs (e.g. skin, kidney, spleen), and vasodilation in others (e.g. liver, skeletal muscles), resulting in feelings of tension and vasoconstriction\(^{12}\). Besides the increased activity of the neuroadrenergic system, cortisol and somatotropin production is also increased. Both act in an indirect and prolonged manner to raise blood glucose levels. At blood sugar levels of around 2.8 mmol/L, cognitive dysfunction occurs; further reduction in blood glucose will lead to confusion, lethargy, loss of consciousness, convulsions and coma\(^{13, 14}\). Severe hypoglycaemia may result in permanent neurological damage.

**Cardiovascular consequences of hypoglycaemia**

The effects of intensive glycaemic control on cardiovascular risk have been investigated in multiple studies (VADT, ADVANCE, ACCORD). However, contrary to expectations, cardiovascular mortality was not shown to be lower with intensive treatment than in the less intensively treated patient group in either the VADT or the ACCORD study\(^{15}\). In the VADT study\(^{16}\), the main predictor of cardiovascular mortality was hypoglycaemia (HR: 4.042, CI: 1.449, 11.276, p<0.01).

More than 10,000 patients with a history of major cardiovascular events or a high cardiovascular risk, with pre-existing type 2 diabetes for 10 years on average, and a HbA1c value of 8.1% have been enrolled in the ACCORD trial. In the intensive treatment group of the study, a target HbA1c below 6% was set. The trial had to be terminated after 3.5 years of follow-up, as an increase in overall mortality by 22% (p=0.04) and in cardiovascular deaths by 35% (p=0.02) was observed in the intensive treatment arm. Severe hypoglycaemic episodes, occurring with a threefold higher incidence compared to the non-intensive therapy arm, may have contributed to the higher cardiovascular mortality in the intensive therapy group\(^{17}\).

Hypoglycaemia, primarily as a result of increased sympathetic nervous system activity, also leads to a number of inflammatory (increased levels of CRP, IL-6, IL-8, TNF-α, endothelin-1) and rheological deviations (enhancement of platelet activation, increase of factor VII levels, increased neutrophil leukocyte activation)\(^{18}\), which increase the risk of cardiovascular events due to endothelial damage and increased thrombotic activity. Data obtained from continuous ECG and blood glucose monitoring confirmed that both symptomatic and asymptomatic myocardial ischaemia can occur in coronary artery patients during hypoglycaemic episodes (17).

**Hypokalaemia in hypoglycaemia**

It was observed as early as in the 1920s that insulin-induced hypoglycaemia is accompanied by hypokalaemia\(^{19}\). Due to the increased activity of the sympathetic nervous system in hypoglycaemia, catecholamine levels become elevated. The latter, through beta-2 receptor activation, enhances Na-K ATP-ase activity, which in turn reduces extracellular potassium levels\(^{20}\). Hypoglycaemia may result in a biphasic change in serum potassium levels, where an early, sharp drop, caused by hyperinsulinaemia, is later followed by a slower and protracted increase due to the increasing activity of the sympathetic nervous system. Hypokalaemia can affect the electrical stability of the heart in many ways. On the one hand, a low level of potassium has direct proarrhythmic effects on the ventricular muscles and, on the other hand, it can enhance drug-induced arrhythmogenic effects. As a result, digitalis toxicity may be enhanced and the proarrhythmic effects of catecholamines –
drugs that prolong QT interval and certain antiarrhythmic preparations (e.g. sotalol) – may become more pronounced. Arrhythmogenic susceptibility may be increased in the presence of structural heart disease\textsuperscript{21}.

**Arrhythmia and hypoglycaemia**

The correlation between hypoglycaemia and atrial fibrillation is known\textsuperscript{22}. However, the prolongation of repolarization and QT interval caused by hypoglycaemia\textsuperscript{23} present an even greater risk. No less importantly, hypoglycaemia may also trigger the development of afterdepolarizations, potentially enhancing the increased risk associated with the relevant complications and co-morbidities of diabetes (e.g. cardiac failure, myocardial infarction, left ventricular hypertrophy). The importance of hypoglycaemia-induced QT prolongation lies in the fact that it is an independent risk factor of sudden death as well as Torsade de pointes\textsuperscript{24, 25} (Figure 2).

