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History of Severe Hypoglycemia in Type 2 Diabetes Mellitus Unmasked Significant Atherosclerotic Coronary Artery Disease: A Comparative Case Control Study

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Abstract

Objectives. A history of severe hypoglycemia (SH) is associated with cardiovascular (CV) events among patients with type 2 diabetes mellitus (T2DM). In this study, we compared the severity of atherosclerotic coronary artery disease (ACAD) in T2DM patients with and without a history of SH.

Methodology. We conducted a comparative case-control study involving 28 T2DM patients with a history of SH within the last 5 years with no documented ACAD, and matched them with 28 T2DM patients with no history of SH. All subjects underwent coronary artery calcium scoring (CACS) with or without coronary computed tomographic angiography (CCTA) to evaluate the severity of ACAD.

Results. A history of SH in T2DM was associated with a higher prevalence of significant ACAD (79% versus 46%, *p*=0.026). A high CACS (≥100) was seen in a greater number of patients with a history of SH compared to those without (75% versus 43%, *p*=0.029). Similarly, there was a higher prevalence of obstructive CAD in those with a history of SH compared to those without (72% versus 39%, *p*=0.036). Median C-reactive protein level was also higher among patients with a history of SH (0.41 mg/dL versus 0.16 mg/dL, *p*=0.029).

Conclusion. In patients with T2DM, a history of SH is significantly associated with ACAD compared to those without SH. A history of SH warrants screening for ACAD.

Key words: hypoglycemia, coronary artery disease, type 2 diabetes mellitus, C-reactive protein

INTRODUCTION

Hypoglycemia is a common adverse complication of intensive glycemic control in several T2DM prospective studies. When a patient requires third party intervention to rectify hypoglycemia, the event is called severe hypoglycemia (SH). SH 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 augmented sympatho-adrenal responses. These cause electrophysiologic derangements which precipitate arrhythmias, an increase in cardiac workload leading to potential reduction of myocardial perfusion, and a tendency to induce 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 atherosclerotic coronary artery disease (ACAD) screening when they develop symptoms suggestive of CAD or are admitted for acute coronary syndrome.

We sought to compare the prevalence of ACAD in patients with T2DM with and without a history of SH. To our knowledge, there are no published studies that have objectively determined the severity of ACAD in T2DM patients with a history of SH and its relationship with inflammatory biomarkers. Our findings may help aid us in understanding SH in T2DM patients as an indicator of significant ACAD.

METHODOLOGY

Research design, setting and participants

This is a comparative case-control study conducted in our institution from December 2019 to July 2020. We recruited

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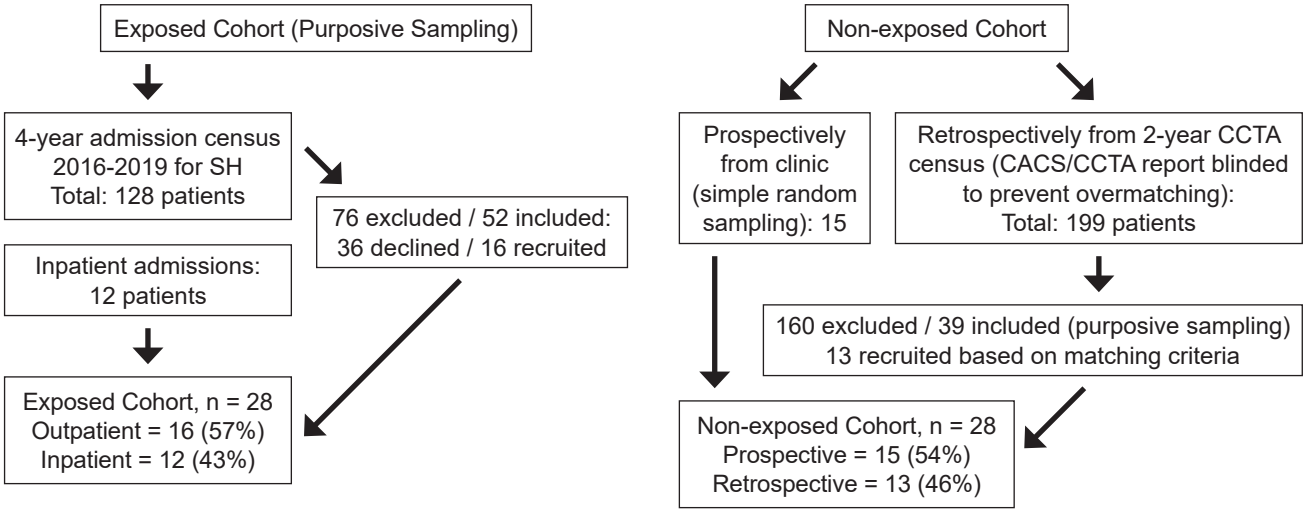

