VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
E-ISSN 2450–8187

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Association between Hyperglycemic Crisis with Major Cardiovascular Events in Patients with Diabetes: A Single Center Retrospective Cohort Study

ABSTRACT

Introduction: Hyperglycemic crisis caused by an increase of insulin requirement and one of the predisposing factors are cardiovascular disease; this condition can induce an increasing cytokine which also acts as a coronary heart disease marker. The latest study remains unclear about the association with cardiovascular outcomes. This study aimed to investigate the association between hyperglycemic crisis and major adverse cardiovascular events (MACEs).

Materials and methods: This study is an analytical study with cohort retrospective design conducted at Sanglah General Hospital from February until April 2019. The data was taken using the total sampling method; 126 samples were collected from the medical record with 43 samples hyperglycemic crisis as a case group and non-hyperglycemic crisis as a control group with 83 samples according to inclusion and exclusion criteria — the analysis using univariate and bivariate survival analysis. The primary outcome was the risk ratio.

Results: The median age in this study was 45.69 years old (SD 2.53) for the case group and control 55.73 ± 1.21 years old. The gender ratio between males and females in both groups is 1:1–2; the mean of HbA1c in the case group is higher than the control group, 12.06 ± 3.06 *vs.* 7.9 (5.1–14.8) %. Relative risk analysis between hyperglycemic crisis and MACE is obtained RR 5.576 with 95% CI: 2.87–10.8 and p-value = 0.000 with potential confounding variable are not associated.

Conclusions: There is a significant association between hyperglycemic crisis and MACE statistically. (Clin Diabetol 2022, 11; 3: 146–150)

Keywords: diabetes mellitus, hyperglycemic crisis, MACE

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Clinical Diabetology 2022, 11; 3: 146–150
DOI: 10.5603/DK.a2022.0019
Received: 01.11.2020 Accepted: 8.04.2022

Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are life-threatening emergencies in patients with type 1 diabetes and type 2 diabetes [1]. DKA and HHS remain important causes of morbidity and mortality among diabetic patients despite well-developed diagnostic criteria and treatment protocols [2].

Hyperglycemic produces alterations in various metabolic and cellular functions, including endothelial dysfunction, oxidative stress, and alterations in

cardiac metabolism as consequences [3, 4]. The endothelial dysfunction contributes to cardiovascular disease (CVD), including hypertension, atherosclerosis, and coronary artery disease, which are also caused by insulin resistance [5]. These pathogeneses are increasing basal metabolism due to predisposition factors such as infection or CVD [6–9]. Hyperglycemic crisis caused by an increase of insulin requirement and one of the predisposing factors are cardiovascular disease [10]; this condition can induce an increasing cytokine which also acts as a coronary heart disease marker. In hyperglycemic crisis, there is a two to four times increase of inflammatory cytokines, oxidative stress such as interleukin-1β; 6; 8, tumor necrosis factor-α, C-reactive protein (CRP), homocysteine, that also acts as a marker of coronary heart disease. The titer sustained temporarily despite the resolution of the hyperglycemic crisis [11–14]. All of this cascade could be a bidirectional relationship and contribute to each other [15].

The latest study` remains unclear about the association with long term MACE. This study aimed to investigate the association between hyperglycemic crisis and major adverse cardiovascular events (MACEs).

Materials and methods

This study is an analytical study with retrospective cohort design follow-up time was five years. The place and time of this study are held on Sanglah hospital from February until April 2019. Samples were taken from the medical record installation room of Sanglah Hospital Denpasar. Simple randomized are used in this study as a method of sampling for control, while total sampling for case groups according to inclusion and exclusion criteria. Criteria of inclusion are patients who diagnosed DM with crisis hyperglycemic by clinical manifestation and laboratory findings at Sanglah Hospital for one year in 2018 until 2019 for exposure group and without crisis hyperglycemic for the control group as inclusion criteria, while exclusion criteria are patients aged < 20 or > 100 years with either child. 126 samples were collected: 43 samples as exposure group and control group with 83 samples. Secondary data was taken by using medical records.

