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CLINICAL CHARACTERISTICS OF NON-DIABETIC HYPERGLYCEMIA PATIENTS TREATED IN INTENSIVE CARE

[1]Amaliah, [1]Satriawan Abadi, [1]Andi Makbul Aman, [1]Syakib Bakri, [1]Hasyim Kasim, [1]Khalid Saleh, [1]Himawan Sanusi, [1]Fabiola.M.S.Adam, [2]Arifin Seweng.

[1] Department of Internal Medicine, Medical Faculty, Universitas Hasanuddin, Makassar 90245, Indonesia

[2] Department of Biostatistics, Public Health Faculty, Universitas Hasanuddin, Makassar 90245, Indonesia

* Equal contributor

Corresponding author

Name : Amaliah

Telephone : +621342168722

Email address : liakamal02@gmail.com

Mailing address: Department of Internal Medicine, Universitas Hasanuddin, Faculty of Medicine, Perintis Kemerdekaan Km 10, Tamalanrea, Makassar 90245, South Sulawesi, Indonesia.

Abstract

Background of study: Hyperglycemia often occurs in critically ill patients even without a history of diabetes. Hyperglycemia, in hospital, according to the American Diabetes Association (ADA) is defined as a condition in which blood glucose levels are ≥140 mg/dl and HbA1c ≤6.5, without any prior diabetes history. Hyperglycemia results from an endocrine and metabolic response to stress. Studies and literature regarding hyperglycemia in non-diabetic patients in Indonesia are deemed limited, especially case studies of non-diabetic hyperglycemia in intensive care and the prevalence of hyperglycemia related to age, sex, metabolic risk (obesity, hypertension, dyslipidemia), history of parenteral nutrition, history of corticosteroids use, and disease diagnosis.

Methods: The present study is a retrospective descriptive study using medical record data of patients at the HCU, ICU, Brain Center, and CVCU PJT Wahidin Sudirohusodo Hospital in August 2020 - October 2020. This study involved 90 non-diabetic subjects in intensive care. The inclusion criteria were based on the ADA criteria for non-diabetic hyperglycemia in the hospital.

Results: This study involved 44 non-diabetic hyperglycemic patients and 46 non-diabetic patients without hyperglycemia with a mean age of 53.5 years in non-diabetic hyperglycemic subjects and 57.7 years old in subjects without hyperglycemia. Non-diabetic hyperglycemia subjects with obesity (34.1%), hypertension (61.5%), and dyslipidemia (46.9%). Subjects with hyperglycemia with a history of corticosteroid use (95%). Based on the diagnosis of the disease when the subject was in intensive care, the subject with a diagnosis of CHD had hyperglycemia (36.8%), stroke with hyperglycemia (58.8%), and other diagnoses (infection, tumor, postoperative, and trauma) accompanied by hyperglycemia (57, 1%). There was a

significant relationship between hypertension, history of corticosteroid use, and hyperglycemia in non-diabetes (p <0.05).

Conclusion: The history of corticosteroids use and hypertension is associated with the occurrence of hyperglycemia in non-diabetic patients in intensive care.

Keywords: Hyperglycemia, non-diabetes, intensive care, corticosteroid

1. Introduction

Hyperglycemia often occurs in critically ill patients even without a history of diabetes. [(1)] Hyperglycemia in a hospital, according to the American Diabetes Association (ADA) is defined as a condition in which blood glucose levels are ≥140 mg/dl and HbA1c ≤6.5, without any prior history of diabetes. [(2)] [(3)] Hyperglycemia due to endocrine and metabolic responses to stress occurred in 20.33% of critically ill patients admitted to the intensive care unit. [(4)] Observational studies have reported a prevalence of hyperglycemia ranging from 32% to 38 % in community hospitals, 16% of them had no prior diabetes history. [(5)]

Hyperglycemia adversely affects critical patient outcomes in terms of mortality, morbidity, length of stay, infections, and complications. In patients who were admitted to the ICU, it was found that subjects newly diagnosed with hyperglycemia had a death rate 3 times higher (31%) than that of patients with a previous history of diabetes (10%) or with normoglycemia (11.3%). [(6)] In a study, Graham et al. found that mortality in critically ill patients was reported to be significantly higher in patients without a history of diabetes mellitus compared with diabetes patients (7).

