History of severe hypoglycemia in type II diabetes mellitus unmasked significant atherosclerotic coronary artery disease: a matched case-control study

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Research

Keywords: Severe hypoglycemia, coronary artery disease, CT coronary angiography, coronary artery calcium scoring, C-reactive protein

Posted Date: October 29th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-97651/v1

Abstract

Background

History of severe hypoglycemia (SH) has been associated with cardiovascular (CV) events among patients with type II diabetes mellitus (T2DM). In this study, we screened patients with SH for atherosclerotic coronary artery disease (ACAD) .

Methods

We conducted a matched case-control study involving 28 T2DM patients with SH within the last 5 years with no documented ACAD and matched them with 28 T2DM patients with no SH. All subjects underwent coronary artery calcium scoring (CACS) followed by CT coronary angiography (CCTA) if indicated.

Results

History of SH in T2DM was associated with 78% (22 out of 28) incidence of significant ACAD compared to 46% (13 out of 28) in those without SH, based on either CACS≥400, or at least one coronary artery with ≥50% stenosis from CCTA, (P =0.026).

Conclusion

This study supported that SH in T2DM is associated with ACAD compared to T2DM without SH.

Introduction

Hypoglycemia is a common adverse complication of intensive glycemic control in several T2DM prospective studies. Severe hypoglycemia (SH) on the other hand, where patients require third party intervention to rectify the hypoglycemia, has been identified to be one of the strongest predictors of cardiovascular events, adverse clinical outcomes and mortality in people with T2DM.[1–4]

Hypoglycemia affects the cardiovascular system via several physiological process such as augmented sympatho-adrenal responses, electrophysiological derangements which precipitate arrhythmias, increased cardiac workload leading to potential reduction of myocardial perfusion, tendency of a prothrombotic state and systemic release of numerous inflammatory markers.[5–9] These physiological responses to hypoglycemia may be harmful for people with a long history of T2DM, as they may have already developed significant atherosclerotic coronary heart disease, autonomic dysfunction, and underlying cardiomyopathies.

Most T2DM patients who developed episodes of SH are treated as having isolated events due to consequences of therapy, inadequate caloric intake, or strenuous exercise. They are only subjected to extensive CAD screening when they develop symptoms suggestive of coronary artery disease (CAD) or are admitted for acute coronary syndrome.

We seek to answer the question of whether T2DM patients with SH have higher incidence of ACAD compared to those without history of SH. Currently no study has been done to objectively determine the severity of ACAD in T2DM patients with a history of SH. The finding of this study will aid us in deciding whether we should treat episodes of SH in T2DM patients as an indicator of significant ACAD.

Methods

Research design and participants

This is a case-control study conducted in our institution from December 2019 till July 2020. We recruited 28 T2DM patients with a history of SH within the last five years and closely matched them with 28 T2DM patients with no history of SH.

Our inclusion criteria for our case cohort were T2DM patients with a history of glucometer documented SH within the last five years. Our exclusion criteria were type 1 diabetes mellitus, age under 40 years old, creatinine clearance of less than 30 ml/min/1.73 m^2, established ACAD before index CT scan, established risk of developing SH such as advanced malignancy, advance chronic liver disease, adrenal insufficiency, and deliberate overdose on oral hypoglycemic agents or insulin.

For the definition of SH in our study, we set no minimum capillary glucose levels as each patient varies in his or her threshold for developing symptoms of hypoglycemia. We included any episode of symptomatic hypoglycemia that required third party intervention such as administration of oral or intravenous glucose or glucagon administration and upon correction brought resolution of the hypoglycemic symptoms. Recurrent SH is defined by episodes of more than one SH in a span of at least a month. All of our T2DM patients had their capillary blood glucose tested prior to the treatment of the SH.

Comparison between both groups were done based on 3 main parameters. First is clinical CVD risk scoring; second is levels of inflammatory biomarkers and third is by CT imaging. For clinical CVD risk scoring, we used two risk scores, which is the American College of Cardiology/American Heart Association (ACC/AHA) (2013), and Framingham (2008) risk CVD risk scores, as their use were the most widespread. Both risk scores predict the risk of CVD within the next 10 years.[10–11]

We had chosen high-sensitivity C-reactive protein (hs-CRP) as an inflammatory biomarker of choice as it is well known to prognosticate CVD risk based on multiple epidemiological and interventional studies. [12–13] We had also chosen serum MMP-9 level to demonstrate the degree of arterial inflammation, and risk of plaque destabilization and rupture. In coronary atherosclerosis, there is an enhanced expression of this MMP which is predictive of the severity of the disease.[14–17]

For objective determination of severity of CAD, we had chosen coronary calcium score and CCTA, as many studies indicate that a negative CCTA and CACS of zero can effectively rule out obstructive CAD. In a 2008 meta-analysis, 64-slice CCTA had a sensitivity of 99% and negative predictive value (NPV) of

100% for patient-based detection of significant CAD. As all our study patients were asymptomatic, a non-invasive test will be a more acceptable modality for the diagnosis of ACAD.[18–22]

Ethics statement

This study protocol was reviewed and approved by the ethics committee of our institution. Written consent was obtained from all patients involved in the study prior to their participation. All patients were counselled and understood on the risk and benefit of their involvement in the study.