Diabetes mellitus (DM) is diagnosed based on anamnesis, physical examination, and laboratory examination, according to ADA criteria yield; "FPG ≥ 126 mg/dL (7.0 mmol/L) or 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT or A1c ≥ 6.5% (48 mmol/mol) or in a patient with classic symptoms of hyperglycemic or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)". Hyperglycemic crisis is defined as ketoacidosis diabetic (DKA) and hyperosmolar hyperglycemic (HHS), DKA and HHS are diagnosed based on Indonesian diabetic association guidelines based on ICD-10 CM anamnesis, laboratory result yield pH artery below than 7.3; bicarbonate serum ≤ 18 mEq/L, positive ketone in either urine and serum for DKA; while osmolarity above 320 mOsm/kg for HHS, pH artery above 7.3, bicarbonate serum >18 mEq/L. Biochemical data were presented, such as glycated hemoglobin (HbA1c) and serum lipids. Complication such as cerebrovascular, cardiovascular, PAD, neuropathy, retinopathy, nephropathy, and neuropathy was based on ICD-X, assessed anamnesis, physical examination and laboratory assessment, imaging. Duration of diabetes was recorded when data was pooled. Major advanced cardiovascular event (MACE) is described as were defined as compositions of acute myocardial infarction, congestive heart failure, ischemic or hemorrhagic stroke, and malignant dysrhythmia. Inclusion criteria were diabetes patient, age 18 to 65, completed medical record for five-year prior data pooled, while diabetic patients with history of previous MACEs, patients aged < 20 or > 65 years were excluded.

This study also identified confounding factors such as age, gender, duration and status of diabetes, and comorbidity — the primary outcome in this study to assessed relative ratio as an association parameter between MACE and crisis hyperglycemic.

This research has been obtained and approved the letter of ethical negligence of the research ethics commission Udayana University Faculty of Medicine/ /Sanglah General Hospital Denpasar and a formal letter of permission from the Education and Research Division of Sanglah General Hospital Denpasar. All the subject information collected from the medical record will be kept confidential.

Statistical analysis

In this study, we were using univariate and bivariate analysis. This study's variable includes sex, type of DM, crisis glycemic, diabetic status (A1c), and comorbidity. Numeric data such as A1c, age, profile lipid was tested using normality test (Kolmogorov-Smirnov) and categorical by cut-off taken from consensus and the latest research. Numeric data were presented using means and standard deviations (SD) for normally distributed data, while abnormally distributed data using median and interquartile range (IQR). Normality and frequency test was used as univariate analysis to describe the characteristic, proportion of the Sample and determine the type of test used in bivariate analysis. Association between hyperglycemia crisis and MACE is the aim of bivariate analysis. Chi-square test was used to describe the association between MACE with case and control with calculating other variables such as age, sex, diabetic status, and cardiovascular status.

Table 1. The Baseline Characteristics (n = 126)

	Hyperglycemic crisis (n = 43)	Non-hyperglycemic crisis (n = 83)
Age [years]	45.69 ± 2.53	55.73 ± 1.21
Sex (M/F)	25 (59.5%)/17 (40.5%)	41 (59.4%)/28 (40.6%)
Duration of DM [years]	4 (0–17)	3 (0–21)
Mean HbA1c [%]	12.06 ± 3.06	7.9 (5.1–14.8)
T1DM/T2DM	8/35	0/83
Infection*	6 (13.9%)	7 (8.43%)
Smoking	4 (9.3%)	2 (2.4%)
Comorbidity		
Cardiovascular	1 (2.23%)	19 (22.8%)
Cerebrovascular	1 (2.23%)	7 (8.43%)
Neuropathy	2 (4.46%)	6 (7.22%)
PAD	3 (6.69%)	8 (9.63%)
Retinopathy	1 (2.23%)	13 (15.6%)
Nephropathy	1 (2.23%)	15 (18.07%)
Lipid profile [mg/dL]		
Triglyceride	223.96 ± 118.59	91.05 ± 5.58
HDL	29.64 ± 13.46	98.5 ± 98.28
LDL	113.73 ± 52.9	123.64 ± 54.13
Total cholesterol	179.36 ± 58.55	212.0 ± 77.78

* Infection was defined as any moderate infection as etiologic admitted to hospital; DM —diabetes mellitus; F — female; HbA1c — glycated hemoglobin; HDL — high-density lipoprotein; LDL — low-density lipoprotein; M — male; PAD — peripheral arterial disease; T1/2DM — type 1/2 diabetes mellitus

Nevertheless, the results for another variable are not significant ($p > 0.25$) and not be continued to multivariate analysis. That variable is not associated with MACE in this study. Statistical analysis was done by using SPSS 23.

Results

The characteristic of this study described in Table 1. Mean age is 45.69 years old (SD 2.53) for hyperglycemic crisis group and non-hyperglycemic crisis 55.73 ± 1.21. Gender is nearly 1:1–2 between male and female in both case and control group. The mean of HbA1c in the case group is higher than control, 12.06 ± 3.06 *vs.* 7.9 (5.1––14.8) %. Peripheral artery disease is the most comorbidity that occurs in cases, during cardiovascular for case group.

Another variable such as sex, smoking, type of DM hypoglycemia is analyzed using chi-square test, the result for each variable is above 0.05 (0.553; 1; 0.06; 0.91). There is a significant association between hyperglycemic crisis with MACE, and the others are not significant as statistically (Tab. 2).

Relative risk analysis between crisis hyperglycemic and MACE is obtained: RR 5.576 with 95% CI: 2.87–10.8 and p-value = 0.000 (Tab. 3).