Acute hyperglycemia, at non-diabetic critically ill in intensive care (ICU), is a physiological marker of a stress response. The stress phenomenon hyperglycemia is associated with hormonal stress reactions that involve the release of catecholamines, glucocorticoids, epinephrine, norepinephrine, and glucagon, due to stress, sepsis, trauma, post-surgery and associated with high-dose corticosteroid therapy [(10)] [(11).]

In the previous studies regarding the occurrence of hyperglycemia, it was found out that several factors are associated with the occurrence of hyperglycemia. Temel, et al stated that the occurrence of hyperglycemia increased in the age range 42 ± 18 years. [(4)] The research of Khan et al (2011) in South Asia and China suggested that men are more prone to diabetes than women [(13)], while the study of Spielgelman and Marks found out that diabetes more dominantly occurs in women than in men. [(14)]

Laura et al confirmed the prevalence of hyperglycemia in non-diabetic subjects with obesity of 40.7%. [(15)] Yan, et al. Stated that basal blood pressure and progression are strong and independent predictors of the occurrence of hyperglycemia. [(16)] Anna, et al found the prevalence of dyslipidemia in non-diabetic subjects with hyperglycemia of 48.6%

Pieralli, et al reported 34% of subjects with a diagnosis of CHD without a history of diabetes with hyperglycemia. (18) Bilal, et al. found that in 150 non-diabetic subjects with a diagnosis of acute stroke, the prevalence of hyperglycemia was 21.33%. (19) Wernly et al. in 522 subjects, the prevalence of sepsis with hyperglycemia in subjects without diabetes was 66%.

(20) Shi, et al, in 184 subjects with post-traumatic brain injury (TBI) hyperglycemia, 82.6% of them had no history of diabetes. (21) Harris, et al. in their study also reported the prevalence of corticosteroid-induced hyperglycemia in subjects without a history of diabetes. Pasquel et al. reported that hyperglycemia is associated with increased complications and mortality in patients receiving total parenteral nutrition (TPN).

Studies and literature on hyperglycemia in non-diabetic patients in Indonesia are still deemed to be lacking, especially case studies of non-diabetic hyperglycemia in intensive care and factors related to the prevalence of non-diabetic hyperglycemia.

2. Method

2.1 Research Subject

This study was a retrospective descriptive study using medical record data on non-diabetic hyperglycemic patients who were treated at the HCU, ICU, Brain Center, and CVCU PJT Wahidin Sudirohusodo Hospital in August 2020 - October 2020. The variables assessed included age, gender, metabolic risk factors (obesity, hypertension, dyslipidemia), history of parenteral nutrition, history of corticosteroid use, and ICU hospital diagnosis.

2.2 Inclusion Criteria and Exclusion Criteria

The subjects were men and women above 18 years, admitted to intensive care with GDS data ≥ 140 mg/dl, HbA1C ≤ 6.5 mg/dl at the time of entry to intensive care. They had no history of diabetes and were not in the middle of diabetes treatment. Patient exclusion criteria were known to be diabetic, GDS ≤ 140, HbA1C ≥ 6.5 mg/dl, the incomplete medical record for the study.

2.3 *Data Collection*

Sampling was conducted nonrandomly on medical records. Data on age, sex, BMI, GDS, HbA1C, lipid profile, blood pressure, history of parenteral nutrition, history of corticosteroid use, and ICU diagnosis were referred to the medical records.