Evaluation of the R-R and QT interval was performed by two blinded investigators who considered a QTc interval longer than 440 ms as abnormal (Bazett’s formula). The QTc dispersion was calculated based on the difference between the shortest and longest QTc detected in any leads. A QTd longer than 80 ms was considered as abnormal.

![Effect of experimental hypoglycaemia on QTc (20)](fig1.png)

**TABLE I**

<table>
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<th>QTc (ms)</th>
<th>ΔQTc (ms)</th>
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<td>T1DM</td>
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<td>448</td>
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<td>30</td>
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<tr>
<td>Lee\textsuperscript{32}</td>
<td>T2DM</td>
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Abbreviations:
T1DM: Type 1 diabetes mellitus
T2DM: Type 2 diabetes mellitus

The study period lasted for 15 years (from 1991 to 2006). The independent predictor value of QTc and QTd for all-cause and cardiovascular mortality was analysed using the Cox proportional hazards model. Based on the multivariate analysis, the risk of cardiovascular mortality (HR, hazard ratio) significantly increased with the elevation in QTd (HR: 1.26 [95% CI, 1.02–1.55]). However, in this study, prolonged QTc interval was not associated with increased cardiovascular risk\textsuperscript{34}.

In another study involving a much lower number of diabetic patients (MONICA/KORA Augsburg Cohort Study), the effects of decreased heart rate variability (HRV), prolonged

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Prolongation of the QT(c) interval is a risk factor of cardiac death, both in the general population and in many other groups of diseases such as cardiac failure, AMI, type 1 and 2 diabetes.

Several studies have investigated the effects of hypoglycaemia on the QT interval. Significant QTc prolongation has been demonstrated in healthy people and in (type 1 and 2) diabetic patients during hypoglycaemia (Table 1, Figure 3)\textsuperscript{26-32}.

In the EURODIAB (Europe and Diabetes) study (see above), higher HbA1c value, female sex and elevated systolic blood pressure showed correlation with QTc prolongation in subjects with normal baseline QTc interval, while physical activity and normal body weight provided a protective effect. Sawicki at al.\textsuperscript{33} have found that QT dispersion rate is the most important independent risk factor for overall mortality and cardiac and cerebrovascular mortality.

**Effect of QTc on morbidity and mortality in diabetic patients**

The prospective Casale Monferrato Study was seeking to investigate the predictive effect of QTc and QTd on the cardiovascular and overall mortality rate in type 2 diabetic patients. The 1540 patients with type 2 diabetes enrolled in the study lived near Casale Monferrato. ECG findings suitable for evaluation of QTc and QTd were available for 1359 of these patients (580 male and 779 female).
QTc and elevated QTd on mortality were investigated in a 9-year follow-up of older patients (age = 65.2±5.5 years, n=160). As in non-diabetic patients, prolonged QTc was a predictive factor for mortality in diabetic patients (HR3.00 [95% CI 1.34–6.71]; P ≤ 0.007); however, QTd did not have a predictive effect. Reduced HRV did not have a predictive value in this patient population.35

However, in an overall 57-month prospective study conducted by Cardoso at al. in a larger patient population (471, type 2 diabetic patients), the Cox multivariate proportional risk analysis demonstrated that QTc and QTd are independent predictors of cardiovascular and cardiac death (HR: 1.34, 95% CI: 1.12-1.59 for each 10 ms elevation of QTd, and HR: 1.17, 95% CI: 1.03-1.21 for each 10 ms prolongation of QTc, regarding cardiovascular mortality). When the data of subjects with a history of cardiac disease were not included in the analysis, the predictive value of QTd did not change, while that of QTc decreased.36