Table 2. Association between Hyperglycemic Crisis and MACE

	MACE	
	Yes	**No**
Type of DM 1/2	6 /29	2/89
Hyperglycemic Crisis	26 (74.3%)	17 (18.7%)
Sex (M/F)	22/12	45/34
Smoking	1 (2.85%)	3 (3.29%)
Hypoglycemia	1 (2.85%)	0
Cardiovascular	3 (8.57%)	17 (18.6%)

CI — confident interval; DM — diabetes mellitus; F — female; M — male; MACE — major cardiovascular event; RR — risk ratio

Table 3. Relative Risk between MACE and Crisis Hyperglycemic

	MACE		P	RR	95% CI
	Yes	**No**			
Case	26 (74.3%)	17 (18.7 %)	0.000	5.576	2.87–10.81
Control	9 (25.7%)	74 (81.3%)			

CI — confident interval; MACE — major cardiovascular event; RR — risk ratio

Discussion

In this study, the results showed RR of 5.576, with the percentage of men being more dominant with 59.5%. In addition, it was also found that the mean age of 45.69 years (SD ± 2.53) with type 2 diabetes predominating in both cases and controls (Tab. 3).

The pathophysiology that can explain the association between hyperglycemic and MACE is a stress response in hyperglycemic crisis conditions, resulting in increased catecholamines, cortisol, and glucagon concentrations, and decreased insulin production and sensitivity in peripheral receptors. This results in a stimulus for the breakdown of glycogen, glucogenesis, and the formation of fatty acids, which can induce myocardial damage [16]. In addition, hyperglycemic crisis can also cause vascular dysfunction through the mechanism of molecular injuries, including reactive oxygen species (ROS) and angiotensin II (Rubaiy, 2017). Insulin resistance in endothelial cells causes an increased level of prothrombotic factors, proinflammatory markers, and ROS, that lead to an increase in the intracellular levels of adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM-1), which also contributes to inflammation, disrupting the balance between endothelial vasodilator and vasoconstrictor mechanisms and increases the risk of cardiovascular disease [17, 18]. Myocardial has the function to pump the heart, and if there is damage to the myocardium, it can cause the inability of the heart muscles to contract correctly, and stroke volume and cardiac output of the heart is decreased. This disease is known as heart failure, which is part of MACE [19].

In addition, patients with hyperglycemic crises can go through metabolic maladaptation, and a great loss of metabolic flexibility leads to intramyocardial lipid accumulation [20]. This lipid accumulation may contribute to apoptosis, impairing mitochondrial function, cardiac hypertrophy, and contractile dysfunction [21]. Therefore, the resultant defect in myocardial energy production impairs myocyte contraction and diastolic function. These alterations produce functional changes that also lead to heart failure [22].

In the results of the research that has been done, the subjects by male sex appeared in most cases with a percentage of 59.5%. This is consistent with the research conducted by Chang et al. in Taiwan in 2016, which also found that hyperglycemic crises were more common in men (54.8%) than women (45.1%) [11]. (Until now, there is no specific reason why it is more common in men. However, some studies suspect that this happens because of diabetes conditions that are uncontrolled and the assumption that men have more opportunities and the ability to eat at a particular time than women [23].

This research also found RR was 5.576, the same research results were also found in a study conducted by Chang et al. in Taiwan in 2016 [24].

The study found the results of adjusted H.R. 95% CI of 1.76, which showed results with the same interpretation and similarity that the hyperglycemic crisis can increase the risk of MACE. This is likely happened due to an increase in cardiovascular markers such as CRP, homocysteine, and oxidative stress which tends to increase in people with a hyperglycemia crisis [6]. This condition can cause vascular dysfunction and endothelial dysfunction through molecular mechanisms that can cause MACE due to blood vessel injuries. Therefore, a positive relationship was found between the hyperglycemic crisis and MACE.

The limitation in this study is that the research is still not long enough with case and control groups that are less matched, the duration for the study sample to have hyperglycemia crisis and MACE also cannot be identified. Researchers suggest carrying out further studies with more extended sampling with adjustment for case and control groups with more matching data, additional data such as medications including compliance not assessed is also necessary because of the confounding factors. Because of the retrospective study design, the direct causality between hyperglycemic crisis and long-term MACEs could not be clarified. A further prospective study should be conducted to validate the results of this study. This study is a preliminary study on the management of hyperglycemia crisis if it has a bidirectional correlation so that patients do not fall into MACE.

Conclusions

There are association between hyperglycemic crisis and MACE.

Acknowledgments

The authors thank the patients enrolled in this study and the Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Udayana University, Sanglah Hospital, Denpasar, Bali, Indonesia, for collaboration, enrolment, and participation in this study.

Funding

No funding was received for the study.

Conflict of interest

None declared.

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