2.4 Objective Criteria

Based on the ADA criteria, patients were categorized as non-diabetic hyperglycemia in the hospital if GDS ≥ 140 mg/dl and HbA1C ≤ 6.5% without any previous diabetes history. Control subjects were non-diabetic without hyperglycemia, with GDS ≤140, HbAIC ≤ 6.5 without a history of diabetes.

BMI assessment based on WHO criteria for Asia Pacific countries is categorized as underweight if weight <18.5 kg / m2, norm weight: 18.5 - 22.9 kg / m2, overweight: 23-24.9 kg / m2, obesity:> 25 kg / m2. Subjects are categorized as hypertensive if their systolic blood pressure was> 140 mmHg and diastolic blood pressure> 90 mmHg. Dyslipidemia criteria if total cholesterol level> 200 mg / dl, hypertriglyceridemia if triglycerides> 150, and mixed dyslipidemia if LDL> 100 mg / dl, triglycerides> 150 mg / dl and HDL <40 mg / dl.

Data history of parenteral nutrition and the use of corticosteroids given before entering intensive care were confirmed in the medical records. Based on the previous research data, hospitalization in intensive care was reported to be associated with hyperglycemia, namely CHD,

stroke, disease, or other conditions (infection, trauma, malignancy, post-surgery). All medical record data that met the inclusion criteria were collected, the necessary data were recorded, analyzed, and presented.

2.4 *Statistical Analysis*

Data analysis was conducted using SPSS version 22. The statistical analysis carried out was descriptive statistical calculations and frequency distribution, as well as the Independent-t statistical test, Chy Square test, and calculation of the Odds Ratio (OR) value. The result of the statistical test is confirmed if the p-value <0.05.

2.5 Ethical Permit

This research has met the ethical requirements of the Biomedical Research Commission on Humans, Medical Faculty of Hasanuddin University number: 207 / UN4.6.4.5.31 / PP36 / 2020.

3. Result

Data analysis was performed on 90 non-diabetic patients in intensive care consisting of 44 non-diabetic hyperglycemic patients and 46 non-diabetic patients without hyperglycemia. Table 1 shows that the research subjects consisted of men (60%) and women (40%). Most of the research subjects were 18-60 years old (57.8%).

Subjects with a risk factor for obesity were 27.8% while those who were non-obese were included in this category as subjects with underweight, normoweight were 72.2%. Subjects with risk factors for hypertension were 43.3%, and those with dyslipidemia were 35.6%. Subjects who received parenteral nutrition were 4.4% and those who did not received parenteral nutrition were 95,6%. Subjects who received corticosteroid therapy were 22.2% and those who did not receive corticosteroid therapy were 77.8%.

Based on the diagnosis of disease in intensive care subjects, subjects with a diagnosis of CHD were 42.2%, stroke with hyperglycemia were 18.9% and other diseases (infection, malignancy, trauma, post-surgery) were 38.9%. Subjects who died were 27.8%, while those who improved were (72.2%).

Table 1.Categories of research variables (n = 90)

Variable		n	%
Gender	Male	54	60,0
	Female	36	40,0
Age	18-60 yo	52	57,8
	>60 yo	38	42,2
BMI	Obesity	25	27,8
	Non Obesity	65	72,2
Hypertension	Yes	39	43,3
	No	51	56,7

Dyslipidemia	Yes	32	35,6
	No	58	64,4
Received Parenteral Nutrition	Yes	4	4,4
	No	86	95,6
Received Corticosteroid	Yes	20	22,2
	No	70	77,8
Diagnosis	CVD	38	42,2
	Stroke	17	18,9
	Other Disease	35	38,9
Hypergiycemia	Yes	44	48,9
	No	46	51,1
Mortality	Died	25	27,8
	Life	65	72,2

Table 2 shows that the study subjects consisted of men (46.3%) in non-diabetes with hyperglycemia and without hyperglycemia (53.7%), and women (52.8%) in non-diabetes with hyperglycemia, (47.2 %) without hyperglycemia with a mean age of 53.5 years in non-diabetic hyperglycemic subjects and 57.7 years old in subjects without hyperglycemia. Research subjects with non-diabetic obesity nutritional status were hyperglycemic (34.1%), and without hyperglycemia (21.7%).

