Hypoglycaemia in the context of cardiovascular health

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Key words

- **cardiac arrhythmia**
- **cardiovascular risk**
- **"dead-in-bed" syndrome**
- **hypoglycaemia**
- **type 1 diabetes**
- **type 2 diabetes**

Abstract

The clinical problem of hypoglycaemia has been with us since the discovery of insulin and is not going away in any foreseeable future. In the context of diabetes, hypoglycaemia is defined as "all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm". Hypoglycaemia has complex, known and yet unknown, negative effects on human body. From the clinical perspective, hypoglycaemia represents a major barrier to the achievement of improved metabolic control and prevention or significant reduction of long-term diabetic complications. The focus of this review paper, which is based on the Somogyi award lecture 2024, will be the effects of hypoglycaemia on the cardiovascular risk and health. I will discuss proarrhythmogenic effects of hypoglycaemia, the efforts to identify the individuals who are at greatest risk of sustaining hypoglycaemia-induced cardiac arrhythmias and the modulatory effects of hypoglycaemia on subsequent innate immune system responses.

Kulcsszavak

- **1-es típusú diabetes mellitus**
- **2-es típusú diabetes mellitus**
- **arrhythmia**
- **„dead-in-bed" szindróma**
- **hipoglikémia**
- **kardiovaszkuláris kockázat**

A hypoglycaemia a kardiovaszkuláris egészség tükrében

A hipoglikémia klinikai problémája az inzulin felfedezésével együtt jelent meg, és előreláthatóan nem is fog eltűnni. A diabétesz kontextusán belül a hipoglikémia „olyan abnormálisan alacsony vércukorkoncentrációval járó epizód, ami potenciálisan ártalmas a betegre nézve". A hipoglikémia számos komplex, ismert és eddig ismeretlen negatív hatást vált ki az emberi testben. Klinikai szempontból a hipoglikémia jelentős akadályt képvisel az ideális anyagcserekontroll elérésében,

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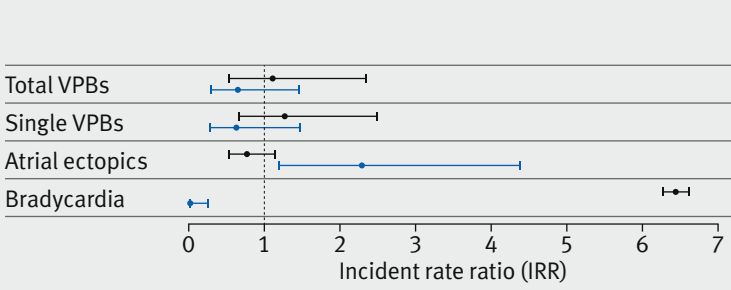
valamint a hosszú távú diabéteszes szövődmények kialakulásának megelőzésében vagy csökkentésében. E cikk a szerző 2024-es Somogyi-díjas előadásán alapul, górcső alá véve a hipoglikémia kardiovaszkuláris kockázatait, proarrhytmiás hatásait, a hipoglikémia okozta szívritmuszavar fokozott kockázatának kitett egyének felismerésére tett erőfeszítéseket, és a hipoglikémia által kiváltott immunrendszeri reakciókra gyakorolt moduláló hatásait.

INTRODUCTION AND HISTORICAL CONTEXT

The clinical problem of hypoglycaemia has been with us since the very start of modern diabetes management hallmarked by the discovery of insulin by *Frederick Banting, Charles Best, John Macleod,* and *James Collip* back in 1921 in Toronto, Canada.[1] As a matter of fact, the first definition of a unit of insulin came from the biochemist *James Collip,* without whom the purification and subsequent first successful use of insulin in a human wouldn't have been possible. In 1922, *James Collip* defined one unit of insulin as *"the amount of insulin required to cause hypoglycaemia in a rabbit".* Of course, this definition has been refined since then, but it gives us a hint about the nature of the first experience with the use of insulin. Moving on to humans, in 1923 *Frederick Banting* writes in his paper "Further Clinical Experience with Insulin (Pancreatic Extracts) in the Treatment of Diabetes Mellitus" on the matter of hypoglycaemia the following: *"Up to the present time no serious mishap has occurred as a result of these hypoglycaemic reactions, but while this is so it is felt that hypoglycaemia constitutes a real source of danger".*[2] Another important biochemist of that time, *Michael Somogyi,* whose expertise in insulin purification significantly contributed to the rapid production of large amounts of insulin required for the management of people with diabetes, argued in 1949 against the use of high amounts of insulin in the management diabetes. *Michael Somogyi* reasoned that such treatment was potentially dangerous and suggested dietary modifications and weight loss instead. These historical observations are perfectly in line with the current understanding of hypoglycaemia and the whole concept of diabetes management, indeed. At present, hypoglycaemia is in the context of diabetes defined as *"all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm".*[3] This joint definition of American Diabetes Association and Endocrine Society covers all, known and yet unknown, detrimental effects of hypoglycaemia on the human body, not only the "classical" autonomic and neuroglycopaenic symptoms of hypoglycaemia that can be found in the textbooks. To be more specific, hypoglycaemia leads to accidents at home, at work and behind the wheel and significantly impairs the quality of life of those affected. Hypoglycaemia potentiates fear from further episodes of hypoglycaemia and this constitutes one of the main reasons why individuals with diabetes fail to achieve optimal glycaemic control. Last but not least, hypoglycaemia has a complex negative effect on cardiovascular health which is the main focus of this review paper.