Figure 1. Patient recruitment flow chart.

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.

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

Our matching criteria for both cohorts were calculated based on propensity score matching on characteristics such as age, gender, ethnicity, duration of diabetes, smoking status, comorbidities, functional status, body mass index, creatinine clearance and type of medications.

For the definition of SH in our study, we did not set a minimum capillary glucose level, 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 administration of glucagon, with resolution of hypoglycemic symptoms after correction. Recurrent SH was defined as more than one episode of SH in a span of at least a month.

To reduce the probability of misclassification bias for any history of SH, we recruited patients with a diagnosis of SH and glucometer-documented reading during admission from our discharge registry. To address misclassification bias to ensure the absence of baseline ACAD, medical records were reviewed to determine documented history of ACAD rather than relying on recall. As the number of patients with a history of SH (exposed cohort) was scarce, purposive sampling was done to accomplish the minimal sample size. For the cohort without a history of SH (non-exposed cohort), prospective patients were sampled with simple random sampling after the exposed cohort were recruited. Retrospective patients were sampled based on matching criteria with the blinded CACS/CCTA report (Figure 1).

During recruitment of the exposed cohort from our hospital database, 52 out of 128 patients met the inclusion criteria. Sixteen patients agreed to volunteer for the study; the other 36 patients refused to be recruited or were uncontactable. As our study incorporated CT scan and intravenous contrast administration, most were reluctant to proceed. To attain the minimum number of patients, we also recruited inpatients who had episodes of severe hypoglycemia who required interventions.

Our study outcomes were based on three main parameters. For the first parameter, clinical CVD risk scoring, we employed the widely used American College of Cardiology/American Heart Association (ACC/AHA) (2013) and Framingham (2008) CVD risk scores. Both risk scores predict the risk of CVD within the next 10 years.[10,11]

For the second parameter, levels of inflammatory biomarkers, we used high-sensitivity C-reactive protein (hs-CRP) as it is well known to prognosticate CVD risk based on multiple epidemiological and interventional studies.[12,13] We also used serum matrix metalloproteinase-9 (MMP-9) 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 disease.[14-17]

For the third parameter, severity of ACAD, we used coronary artery calcium scoring and coronary computed tomography angiography, 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 of 100% for patient-based detection of significant CAD. As all our study patients were asymptomatic, a non-invasive test was a more acceptable modality for the diagnosis of ACAD.[18-22]

Selection bias was minimized via purposive sampling of our exposed cohort based on our inclusion and exclusion

criteria. Patient selection for the non-exposed cohort was performed using simple random sampling from the outpatient clinics.

Ethics statement

This study protocol was reviewed and approved by our institutional review board for ethics (Internal Review Board Reference Number: FF-2019-391). Written consent was obtained from all patients involved in the study prior to their participation. After proper counseling, all patients understood the risks and benefits of their involvement in the study.

Sample size calculation

We utilized the Kelsey formula with two-sided significance level of 95%, power of 80% and 1:1 participant ratio for both groups in our sample size calculation. As there are no studies in literature on the prevalence of ACAD in persons with T2DM with a history of SH, we set 80% as the expected prevalence of significant CAD in T2DM patients with history of SH, and 40% as the expected prevalence of significant CAD in the general population of T2DM patients without a history of SH.[23] The minimum sample size calculated was 26 subjects. 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 (HbA1c) and hs-CRP. For serum MMP-9 levels, we used the MMP-9 ELISA test kit (BioLegend®, United States of America) and performed duplicate tests 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.