Non-diabetic hypertensive subjects experienced hyperglycemia (61.5%), while those without hyperglycemia (38.5%). Subjects with risk factors for dyslipidemia were accompanied by hyperglycemia (46.9%) and no dyslipidemia (53.1%). Most of the study subjects had no history of parenteral nutrition. Only 4 subjects with a history of parenteral nutrition and 3 of them had hyperglycemia.

Subjects with hyperglycemia with a history of corticosteroid use were 95% and those without hyperglycemia were 5%. Based on the diagnosis of the disease when the subject was in intensive care, the subject with a diagnosis of CHD had hyperglycemia (36.8%), stroke with hyperglycemia (58.8%), and other diagnoses (infection, tumor, postoperative, and trauma) accompanied by hyperglycemia (57, 1%). Table 2 shows that there was no significant relationship between sex, age, obesity, dyslipidemia, history of parenteral nutrition, and diagnosis during intensive care with the occurrence of hyperglycemia in non-diabetic subjects ($p > 0.05$).

Based on the risk factors for hypertension, there was a significant relationship between hypertension and hyperglycemia in non-diabetes ($p < 0.05$), in which the percentage of hyperglycemia occurrence was higher in hypertension (61.5%) than in those without hypertension (38.5%). Based on the history of corticosteroid use, there was a significant association with hyperglycemia in non-diabetes ($p < 0.001$), in which the percentage of

occurrence of hyperglycemia was higher in subjects with a history of corticosteroid therapy (95%) than in subjects who did not receive corticosteroid therapy (35.7%).

Table 2 : Clinical Characteristics and Demography of Non Diabetic Hyperglycemia in Intensive Care

Variable		Hypergycemia (n=44)			No Hyperglycemia (n=46)			p
		n	%	Mean	n	Mean	%	
Gender	Male	25	46,3		29		53,7	0,547
	Female	19	52,8		17		47,2	
Age	18-60 yo	28	53,8	53,5	24	57,7	46,2	0,271
	>60 yo	16	42,1		22		57,9	
BMI	Obesity	15	34,1		10		21,7	0,191
	Non Obesity	29	65,9		36		78,3	
Hypertension	Yes	24	61,5		15		38,5	0,036
	No	20	39,2		31		60,8	
Dyslipidemia	Yes	15	46,9		17		53,1	0,776
	No	29	50,0		29		50,0	
Received Parenteral Nutrition	Yes	3	75		1		25	0,285
	No	41	47,7		45		52,3	
Received Corticosteroid	Yes	19	95,0		1		5,0	0,000
	No	25	35,7		45		64,3	
Diagnosis	CVD	14	36,8		24		63,2	0,147
	Stroke	10	58,8		7		41,2	
	Other Disease	20	57,1		15		42,9	

Table 3 shows the results of the multivariate analysis carried out to assess the factors associated with hyperglycemia in non-diabetes, by assessing the interaction between all the variables analyzed. This analysis uses the Multiple Logistic Regression - Backward Wald method. This method assesses each variable at each step of the analysis and removes the variable that is least significant for hyperglycemia. Based on this analysis, it was found out that 2 (two) variables were significantly associated with the occurrence of hyperglycemia, namely the history of corticosteroid use and hypertension.