HYPOGLYCAEMIA AS A CAUSE OF ACQUIRED LONG QT SYNDROME

First suspicion on hypoglycaemia as a potential cause of cardiac arrhythmias was expressed in the seminal paper by *Tattersall* and *Gill* in 1991 in which sudden, unexpected, nocturnal deaths of young and otherwise healthy individuals with type 1 diabetes mellitus (T1DM) were scrutinised.[4] Later on, when further similar reports followed, the term "dead-in-bed" syndrome was introduced to describe these tragic events. The Sheffield based group led by *Simon Heller* researched into this phenomenon and significantly contributed to the perception that hypoglycaemia leads to QT interval prolongation on the resting electrocardiogram (ECG). This was first established in experimental settings by the help of hypoglycaemic clamp studies.[5,6] High amounts of insulin were used in these clamp experiments, however, that often



	Nighttime IRR (95% CI)	p	Daytime IRR (95% CI)	p
Total VPBs	1.11 (0.52–2.35)	=0.801	0.65 (0.29–1.47)	=0.303
Single VPBs	1.27 (0.65–2.50)	=0.488	0.63 (0.27–1.48)	=0.287
Atrial ectopics	0.77 (0.52–1.15)	=0.201	2.29 (1.19–4.39)	**=0.013**
Bradycardia	6.44 (6.26–6.63)	**<0,001**	0.02 (0.002–0.26)	**=0.002**

Figure 1. Incident rate ratios (IRRs) of distinct types of arrhythmias during hypoglycemia vs. euglycemia; comparison between nocturnal (23.00–07.00h) and daytime episodes (adapted from Novodvorsky P. et al.[7])

P values indicate significance of difference in arrhythmia rates during hypoglycemia vs. euglycemia. Values in boldface type indicate statistical significance.

lead to hypokalaemia which per se caused QT interval prolongation. The next obvious question was whether hypoglycaemia could also lead to QT interval prolongation and pro-arrhythmogenic ECG changes in people with T1DM in the clinical settings. To this end, we designed an observational study in which 37 young and otherwise healthy individuals with T1DM up to the age of 50 years (thus matching the characteristics of those affected with the dead-in-bed syndrome described in the initial reports including the one by *Tattersall* and *Gill*) underwent 72 hours of simultaneous blinded continuous glucose monitoring (CGM) and Holter-ECG monitoring. No interference with participants' insulin doses and overall diabetes management from the research team was allowed throughout the course of the study period and individuals were asked to record symptomatic hypoglycaemic episodes into the provided diaries. What were the main findings of the study? First, we observed that nocturnal hypoglycaemia can, in some individuals with T1DM, result in more frequent sinus bradycardia *(Figure 1)*.[7] This was a rather interesting finding, because increased frequency of bradycardia during nocturnal hypoglycaemia is potentially clinically relevant. Bradycardia can lead to so-called early afterdepolarizations (EADs) via increased intracellular calcium concentration in cardiomyocytes.[8] EADs represent one of the most important arrhythmogenic mechanisms promoting arrhythmias in acquired and congenital long QT syndromes including torsade des pointes, polymorphic ventricular tachycardia and ventricular fibrillation.[8] Intriguingly, similar observations of increased frequency of bradycardia during nocturnal hypoglycaemia (in comparison to nocturnal normoglycaemia) were noted by our group in a cohort of individuals with type 2 diabetes mellitus (T2DM) and high cardiovascular (CV) risk[9] suggesting a degree of universality of this phenomenon that seems to be independent on the type of diabetes or the CV risk of the studied population. Admittedly, we didn't observe any clinically significant cardiac arrhythmias throughout the course of the study, perhaps due to its short duration and relatively low number of participants. This mechanism therefore remains a hypothesis that needs to be confirmed in clinical practice. This might be tricky, however, given the rarity of dead-in-bed syndrome and the necessity of simultaneous CGM and ECG monitoring at the time of the event. Other important findings of the study were that hypoglycaemia was far more common than patients with T1DM (and their physicians) thought. In a group of 37 individuals with T1DM of whom only 3 had a confirmed diagnosis of impaired awareness of hypoglycaemia (IAH), approximately 50% of all daytime hypoglycaemic episodes and more than 75% of nocturnal hypoglycaemic episodes were asymptomatic and therefore went unnoticed by the patients. We also confirmed that nocturnal hypoglycaemic episodes lasted on average longer than daytime episodes.[7]