Computed tomography 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 CACS using the Agatston method. CCTA was then performed with an intravenous injection of a bolus (80 to 100 mL at 4 to 6 mL/s) of non-ionic iodinated contrast agent (iopromide 370 mg/mL, Ultravist™, Bayer Healthcare, Germany) followed by a saline chaser (50 mL at 4 to 6 mL/s). If the heart rate was monitored to be >65 beats per minute, beta-blockers (oral metoprolol 50 to 100 mg) were provided if tolerated. Sublingual nitroglycerin (0.5 mg) was also administered before the examination to optimize visualization of small coronary vessels.

For patients with extremely high CACS (≥800 Agatston 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. 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 in patients who completed CCTA investigation.

Computed tomography 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] A CACS level of ≥400 was chosen as the cutoff level of significant ACAD.[22,26] All CCTA investigations were evaluated by two experienced observers, using a standard approach of analysis.

We created two simple CAD severity scoring methods based on the CCTA for this study. The first describes the percentage of coronary artery segments involved, that is, the percentage of coronary artery segments with plaques regardless of degree of stenosis (e.g., 0% indicating no plaque involvement in all segments and 100% indicating all segments were involved with plaque). The second describes the percentage of severity of segment stenosis, calculated as the percentage of total sum of scores of all segments based on severity of stenosis to maximum possible score (e.g. 0 indicating no plaque, 1 with plaque present or mild stenosis at <50%, 2 with moderate stenosis of 50 to 75%, and 3 with severe stenosis of >75%).

Statistical analysis

Categorical variables were presented as frequency rates and percentages. Continuous variables were depicted as mean [standard deviation (SD)] if they were 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 χ^2 test, although the Fisher exact test was used when data were limited. All statistical analyses were performed with SPSS® (version 25.0) (IBM®) for Windows. A 2-sided $p<0.05$ was deemed statistically significant.

RESULTS

Baseline characteristics

Despite matching baseline characteristics, patients with a history of SH had higher median ACC/AHA CVD and Framingham risk scores of more than 30%, but the difference did not reach statistical significance.

For laboratory investigation, T2DM patients with a history of SH had higher levels of total cholesterol and low density lipoprotein-cholesterol (LDL-C), but lower levels of high density lipoprotein-cholesterol (HDL-C) and HbA1c levels. This might account for the higher clinical risk scores and susceptibility to SH. However, all the differences failed to reach statistical significance.

The hs-CRP levels were significantly higher among patients with a history of SH, compared to those without (p=0.029). This finding suggests 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).

Comparison of CCTA and CACS

We performed CACS for all patients. However, 12 (21%) patients (10 from the SH group and 2 from non-SH group) did not proceed with CCTA mostly due to extremely high

