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The Relationship between Hypoglycaemic Episodes and Arrhythmias in Type 2 Diabetes Subjects after Acute Myocardial Infarction with ST-Segment Elevation—A Case Series

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Abstract

Background and Aims: Several studies have shown that hypoglycaemia, especially a severe episode is associated with an increased mortality rate in diabetes mellitus subjects with previous cardiovascular disease or acute coronary syndrome. One of the presumed mechanisms is the proarrhythmic effect of hypoglycaemia related to the prolongation of the action potential, or the catecholamine surge that follows an episode. The aim of this case series analysis was to investigate the relationship between hypoglycaemia and glucose variability with arrhythmic events in type 2 diabetes patients who suffered an acute myocardial infarction. **Materials and Methods:** We selected patients admitted consecutively to the cardiology department of Clinical Emergency Hospital in Bucharest for a period of three months with acute myocardial infarction and previously diagnosed type 2 diabetes. For each patient, a retrospective continuous glucose monitoring system (CGMS) or glucose sensor (Medtronic® Enlite, USA) and a dual electrocardiograph and blood pressure monitor for 24 hours were available. Also, patients had an oscillometric device (Arteriograph® TensioMed Ltd) for 24 hours or non-invasive monitoring of central blood pressure, pulse wave velocity and augmentation index. The data were analysed using Medtech®, TensioWin® and Carelink iPro® softwares. We used SPSS® version 20.0 (IBM) for the statistical analysis. The results are presented as median and interquartile range (IQR). **Results and Discussion:** Ten type 2 diabetes patients (4 males, 6 females) with anterior (4/10) and in-

ferior acute myocardial infarction (6/10) were included. They were treated with insulin (3/10), sulphonylurea (Gliclazide) plus Metformin (4/10), Metformin monotherapy (2/10), or all three (1/10). The patients had a median age of 67.5 (3.25) years with a median disease duration of 8 (7.75) years. The median body mass index was 29.54 (5.65) kg/m^2. The median HbA1c was 7.9% (3.15) % and C-peptide 3.3 (2.66) ng/ml. There were no significant differences regarding the number of atrial or ventricular premature beats, ventricular or atrial tachycardia or fibrillation, the duration of QT interval, systolic and diastolic blood pressure, aortic pressure, augmentation index, pulse wave velocity between subjects with hypoglycaemia and those without. There was a negative correlation between QTc and glucose values in patients with hypoglycaemia (Spearman coefficient correlation $r = -0.232$; $p < 0.01$). **Conclusion:** Mild hypoglycaemia in type 2 diabetes patients with systolic dysfunction after ST-elevated myocardial infarction did not increase the number of supraventricular premature beats and QTc duration. We suggest that non-severe hypoglycaemia does not increase the risk of arrhythmias in patients with type 2 diabetes.

Keywords

CGMS, Hypoglycaemia, STEMI, Glycemic Variability

1. Background and Aims

Various studies have established the relationship between hypoglycaemia and cardiac arrhythmias in type 2 diabetes subjects with cardiovascular disease or high cardiovascular risk [1] [2]. In patients with recent acute myocardial infarction with ST-elevation, low admission glucose seems to be a strong predictor of mortality [3]. History of severe hypoglycemia was found to be a risk factor for the development of atrial fibrillation, bradycardia, atrial and ventricular tachycardia as well as atrial and ventricular premature beats in patients with type 2 diabetes [4] [5] [6]. It has been shown that severe hypoglycaemia is correlated with QTc interval prolongation and changes in T wave morphology [2] [7], even without hypokalemia [8]. The degree of QTc prolongation was associated with the severity of the hypoglycaemic event [9], and it does not seem to differ between high-risk insulin-treated diabetic patients and people without diabetes [7]. Among subjects with diabetes, the incidence of cardiac arrhythmias (atrial and ventricular premature beats, atrial tachycardia) tended to be significantly higher in the elderly group [10]. Another retrospective study observed a high rate of newly diagnosed cardiovascular disease (CVD) and mortality in type 2 diabetes patients presenting with severe hypoglycaemia [11].

The timing of the hypoglycaemic event may influence the type of cardiac arrhythmia that occurs. In the awake state, hypoglycaemia leads to more potent activation of the sympathetic nervous system, which results in larger QT prolongation and an increase in heart rate, whereas during sleep, the hypoglycaemia aware-

ness and counterregulatory response are reduced. This translates into longer periods of hypoglycaemia and the predominance of bradyarrhythmias due to increased vagal tonus [12].

The use of beta-blockers could attenuate the proarrhythmic effect of hypoglycaemia by decreasing the extent of the QTc prolongation which is of significant relevance in the management of diabetic patients with coronary heart disease and myocardial infarction [13].