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CAN WE IDENTIFY THOSE AT HIGHEST RISK OF HYPOGLYCAEMIA-INDUCED ARRHYTHMIAS?

It is obvious that hypoglycaemia is very common and the dead-in-bed syndrome or cardiac arrhythmias are fortunately very rare. If we assume a causal relationship between hypoglycaemia and malignant cardiac arrhythmias we need to address this discrepancy and, even more importantly, identify those individuals who are at greatest risk. We took the advantage of the current knowledge on the mechanisms by which hypoglycaemia prolongs QT interval which lead us to formulate and test a hypothesis for our next study *(Figure 2)*. The first and most important mechanism by which hypoglycaemia leads to QT interval prolongation is sympathoadrenal activation mediated via the activation of β-receptors.[10,11] Other two mechanisms are hypokalaemia and direct inhibition of rapid direct rectifier potassium channels (I_{Kr}) in the cardiomyocyte membrane.[12] Salbutamol, a β-adrenoreceptor agonist with predominant β2-activity, which is commonly used for treatment of asthma and chronic obstructive pulmonary disease, has also QT interval prolonging and hypokalaemic effects that are mediated via β2-adrenoreceptor activity *(Figure 2)*.[13] Given the fact that both hypoglycaemia and salbutamol cause QT interval prolongation and hypokalaemia and the mechanisms are similar, we hypothesised that the magnitude of electrophysiological changes induced by salbutamol and hypoglycaemia might relate to each other. If that was the case salbutamol could be used as a simple non-invasive screening tool for predicting an individual's electrophysiological response to hypoglycaemia. We tested this hypothesis on 18 individuals with T1DM who underwent a challenge with 2.5 mg of nebulised salbutamol and 4 weeks later a hyperinsulinaemic-hypoglycaemic clamp (2.5 mmol/l for 1 hour).[14] As expected, both interventions lead to proarrhythmogenic electrophysiological changes, but the magnitude of these changes were not related in a given individual. We discussed the possibility of the electrophysiological response modulation by the concomitant presence of hypokalaemia (present during the clamp experiment but not after salbutamol administration in our study) and by the variable degree of autonomic dysfunction that might have been present in the study participants. We had to conclude that salbutamol cannot be used to assess an individual's electrophysiological response to hypoglycaemia.[14] Up to the present day, we are not able to predict an individual's electrophysiological response to hypoglycaemia. This can only be done by exposing an individual with diabetes to a hypoglycaemic clamp experiment with concomitant ECG recording and that is not feasible for obvious practical and ethical reasons.