Table 1. Baseline characteristics

Characteristics	Severe Hypoglycemia		*p* value
	Yes (n=28)	No (n=28)	
Demographic			
Female gender (%)	15 (54)	15 (54)	1.000
Age†, year (SD[a])	65.35 (8.99)	64.54 (8.74)	0.730
Background and Comorbidities			
Hypertension	24 (86)	25 (89)	1.000
Hyperlipidemia	25 (89)	27 (96)	0.611
Obese (body mass index ≥30 kg/m^2)	2 (7)	5 (18)	0.422
Active smoking	7 (25)	8 (29)	1.000
History of CVA[b]	4 (14)	4 (14)	1.000
Clinical Parameters			
Body mass index†, kg/m^2 (SD[a])	24.99 (3.56)	25.14 (4.91)	0.893
Systolic blood pressure†, mmHg (SD[a])	130.82 (11.20)	130.21 (11.57)	0.843
Duration of diabetes‡, years (IQR[c])	10 (6.25-20.00)	10 (6.50-14.75)	0.987
On a sulphonylurea	9 (32)	9 (32)	1.000
On insulin injection	9 (32)	8 (29)	1.000
Framingham (2008) Score >30%	18 (64)	15 (54)	0.587
ACC/AHA CVD Risk Score[d]‡, (IQR[c])	25.90 (14.25-35.95)	22.40 (8.88-31.83)	0.461
Laboratory Results			
HbA1c[e]‡, % (IQR[c])	6.85 (6.25-9.73)	7.90 (6.65-9.10)	0.333
Creatinine clearance†, mL/min/1.73 m^2 (SD[a])	72.91 (19.88)	71.68 (22.92)	0.831
Total cholesterol†, mmol/L (SD[a])	4.64 (1.23)	4.49 (1.34)	0.656
LDL-C[f]‡, mmol/L (IQR[c])	2.54 (1.96-3.38)	2.51 (1.83-2.93)	0.491
HDL-C[g]†, mmol/L (SD[a])	1.20 (0.40)	1.31 (0.37)	0.301
hs-CRP[h]‡, mg/dL (IQR[c])	0.41 (0.19-1.74)	0.16 (0.06-0.62)	0.029
MMP-9[i]‡, pg/mL (IQR[c])	4394.00 (3049.75-14081.25)	4117.00 (2648.50-7449.75)	0.235

† Mean value
‡ Median value
[a] SD, standard deviation
[b] CVA, cerebrovascular accident
[c] IQR, interquartile range
[d] ACC/AHA CVD Risk Score, American College of Cardiology/American Heart Association cardiovascular disease risk score
[e] HbA1c, hemoglobin A1c
[f] LDL-C, low density lipoprotein-cholesterol
[g] HDL-C, high density lipoprotein-cholesterol
[h] hs-CRP, high-sensitivity C-reactive protein
[i] MMP-9, matrix metalloproteinase-9

CACS (≥800), known to affect the objective interpretation of the CCTA; technical issues such as suboptimal images; or uncontrolled heart rate. Median CACS was significantly higher in the SH group compared to the non-SH group. For CACS subgroup analysis, the SH group had more patients with CACS ≥100.

In terms of CCTA features, there were only a few patients in the SH group with no significant stenosis. Obstructive CAD in each of the epicardial coronary arteries was found to be more prevalent in the SH group, with a statistically 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: the mean percentage of segments involved and the mean percentage of segment severity were comparatively greater than in the non-SH group, but the difference did not reach statistical significance.

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% (OR 4.231, 95% CI: 1.314 to 13.617, *p*=0.026). The 46% prevalence of significant ACAD in the non-SH T2DM patients correlates well with previous studies which employed CCTA for detection of significant CAD (Table 2).[27,28]

Multinomial logistic regression was done to determine the relationship of SH and other confounders for significant ACAD, such as age, gender, smoking status, family history of premature CVD, creatinine clearance, body mass index, HbA1c level, HDL-C, LDL-C, Framingham risk score and ACC/AHA risk score. Only a history of SH was determined to be statistically significant as an independent risk factor for ACAD (*p*=0.004).

Subgroup analysis within the SH group

A. Recurrent SH versus single episode of SH

There were 5 (18%) patients with recurrent episodes of SH. Compared to patients with a single episode of SH, those with recurrent SH were older and had lower creatinine clearance. These may explain the higher risk of recurrent severe hypoglycemia. All the patients with recurrent SH had significant CAD. The hs-CRP and MMP-9 levels in these patients were also higher, suggesting a greater risk for CV events, but the differences from patients with single SH did not reach statistical significance. CACS were higher in patients with recurrent SH, with a difference that was statistically significant. However, because most patients had extremely high CACS (≥800), CCTA was not performed in this group (Table 3A).