Hypoglycaemia alone might not be the only cause of arrhythmic events in diabetes subjects but also glucose variability. In one study, no association between hypoglycaemic events and cardiac arrhythmias was found, but there was a significant correlation between glucose variability and the incidence of atrial fibrillation and bradyarrhythmias [14]. Glycemic variability determined by a continuous glucose monitoring system (CGMS) appears to be a stronger predictor of poor prognosis than HbA1c in patients with acute coronary syndrome and non-severe diabetes [15] [16] [17]. In another study, increased glucose variability was the most significant independent predictor of midterm major adverse cardiovascular events in diabetes mellitus patients with acute coronary syndrome [18]. Several mechanisms are presumed to be involved, including endothelial dysfunction, increased oxidative stress [19], increased cytokine release [20], induced cardiac ischemia [21], or increased release of hormones like epinephrine or norepinephrine through their vasoconstrictive effect [22]. Different parameters have been used to assess the perturbation of glucose metabolism, beginning with admission blood glucose (AdBG) [23] [24], glycated haemoglobin A1c (HbA1c) [25] [26] or mean amplitude of glycemic excursions (MAGE) recorded by CGMS [16] [27] [28] [29].

On the contrary, hypoglycaemia was not proved to be directly responsible for the excessive mortality that resulted in the group receiving intensified treatment in the ACCORD study (Action to Control Cardiovascular Risk in Diabetes) [30] or ADVANCE (Action in Diabetes and Vascular Disease-PreterAx and DiamicroN Controlled Evaluation) [31], but could not be excluded as an important factor.

Therefore, this case series aimed to observe the relationship between hypoglycaemia, glucose variability and risk of arrhythmias in type 2 diabetes patients after acute myocardial infarction with ST-elevation segment (STEMI).

2. Materials and Methods

This was a single-centre case series that included patients admitted with acute myocardial infarction and previously diagnosed type 2 diabetes in the cardiology department of Clinical Emergency Hospital in Bucharest for three months (between June and September 2016). The diagnosis of STEMI and T2DM were made according to the European Society of Cardiology [32] and American Diabetes Association guidelines [33]. The study respected the Declaration of Helsinki and was approved by the Ethical Committee. Informed consent was ob-

tained from every patient included in the study prior to any trial-related procedure.

The inclusion criteria were: consecutive subjects diagnosed with type 2 diabetes mellitus treated with oral antidiabetic medication and/or insulin; diagnosis of STEMI 4 - 5 days before with haemodynamic stability (blood pressures greater than 100/60mmHg) and without arrhythmias secondary to ischaemia (atrioventricular block, ventricular tachycardia and/or fibrillation) which allowed the subjects to be transferred from the Intensive Care Unit.

Blood samples were collected on admission and the fourth day (after overnight fasting) and stored at −20˚C. The admission sample was analysed for glycaemia, sodium, potassium in the hospital laboratory. The other sample was transported and analysed for glycaemia, HbA1c, C-peptide, insulin, total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, creatinine, uric acid, total calcium, magnesium and phosphorus using BA400 (Biosystems®, Barcelona, Spain) in an external laboratory. Both laboratories are accredited by the Romanian Accreditation Association.

All patients were equipped with a continuous glucose monitoring system (CGMS) (Medtronic Enlite®, USA). After inserting the sensor in the subcutaneous abdominal fat tissue and calibration according to standard operating guidelines, patients were monitored for 72 hours. They monitored their capillary blood glucose at least four times per day using the same OneTouch Select® (Life Scan) glucose meter. The sensor data was downloaded on a computer after this period and analysed with the dedicated software (Carelink iPro®) by a trained diabetologist.

Simultaneously with the installation of the glucose sensor, each subject was equipped with an electrocardiograph and blood pressure Holter for 24 hours (Holter ECG-BP). Afterwards, these were replaced by an oscillometric device (Arteriograph® TensioMed Ltd) for another 24 hours. The data were analysed using Medtech® and TensioWin® softwares by two cardiologists. Echocardiography was performed before discharge for all the subjects. For each subject, we matched the period spent in hypoglycaemia with one in normoglycaemia, and hyperglycaemia respectively. We calculated the MBG based on the Carelink iPro® Excel detailed reports and analysed the median cardiac frequency, number of premature beats, duration of QT, median blood pressures in the same time interval on the Holter ECG-BP monitoring.

We excluded non-STEMI patients, haemodynamically unstable patients admitted to the intensive care unit, and those who did not require treatment for diabetes control.