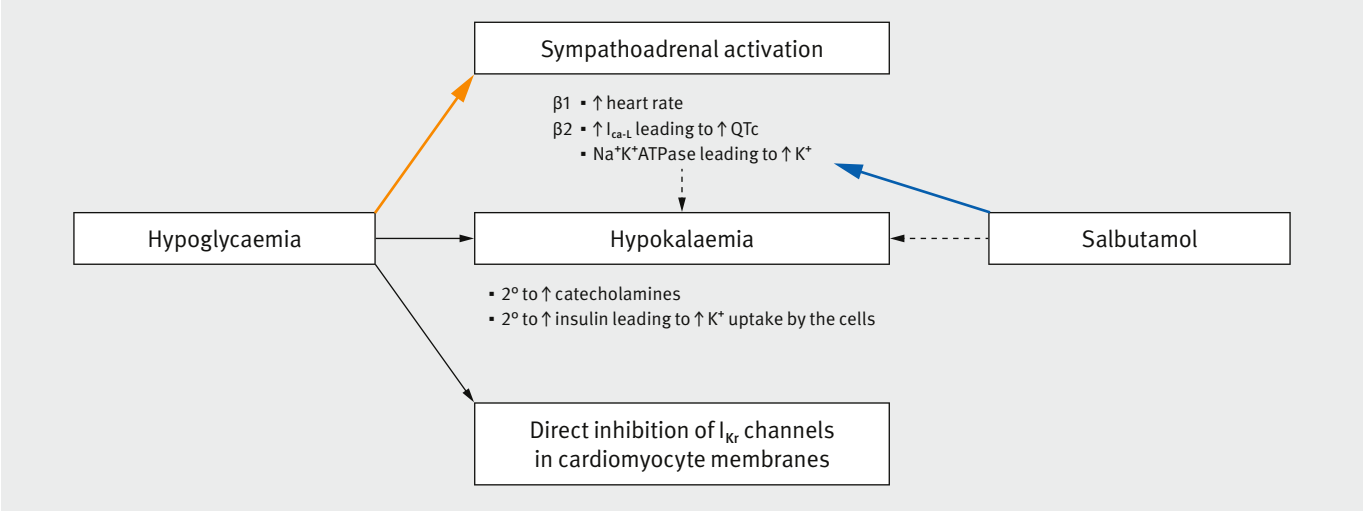

Figure 2. Mechanisms by which hypoglycaemia and salbutamol lead to QT interval prolongation are similar

HYPOGLYCAEMIA AND MODULATION OF SUBSEQUENT INFLAMMATORY RESPONSES

Intensive glycaemic control has a positive effect on the reduction of microvascular complications as evidenced by the hallmark studies in T1DM (DCCT)[15] and T2DM (UKPDS).[16] The evidence for reduction of macrovascular (i.e. atherosclerotic or cardiovascular) complications isn't so straightforward. Significant benefits could be observed only several years after the termination of the original trials.[17,18] Some further larger trials in T2DM populations designed to assess the benefit of intensive (vs. conventional treatment of the time) glycaemic control, such as the ADVANCE[19] or VADT[20] trials didn't show any significant CV benefits and the ACCORD trial had to be terminated prematurely due to the increased risk of overall mortality in the intensive arm of the trial.[21] Severe hypoglycaemia (SH) occurred in much more participants that were randomised into the intensive arms when compared to those who were randomised into the control arms of these trials. In the times when these trials were run CGM technology wasn't available and SH served as a robust and easily recorded event in comparison to non-severe hypoglycaemic episodes which are dependent on subjective perception of hypoglycaemic symptoms that can be diminished. Several lines of evidence confirm that hypoglycaemia has prothrombotic effects and stimulates proinflammatory responses that are of critical importance in the initiation and progression of atherosclerosis.[22] Importantly, as shown in the analysis of the DEVOTE 3 trial, all-cause mortality in participants in whom SH was recorded was elevated in comparison to those in whom no SH was recorded and this increase in mortality persisted long after the incident SH.[23] This observation led us to hypothesise that hypoglycaemia had the ability to modulate subsequent inflammatory responses and that this ability could be one of the mechanisms explaining detrimental effects of hypoglycaemia outside the time when it occurs. We designed a single-blinded prospective trial of three parallel groups in which healthy volunteers underwent clamp studies (hypoglycaemic clamp [2.5 mmol/l for 1 hour], normoglycaemic clamp [5 mmol/l for 1 hour] and sham saline clamp to control for the anti-inflammatory properties of insulin) and four weeks later a stimulation of innate immune system response induced by intravenously administered low-dose bacterial endotoxin.[24] We confirmed that hypoglycaemia stimulated inflammatory responses as evidenced by the increase of total white cell count (caused by the concomitant increase of neutrophils, lymphocytes and monocytes), increase in platelet count and platelet mobilisation and formation of monocyte-platelet aggregates (MPAs). After the administration of endotoxin the anti-inflammatory effects of insulin (which was used in the hypoglycaemic and normoglycaemic groups of the trial) were nearly completely abrogated in the hypoglycaemia group suggesting the modulation of innate immune responses by hypoglycaemia.[24]

CONCLUSION

Hypoglycaemia has complex, known and yet unknown, negative effects on CV health and the human body in general.[25] The recent advantages in diabetes technology, in particular the introduction of advanced hybrid closed loop (AHCL) systems have shown impressive reductions in time spent in hypoglycaemia and have become a standard of care for people with T1DM in developed countries.[26,27] Yet, we cannot assume that the clinical problem of hypoglycaemia will disappear in the foreseeable future. This underlines the necessity of further research into hypoglycaemia and the importance of patient education that has the ability to significantly reduce the frequency of (severe) hypoglycaemia.[28]

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ABBREVIATIONS

CGM: continuous glucose monitoring; **CV:** cardiovascular; **EAD:** early afterdepolarization; **ECG:** electrocardiogram; **SH:** severe hypoglycaemia; **T1DM:** type 1 diabetes mellitus; **T2DM:** type 2 diabetes mellitus

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