Data Collection

Sample size calculation

We utilized the Kelsey formula for our sample size calculation. We set 80% as the expected prevalence of significant CAD in T2DM patients with history of SH, and 50% as prevalence of significant CAD in the general T2DM patients without history of SH. We calculated the ratio of population of T2DM patients to the T2DM patients with prior SH to be 15.67, as prevalence of SH in T2DM patients was 6% in a recent meta-analysis.[23] The minimum sample size calculated was 24 subjects, for which we recruited 28 patients each in the case and control arms, to compensate for any study dropouts.

Laboratory measurements

Laboratory blood biochemistry measurements were done at the Department of Chemical Pathology of our institution. Tests included full blood count, renal profile, fasting lipid profile, hemoglobin A1c, and high sensitivity CRP. For serum MMP-9 levels, we used the MMP-9 ELISA test kit (BioLegend®, United States of America) and were done in duplicates at our research laboratory. To reduce the confounding effects of acute inflammation on hs-CRP or MMP-9 levels, we performed venesection at least 2 weeks from any history of febrile episodes.

CT scan protocol

For our CACS and CCTA protocol, we used a single fast-gated 640 slice helical CT, (Toshiba Aquilion ONE™, Japan). A non-contrast-enhanced, prospectively ECG-triggered CT was performed initially to calculate the Agatston CACS. CCTA was performed afterwards, with an intravenous injection of a bolus (80–100 ml at 4–6 ml/s) of non-ionic iodinated contrast agent (iopromide 370 mg/ml, Ultravist 370™, Bayer Healthcare, Germany) followed by a saline chaser (50 ml at 4–6 ml/s). If the heart rate was > 65 bpm, beta-blockers (oral metoprolol 50–100 mg) were provided if tolerated. Sublingual nitroglycerin (0.5 mg) was also administered before the examination to optimize small coronary vessels visualization.

For patients with extremely high CACS (≥ 800 Agatson units), the interpretation of the CCTA images will be suboptimal due to the high degree of calcification obscuring the true lumen of the vessel, thus reducing the specificity for detection of ACAD. Thus most of these patients were excluded from

proceeding with CCTA to avoid the possibility of false negative results.[24] Comparison of severity of ACAD based on CCTA was only done with patients who completed CCTA investigation.

CT scan data analysis

An overall CACS was documented for each patient based on the scoring algorithm of Agatston et al., where coronary artery calcium was identified as a dense area greater than 1 mm^2 in the coronary artery exceeding the threshold of 130 Hounsfield units.[25] Level of CACS ≥ 400 was chosen as the cutoff level of significant ACAD. [26–27] All CCTA investigations were evaluated by two experienced observers, using a standard approach of analysis.

We created two simple CAD severity scoring based on the CCTA for this study. First, percentage of coronary artery segments involved, that is the percentage of coronary artery segments with plaques regardless of degree of stenosis, e.g. 0% = no plaque involvement in all segments; 100% = all segments were involved with plaque. Second, percentage of severity of segment stenosis, percentage of total sum of scores of all segments based on severity of stenosis to maximum possible score, 0 = no plaque, 1 = plaque present, or mild stenosis < 50%; 2 = moderate stenosis 50–75%; 3 = severe stenosis, > 75%.

Statistical Analysis

Categorical variables are displayed as frequency rates and percentages, and continuous variables are shown as mean (standard deviation, SD) if they are normally distributed, and median (interquartile range, IQR) for non-normally distributed data. The means for continuous variables were compared using independent group t-tests in normally distributed data. Otherwise, the Mann-Whitney U test was used. Proportions for categorical variables were compared using the $\chi 2$ test, although the Fisher exact test was used when data were limited. All statistical analyses were performed with SPSS, version 25.0 (IBM Corp) for Windows. A 2-sided $P < 0.05$ was deemed statistically significant.

Results

A. Baseline characteristics of patients with SH and without SH

We matched our case and control cohort accordingly to minimize confounding factors for CAD such as age, gender, race, BMI, duration of diabetes, smoking status, family history of CAD in first degree relatives, history of cerebrovascular accidents, medication usage, and creatinine clearance, as shown in

Despite matching baseline characteristics, patients with history of SH had a higher median ACC/AHA CVD risk score and Framingham risk score of more than 30%.