3. Statistical Analysis

Given the large number of data resulting from complex monitoring systems, we decided to use non-parametric tests (Mann-Whitney U test) for analysis. All data were analysed using SPSS version 20 (IBM, California, USA). The results are

presented as frequencies and percentages for categorical data, and median interquartile range (IQR) for numerical data, given the small number of patients. A p-value less than 0.05 was considered statistically significant.

4. Results

In our case series**,** we included 10 subjects out of which 6 patients were females, with a median age of 67.5 (3.25) years and a median type 2 diabetes duration of 8 (7.75) years. Anterior left myocardial infarction was present in 4 patients, and inferior ischaemia in 6 of them. Regarding cardiologic treatment, all patients had percutaneous coronary intervention followed by standard therapy, including high dose statin, dual antiplatelet therapy, beta-blockers, and anti-hypertensive medication (9 patients with angiotensin-converting enzyme inhibitors and one with an angiotensin receptor blocker). The socio-demographic characteristics and the median values of laboratory tests are presented in Table 1.

Considering the heart failure guidelines [34], five patients had mildly reduced ejection fraction (41% - 50%) and five had a reduced ejection fraction (below 40%). The results of the three-day CGM data, Holter ECG-BP, and arterial stiffness monitoring are presented in Table 2.

Table 1. General characteristics of patients with type 2 diabetes and STEMI.

Variable	Median (IQR)
Age (years)	67.5 (3.25)
Gender (female/male)	6/4
Body mass index (kg/m^2)	29.54 (5.65)
Waist circumference (cm)	108 (14.5)
Neck circumference of (cm)	41 (3.8)
Glucose at admission (mg/dL)	188 (177.5)
Glucose at hospital release (mg/dL)	139.5 (94)
HbA1c (%)	7.9 (3.15)
C-peptide (ng/mL)	3.3 (2.66)
Insulinemia (uUI/mL)	19.05 (21.6)
Total cholesterol (mg/dL)	164.2 (106.62)
LDL cholesterol (mg/dL)	78 (51.4)
HDL cholesterol (mg/dL)	34.9 (5.35)
Triglycerides (mg/dL)	172 (93.75)
Uric acid (mg/dL)	7.15 (3.44)
Sodium (mmol/L)	140 (4)
Potassium (mmol/L)	4.5 (0.6)
Creatinine (mg/dL)	1.03 (0.34)

IQR (Interquartile Range) = Q3 - Q1.

Table 2. CGMS, rhythm and arterial stiffness monitoring results (median values).

Mean blood glucose (MBG) mg/Dl	140 (50.25)
Standard deviation blood glucose (SBG) mg/dL	38.5 (30.5)
Mean amplitude of glycaemic excursions (MAGE)	69 (53.27)
Number of supraventricular extrasystoles	57 (147)
Number of ventricular extrasystoles	182 (259)
Maximum ST depression (mm)	0.74 (0.89)
Maximum ST elevation (mm)	0.70 (0.26)
Minimum QT interval (ms)	387 (37.5)
Maximum QT interval (ms)	540 (80.5)
Diurnal systolic blood pressure (mm Hg)	126 (15)
Diurnal diastolic blood pressure (mmHg)	74 (24.5)
Nocturnal systolic blood pressure (mm Hg)	121 (16.5)
Nocturnal diastolic blood pressure (mmHg)	70 (15)
Systolic blood pressure aorta (mm Hg)	115 (11)
Pulse pressure aorta (mmHg)	49 (14)
Pulse wave velocity aorta (m/s)	10.1 (1.3)
Augmentation index aorta	25.2 (12.8)

Four subjects had episodes of hypoglycaemia during the CGMS monitoring. These were classified as level 1 (mild) hypoglycaemia (between 54 and 70 mg/dl) [35] and were asymptomatic. One subject had three hypoglycaemic episodes and was treated with metformin and a sulphonylurea, Gliclazide. We observed that two more patients treated with Gliclazide had hypoglycaemic events, either in dual therapy with metformin or in association with basal insulin. The time spent in hypoglycaemia for the four patients was 30, 40, 110, and 270 minutes respectively. Four episodes of hypoglycaemia were during the day and three were nocturnal.

Age was not correlated with MBG, MAGE, cardiac frequency, the number of atrial or ventricular premature beats, but was correlated positively with the percentage of supraventricular premature beats (Spearman correlation coefficient = 0.720; $p = 0.029$). Age was correlated with FEVS (Spearman correlation coefficient = −0.722; $p = 0.18$), systolic BP (Spearman correlation coefficient = −0.720; $p = 0.029$), and diastolic BP (Spearman correlation coefficient = −0.717; $p = 0.030$).