In the study of Landstedt-Halin et al., the risk of cardiac arrhythmias associated with hypoglycaemic episodes as well as the potential effect of glibenclamide on this risk were investigated in type 2 diabetes mellitus during induced hypoglycaemia.31 Hypoglycaemia was induced by insulin injection and, when the blood glucose level of 2.7 mmol/L was achieved, clamp technique was applied for 60 minutes (T = 90–150 min) to maintain hypoglycaemia in the glibenclamide group (GLIB+) and the non-glibenclamide group (GLIB-), while in the third group, in addition to the hyperinsulinaemia similar to that described above, glucose clamp was used at an euglycaemic value (5 mmol/L). In addition to continuous ECG monitoring, 12-lead ECG was performed at minute 0 and minute 150. The length of QTc intervals was measured, and based on that, the QT dispersion characterising the variability of repolarisation was determined. In this study, the length of QT intervals and QT dispersion significantly increased (p<0.001) during hypoglycaemia both in the GLIB+ and the GLIB- groups, while in the GLIB+ group QTd elevation was shown to be more pronounced, although the difference was not statistically significant. Plasma adrenaline levels significantly increased in the hypoglycaemic groups (p<0.0001). Serum potassium levels were significantly decreased in all three groups (p<0.001), but the reduction was most pronounced during hypoglycaemia. A study in Japan has demonstrated a significantly longer QTc interval in subjects treated with glibenclamide compared to type 2 diabetic patients receiving dietary treatment only.38

The mechanism of QTc change

Basically two main mechanisms can account for the prolongation of the QT interval. One is the sympatoadrenergic system activated by hypoglycaemia that releases adrenaline and noradrenaline into the circulation. The other is the decreasing potassium level caused by increased insulin and adrenaline levels.39 Studies in healthy subjects and type 1 diabetic patients have shown that QTc prolongation due to the increased sympatoadrenergic system activity caused by hypoglycaemia could be resolved by beta-blockade.40 In a study by Robinson et al.41 QTc prolongation could be reduced by administration of potassium infusion, even though the reduction was minor.

QTc prolongation can be observed in autonomic neuropathy occurring as a complication of diabetes, as well as in hypoglycaemia. In hypoglycaemia, repolarisation is prolonged by the inhibition of a rapid component of the delayed rectifier potassium current (IKr), which plays an important role in repolarisation.43

During hypoglycaemia, QT interval will be prolonged due to the increased repolarisation time, and that promotes the development of early afterdepolarization (EAD). It means that, prior to resting potential, a membrane oscillation occurs in the 3rd phase of the action potential in the cells capable of triggered activity. Arrhythmia develops when the oscillations reach the threshold potential in one or more cycles.44 In that case, a new depolarisation occurs before completion of repolarisation, and, spreading to the surrounding cardiac muscle cells with less prolonged repolarisation, may result in extrasystole or high frequency torsade de pointes ventricular tachycardia.45 In addition, diabetes alone increases the sensitivity of cardiac muscle cells to the arrhythmogenic effects of calcium overload, and the functioning of potassium ion currents providing repolarisation reserves that enhance the sensitivity of cardiac muscle cells to QT prolonging effects. Calcium overload may also produce arrhythmia in hypoglycaemia by generating delayed afterdepolarization (DAD).46

III. CONCLUSIONS

In type 2 diabetes mellitus, the prevention of macro- and microvascular complications has a great importance and achieving glycaemic targets forms an integral part of this. However, during the efforts to achieve tight glycaemic control, a significant number of patients experience symptomatic or asymptomatic hypoglycaemic episodes. The noradrenergic system provides fine-tuning to the endocrine pancreas activity
through the function of α- and β-adrenergic receptor and its activation plays a fundamental role in hypoglycaemia. At the same time, hypoglycaemia increases cardiovascular mortality through several mechanisms. Besides there are several studies have suggested that alterations beyond hyperglycemia and commonly found in diabetic patients, including insulin resistance, inflammation, cellular stress, and a low endogenous regenerative capacity may contribute to increase cardiovascular risk in type 2 diabetic patients. In view of all this, it is very important to use medicinal products without hypoglycaemic effect for the treatment of type 2 diabetes mellitus.

REFERENCES