For laboratory investigation, T2DM patients with SH had higher total cholesterol and LDL-C, but lower HDL-C and HbA1c levels. This might accounted why these patients had higher clinical risk scores and were more susceptible to SH as a result of having a lower Hba1c level.

Hs-CRP level was significantly higher among patients with history of SH as compared with patients without history of SH (P = 0.029). This indicated that patients with a history of SH had a higher degree of pro-inflammatory state, with subsequent greater risk of plaque rupture and destabilization.

(Table 1)

B. Comparison of CCTA and CACS between group with SH and no SH

We performed CACS for every patient, where 12 (21%) patients (10 from SH group, 2 from non-SH group) did not proceed with CCTA mostly due to extremely high CACS (≥800) which affects the objective interpretation of the CCTA, or technical issues such as suboptimal images, or uncontrolled heart rate.

Median CACS was statistically significantly higher in the SH group as compared with the non-SH group. For CACS subgroup analysis, SH group had fewer patients with CACS 0 and CACS<100, but more patients in the CACS≥100, CACS 100-399, and CACS ≥400 categories.

In terms of CCTA features, SH group has fewer patients with no significant stenosis. Patients in the SH group had more prevalent obstructive CAD in each of the epicardial coronary arteries, with statistical significant finding for the right coronary artery. Both scores that we created to compare the severity of coronary artery disease were also higher in the SH group, mean percentage of segments involved and mean percentage of segment severity.

The SH group had more patients with significant CAD, based on CACS ≥400, and/or presence of at least one epicardial coronary artery stenosis ≥50%, with OR 4.231, CI 1.314-13.617, P = 0.026. The prevalence of significant ACAD in the control T2DM patients, 46.4% correlated with previous studies which employed CCTA for detection of significant CAD.[28-29]

(Table 2)

C. Subgroup analysis within SH group

i. Recurrent SH vs single episode of SH

There were 5 (18%) patients with recurrent episodes of SH. Comparison between patients with recurrent SH and single episode of SH, showed these patients to be older, and had lower creatinine clearance which might had explained the higher risk of recurrent severe hypoglycemia. All the patients with recurrent SH had significant CAD. Their hs-CRP and MMP-9 values were also higher signifying greater risk of CV events. Their CACS values were also statistically more significant, however due to most patients having extremely high CACS values of more than 800, CCTA were not performed in this group of patients.

(Table 3)

ii. Onset of SH within the first month vs more than 1 month

There were 10 (36%) patients who were investigated within the first month of the occurrence of SH. Hs-CRP and MMP-9 levels were higher in this group as compared to those who had SH more than a month ago, signifying possible temporal association of SH with the process of inflammation and risk of plaque rupture.

(Table 4)

Discussion

This study has proven that T2DM patients who had a history of SH had a higher clinical CV risk scores, higher biomarker values, and based on imaging, a more severe degree of coronary artery disease as compared with those without any history of SH. The odds of having significant ACAD in patients with a history of SH based on this study was 4-fold as compared with other T2DM patients with no history of SH with matched baseline characteristics, OR 4.231, CI 1.314–13.617, $P = 0.026$.

The relationship between SH and CV events and mortality are supported by retrospective analysis of randomized clinical trials, cohort studies, and meta-analyses. The adjusted hazard ratios for total mortality of patients experiencing at least one episode of SH in comparison with those with no SH in large prospective randomized trials have been calculated to be between 1.67 and 4.28.[30] What is missing in these data is the extent of the severity of ACAD in these patients that contributed to the higher risk of mortality.

To our knowledge, there was no previous study performed to objectively compare the severity of CAD in T2DM patients who had history of SH as compared with T2DM patients who never had SH. Our study had excluded patients with advanced renal impairment (creatinine clearance less than 30 ml/min/1.73 m^2) and matched them according to multiple CVD risk factors to determine whether history of SH in an independent risk factor for severe ACAD.

SH has been known to promote atherogenic state by hypersecretion of catecholamines and proinflammatory cytokines, leading to platelet aggregation.[31] Apart from that, long-term cardiovascular effects by repeated hypoglycemia can lead to increased endothelial dysfunction and a proinflammatory state, which contributed further to atherosclerosis. In the acute state, hypoglycemia increases susceptibility of the myocardium to post-ischemic reperfusion injury and hampers the patient's ability for ischemic preconditioning.[32]

This study supported the inflammatory effects of SH on the cardiovascular system, as patients with SH had higher hs-CRP values, indicating that these patients are at a higher atherogenic and inflammatory state. Serum MMP-9 values, which is a marker of potential plaque destabilization and risk of rupture in ACAD were also higher in this population. In addition, we demonstrated the dose-response feature of SH, in which recurrent SH had higher CACS, hs-CRP, and MMP-9 values as compared with those with single episode of SH.