B. Onset of SH within the first month versus more than one month

There were 10 (36%) patients who were investigated within the first month of the occurrence of SH. The hs-CRP was higher in this group compared to those

Table 2. Comparison of computed tomographic calcium score and angiography between groups

Characteristics	Severe Hypoglycemia		*p* value
	Yes (n=28)	No (n=28)	
Coronary artery calcium score‡, (IQR[a])	277 (80-869)	56.50 (14.25-458.75)	0.030
0	2 (7)	3 (11)	1.000
1-99	5 (18)	13 (46)	0.044
100-399	9 (32)	5 (18)	0.355
100 or more	21 (75)	12 (43)	0.029
400 or more	12 (43)	7 (25)	0.259
Coronary CT[b] angiography			
Completed coronary CT[b] angiography (%)	18 (64)	26 (93)	NA
Segment involvement percentage†*, % (SD[c])	39.35 (30.36)	33.12 (28.12)	0.488
Segment severity percentage†**, % (SD[c])	20.49 (18.35)	14.88 (13.47)	0.248
No significant stenosis	5 (28)	16 (62)	0.036
Single vessel disease	6 (33)	3 (12)	0.128
Two vessel disease	2 (11)	4 (15)	1.000
Three vessel disease	5 (28)	2 (8)	0.103
Stenosis ≥50% involvement			
Left main stem	2 (11)	0	0.162
Left anterior descending (LAD) (including diagonal 1)	11 (61)	9 (35)	0.125
Left circumflex (LCx) (including obtuse marginal)	6 (33)	5 (19)	0.314
Right coronary artery (RCA)	8 (44)	4 (15)	0.045
Results			
At least one coronary artery with ≥50% stenosis	13 (72)	10 (39)	0.036
Significant CAD[d] (CACS[e] ≥400 and/or at least one major epicardial coronary artery disease ≥50% stenosis)	22 (79)	13 (46)	0.026

† Mean value
‡ Median value
* Segment involvement percentage is the percentage of segments with plaques regardless of degree of stenosis
** Segment severity percentage is the percentage of total sum of scores of all segments based on severity of stenosis: 0 = no plaque, 1 = plaque present or mild stenosis <50%, 2 = moderate stenosis 50-75%, 3 = severe stenosis >75%
[a] IQR, interquartile range
[b] CT, computed tomography
[c] SD, standard deviation
[d] CAD, coronary artery disease
[e] CACS, coronary artery calcium score

Table 3A. Comparison of characteristics of patients with recurrent or single episode of severe hypoglycemia

Characteristics	Recurrent (n=5)	Single (n=23)	*p* value
Age†, year (SD[a])	68 (61-78)	64.78 (48-84)	0.405
CKD G3[b] (%)	3 (60)	5 (22)	0.123
On insulin (%)	3 (60)	6 (26)	0.290
Creatinine clearance†, mL/min/1.73 m^2 (SD[a])	57.47 (18.20)	76.26 18.94)	0.083
hs-CRP[c]‡, mg/dL, (IQR[d])	0.45 (0.16-12.64)	0.39 (0.19-1.95)	0.696
MMP-9[e]‡, pg/mL, (IQR[d])	10770.00 (6800.50-16338.50)	3607.00 (2797.00-9896.00)	0.087
CACS[f]‡ (IQR[d])	668.00 (448.50-4851.50)	202.00 (65.00-677.00)	0.044

† Mean value
‡ Median value
[a] SD, standard deviation
[b] CKD G3, chronic kidney disease glomerular filtration rate category 3
[c] hs-CRP, high-sensitivity C-reactive protein
[d] IQR, interquartile range
[e] MMP-9, matrix metalloproteinase-9
[f] CACS, coronary artery calcium score

Table 3B. Comparison of characteristics of patients investigated within the first month or beyond the first month of severe hypoglycemia

Characteristics	Within first month (n=10)	Beyond first month (n=18)	*p* value
Age†, year (SD[a])	60.90 (6.89)	67.83 (9.41)	0.048
hs-CRP[b]‡, mg/dL, (IQR[c])	2.05 (0.25-8.69)	0.38 (0.12-0.49)	0.045
MMP-9[d]‡, pg/mL, (IQR[c])	7269.50 (3414.25-16226.00)	3444.50 (2853.50-10178.25)	0.308

† Mean value
‡ Median value
[a] SD, standard deviation
[b] hs-CRP, high-sensitivity C-reactive protein
[c] IQR, interquartile range
[d] MMP-9, matrix metalloproteinase-9

who had SH more than a month earlier, signifying a possible temporal association of SH with the process of inflammation and risk of plaque rupture (Table 3B).