We matched the hypoglycaemia period with the Holter-ECG monitoring and analysed the QTc interval and ST modifications. We observed that there were no significant differences regarding the number of atrial or ventricular premature beats, ventricular or atrial tachycardia or fibrillation, the duration of the QT in-

terval, systolic and diastolic blood pressure, aortic pressure, augmentation index, pulse wave velocity between patients with hypoglycaemia and those without. For the same subjects, comparing the period during hypoglycaemia with one with normal blood glucose, the corrected QT interval (QTc) was longer (481 ms versus 439 ms), and with similar BP values.

There was a negative correlation between QTc and interstitial glucose values (Spearman correlation coefficient = −0.232; $p < 0.01$). MAGE was not significantly correlated with the percentage of atrial or ventricular premature beats (correlation coefficient of 0.301 and −0.335), or QT (0.200) ($p > 0.05$).

5. Discussion

In this case series, we observed patients that had concurrent interstitial blood glucose and Holter ECG-BP monitoring during hospital admission and treatment of STEMI. Previous studies demonstrated that glycemic variability (GV) assessed by CGMS in consecutive patients with acute myocardial infarction is more reliable than plasma blood glucose at admission or HbA1c for predicting major adverse cardiac events on short-term (30 days) [15] or long-term (1 year) follow-up [27]. In these studies, GV was an independent predictor after adjusting for GRACE score (Global Registry of Acute Coronary Events).

None of the subjects developed severe hypoglycaemia that required medical intervention. All episodes, either diurnal or nocturnal were asymptomatic. Interstitial blood glucose tended to increase probably after the catecholamine surge, and afterwards, the glycaemia returned to normal after a snack. All episodes were recorded in diabetic subjects treated with sulphonylureas or insulin suggesting that, if possible, these medications should be avoided in the post AMI period.

There was a negative correlation between QTc and interstitial glucose values. The mechanisms behind the altered cardiac repolarization in diabetes subjects could be hyperkalemia secondary to hyperinsulinemia [36] or autonomic dysregulation [37]. However, the potassium levels remained in the normal range in our patients. Similar results were obtained in a separate study [8], in which a correlation was been made between severe hypoglycaemia and QT prolongation, but not hypokalemia. Therefore we suggest altered neural regulation as the possible cause of the increase in QT duration. Also, the severity of ischaemia was related to prolonged QTc interval [38] and could be a confounding factor in our subjects given the fact that all had a reduced ejection fraction. The advanced age was correlated with a lower FEVS, and the percentage of supraventricular premature beats, but this variable did not influence the ventricular ones.

Three of the four patients that had hypoglycaemia were treated with Gliclazide and the other one with insulin therapy. Previous studies showed that this class of medication is not associated with increased mortality after STEMI [39], and arrhythmias were less frequent in patients treated with Gliclazide [40]. In survivors after myocardial ischaemia, glucagon-like peptide-1 receptor agonists (GLP-1

RA) are associated with a lower risk of re-infarction and stroke when compared to sulphonylurea, therefore being a better option in these patients [41]. None of our patients was treated with GLP-1 RA or sodium-glucose co-transporter 2 inhibitors. In the SWEDEHEART registry, the use of GLP-1 RA was also small with only 2% of patients using this class after surviving a cardiovascular event [41].

Withal, beta-blocker therapy was associated with a lower ventricular arrhythmia risk in an observational study [42]. All our subjects had this class in their management, and this could explain the lack of correlation between hypoglycaemia and the number of ventricular premature beats.

In a prospective study [43], adverse cardiovascular outcomes were associated with higher aortic stiffness in patients with STEMI. Median aortic pulse wave velocity (PWV) was lower than in our patients (6.6 m/s versus 10.1 m/s). In the adjusted analysis, diabetes was not associated with PWV, but other studies showed higher values in this population [44] [45].

The advantages of our case series are the originality of the research, being, to our best knowledge, the first one that associated CGMS with Holter ECG-BP monitoring, followed by oscillometric BP measurements, and addressing the pro-arrhythmic risk from the perspective of hypoglycaemia or antidiabetic medication. The main limit is the small number of patients; this series of cases was intended to be the pilot research for a prospective observational study including a larger number of patients. Also, only a few episodes of mild hypoglycaemia (level 1) were registered, thus longer concurrent use of Holter ECG-BP and CGMS are needed for better observation of mutual influence. There are other factors like the beta-blocker treatment, autonomic dysfunction that may influence the correlations, whose effect could not be studied individually.

6. Conclusion

Mild hypoglycaemia in type 2 diabetes patients with systolic dysfunction after ST elevated myocardial infarction did not increase the number of supraventricular premature beats and QTc duration. We suggest that non-severe hypoglycaemia does not increase the risk of arrhythmias in patients with type 2 diabetes.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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