Another significant finding is the temporal association between onset of SH and adverse cardiovascular outcome. In this study, hs-CRP and MMP-9 values were higher in the group with SH investigated within the first month of developing SH as compared beyond the first month. Previous studies had shown that risk for CV events were higher within the first year of onset of SH, as compared with later years.[35]

Doubts had been raised regarding the precise pathophysiological link between SH and CVD. Two large randomized control trials, the double-blind Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) 3 trials and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) did not show a significant result upon adjustment, between history of SH and subsequent CV events.[33–34] Due to such inconsistent results, SH was only argued as a risk factor for CVD rather than a direct causality of CVD, as SH arguably occurs mostly in patients with advanced diabetes, advanced renal disease or on multiple OHA or high doses of insulin who already have higher risk for CVD to begin with.

The issue of direct causality link between severe hypoglycemia and CVD proves to be difficult, as a prospective intervention study to compare a group with SH and without SH is needed. However, a large retrospective analysis done in Korea by Jae Seung-Yun et al (2019). has assessed causality of SH with CVD, by looking at strength, temporality, dose–response, consistency, and biological plausibility of the relationship, which were all significant in this respective study.[35]

Based on the recent Malaysian guidelines on the primary and prevention of CVD, it was suggested to adjust anti-diabetic medications to reduce the risk of hypoglycemia. A less stringent approach to the glycemic target will also be needed. Their overall CV risk profile should be reassessed and optimized to reduce the risk of CVD.[36] On the issue of screening asymptomatic patients for ACAD based on prior SH alone, there is no randomized clinical trial to determine if screening of CVD is beneficial. We recommend an individual approach based on a premise of strict CVD risk stratification.

Numerous studies have enumerated the fact that screening asymptomatic diabetic patients for CAD makes no difference to the final outcome, even in patients with confirmed subclinical CAD.[37–39] Bear in mind that most patients who developed SH already had multiple risk factors for CAD, such as advanced age and chronic kidney disease.[40]

Limitations And Strengths

We identified a few limitations in the study. First it was performed in a single center and was limited to a specific geographical area. Large-scale studies involving multiple centers throughout the world are needed to validate our results. Our definition of significant ACAD is also based on anatomical assessment of coronary artery disease. If combined with functional assessment such as myocardial perfusion imaging, a more prognostic value could be added.

The strength of this study was that our case cohort was mainly based on patients with capillary blood glucose documented episodes of SH, and not based on any unsubstantiated claim that lead to misclassification of SH. We also compared our case cohort with controls of matched risk factors, thus reducing confounding factors affecting severity of ACAD. For objective assessment of ACAD, we employed a rather accurate and reproducible imaging technique by means of CCTA and CACS.

Conclusion And Relevance

This study showed the prognostic importance of prior history of SH on severity of CAD, and the biological plausibility, dose response and temporal association to it. In patients who experienced SH despite not having typical CAD symptoms, timely cardiac assessment will be vital to prevent future major cardiovascular outcomes. A larger and more objective study perhaps is needed to discern the direct causality of SH on severity of CAD.

Abbreviations

SH: severe hypoglycemia

T2D: type II diabetes

ACC/AHA: American College of Cardiology/American Heart Association

ACAD: atherosclerotic coronary artery disease

CV: cardiovascular

CVD: cardiovascular disease

CCTA: coronary CT angiography

CS: calcium score

Hs-CRP: high sensitivity C-reactive protein

MMP-9: matrix metalloproteinase-9

LMS: left main stem

LAD: left anterior descending artery

LCx: left circumflex artery

RCA: right coronary artery

D1: diagonal 1 artery

OM: obtuse marginal artery

Declarations

Ethics approval

This study protocol was reviewed and approved by the Ethics committee of UKM Medical Centre, reference number, FF-2019-391. All patients were counselled on the risk and benefit of performing the study, and fully understood about it.

Consent for publication

Written and/or verbal consent was taken from each patient.

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

Funding

Our study was funded by the faculty of medicine research grant, reference number, FF-2019-391.

Authors' contributions

NAK, NS, and MAR conceptualized the research design and methods. TWJ, SFM, SG, HH, and NDMF recruited patients for the study, collected baseline data from the patients, and followed up patients based on their report. HAH interpreted and reviewed CCTA images and verified the calcium score calculations. AMN performed statistical analysis of the study. MAR prepared the original draft. Data editing also was performed by all authors. All authors read and approved the final manuscript

Acknowledgements

We would like to acknowledge Madam Amyliaton MR from Clinical Research Lab, Department of Medicine, UKMMC, for performing the ELISA test for serum MMP-9 levels in the study.

CT scan unit, Department of Radiology, UKMMC for providing necessary facilities to implement our study.

Department of Pathology, UKMMC for performing baseline laboratory investigations for our study patients.

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Tables

Due to technical limitations, table 1 to 4 is only available as a download in the Supplemental Files section.

Supplementary Files

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