DISCUSSION

In our cohort of patients with T2DM who had a history of SH, we found higher hs-CRP and more severe coronary artery disease based on imaging compared to those without any history of SH. The odds of having significant ACAD in patients with a history of SH based on this study was four-fold compared with other T2DM patients with no history of SH with matched baseline characteristics (OR 4.231, 95% CI: 1.314 to 13.617, p=0.026).

The relationship between SH and CV events and mortality are supported by analyses 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 to those with no SH in large prospective randomized trials have been shown to be between 1.67 and 4.28.[29] 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 are no published studies that have sought to objectively compare the severity of ACAD in T2DM patients who had a history of SH compared to those 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 a history of SH was an independent risk factor for severe ACAD.

SH has been known to promote an atherogenic state by hypersecretion of catecholamines and pro-inflammatory cytokines, leading to platelet aggregation.[30] In the acute state, hypoglycemia increases susceptibility of the myocardium to post-ischemic reperfusion injury and hampers the patient's ability for ischemic preconditioning.[31] The long-term cardiovascular effects of repeated hypoglycemia are due to increased endothelial dysfunction and a pro-inflammatory state, which contribute further to atherosclerosis.

Higher hs-CRP values were also seen in patients with SH, suggesting a more atherogenic and pro-inflammatory state. Serum MMP-9 levels, a marker of potential plaque destabilization and risk of rupture in ACAD, were also higher in this population, but this did not reach statistical significance. In addition, we demonstrated an apparent dose-response effect of SH, as seen in the significantly higher CACS in patients with recurrent SH compared to those with a single episode of SH.

Another significant finding is the temporal association between the onset of SH and elevated hs-CRP which demonstrates a higher risk for CV events. In this study, hs-CRP levels were significantly higher in the group with SH investigated within the first month of developing SH. Previous studies had shown that risk for CV events were higher within the first year of onset of SH, as compared with later years.

There have been doubts raised regarding the precise pathophysiological link between SH and CVD. Two large randomized control trials, DEVOTE 3 and TECOS, did not show a significant result between a history of SH and subsequent CV events.[32,33] Due to inconsistent results, SH was only perceived as a risk factor for CVD rather than a direct cause of CVD, as SH arguably occurs mostly in patients with advanced diabetes, advanced renal disease, on multiple oral anti-diabetes agents or high doses of insulin. Patients with these characteristics already have a higher risk for CVD to begin with.

The establishment of direct causality link between severe hypoglycemia and CVD will 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 that assessed causality of SH with CVD by looking at strength, temporality, dose-response, consistency and biological plausibility of the relationship found all these factors to be significant.[34]

The recent Malaysian guidelines on the primary and prevention of CVD suggest adjustment of anti-diabetic medications to reduce the risk of hypoglycemia. A less stringent approach to glycemic targets will also be needed. Their overall CV risk profile should be reassessed and optimized to reduce the risk of CVD.[35] 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 individualized approach based on a premise of strict CVD risk stratification.

Numerous studies have suggested that screening asymptomatic patients with diabetes for CAD confers no additional benefit to the final outcome, even in patients with confirmed subclinical CAD.[36-38] Most patients who have experienced SH already have multiple risk factors for CAD, such as advanced age and chronic kidney disease.[39]

Limitations and Strengths

We identified a few limitations in the study. Our study was performed in a single center and was limited to a specific geographical area. Large-scale studies involving multiple centers in other areas of the world are needed to validate our results. Our definition of significant ACAD is also based on anatomical assessment of coronary artery disease. Combining anatomic with functional assessment such as myocardial perfusion imaging may provide a more prognostic value.

The strength of this study was that our exposed cohort was mainly based on patients with capillary blood glucose-documented episodes of SH, and not based on any unsubstantiated claim that led to misclassification of SH. We also compared our exposed 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

The results of the study suggest the prognostic importance of a prior history of SH, biological plausibility, dose

response and temporal association on the severity of ACAD. 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 the severity of CAD.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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