Table 3: Results of Multivariate Analysis of Variables associated with Hyperglycemia

							95% C.I.for EXP(B)	
Step	Variable	B	S.E.	Wald	p	OR	Lower	Upper
Step 1	Age	0,169	0,614	0,075	0,784	1,2	0,36	3,94
	Gender	-0,267	0,652	0,168	0,682	0,8	0,21	2,75
	BMI	0,817	0,647	1,598	0,206	2,3	0,64	8,04
	Hypertension	1,921	0,630	9,306	0,002	6,8	1,99	23,47
	Dyslipidemia	0,190	0,589	0,104	0,747	1,2	0,38	3,83
	Received Parentera Nutrition	-2,602	1,684	2,389	0,122	0,1	0,00	2,01
	Received Corticosteroid	4,832	1,240	15,187	0,000	125,5	11,05	1.426,2
	Diagnosis	0,296	0,405	0,535	0,465	1,3	0,61	2,97
Step 2	Gender	-0,254	0,650	0,153	0,696	0,8	0,22	2,77
	BMI	0,888	0,595	2,227	0,136	2,4	0,76	7,80
	Hypertension	1,886	0,615	9,405	0,002	6,6	1,98	22,02
	Dyslipidemia	0,203	0,587	0,119	0,730	1,2	0,39	3,87
	Received Parentera Nutrition	-2,602	1,683	2,392	0,122	0,1	0,00	2,00
	Received Corticosteroid	4,842	1,237	15,322	0,000	126,7	11,22	1.431,06
	Diagnosis	0,297	0,405	0,536	0,464	1,3	0,61	2,98
Step 3	Gender	-0,226	0,643	0,124	0,725	0,8	0,23	2,81
	BMI	0,918	0,589	2,428	0,119	2,5	0,79	7,94
	Hypertension	1,907	0,613	9,677	0,002	6,7	2,02	22,39
	Received Parenteral Nutrition	-2,505	1,655	2,290	0,130	0,1	0,00	2,09
	Received Corticosteroid	4,779	1,220	15,350	0,000	119,0	10,90	1.299,97
	Diagnosis	0,280	0,402	0,486	0,486	1,3	0,60	2,91
Step 4	BMI	0,913	0,590	2,396	0,122	2,5	0,78	7,91
	Hypertension	1,909	0,613	9,706	0,002	6,7	2,03	22,42
	Received Parenteral Nutrition	-2,337	1,576	2,199	0,138	0,1	0,00	2,12
	Received Corticosteroid	4,729	1,207	15,363	0,000	113,2	10,64	1.204,26
	Diagnosis	0,216	0,357	0,366	0,545	1,2	0,62	2,50
Step 5	IMT	0,948	0,587	2,607	0,106	2,6	0,82	8,16
	Hypertension	1,863	0,603	9,538	0,002	6,4	1,98	21,01

	Received Parenteral Nutrition	-2,048	1,489	1,892	0,169	0,1	0,01	2,39
	Received Corticosteroid	4,512	1,140	15,658	0,000	91,1	9,75	850,84
Step 6	BMI	0,867	0,576	2,266	0,132	2,4	0,77	7,36
	Hypertension	1,707	0,574	8,857	0,003	5,5	1,79	16,97
	Received Corticosteroid	4,418	1,121	15,525	0,000	82,9	9,21	746,79
Step 7	Hypertension	1,862	0,562	10,981	0,001	6,4	2,14	19,37
	Received Corticosteroid	4,316	1,115	14,984	0,000	74,9	8,42	665,87

Table 4 shows that in subjects with hypertension and non-diabetes, there was no significant relationship between the history of corticosteroid use and the occurrence of hyperglycemia (p> 0.05), whereas, in subjects without hypertension and non-diabetes, there was a significant relationship between the history of corticosteroid use and the occurrence of hyperglycemia (p> 0.05). the occurrence of hyperglycemia (p <0.001), in which the percentage of the occurrence of hyperglycemia was significantly higher (more than 6 times) in subjects with a history of corticosteroid use than in subjects who did not use corticosteroids, namely 100% compared to 14%.

Table 4 : Relationship of Hypertension and Received Corticosteroid with Hyperglycemia

Hypertension	Received Corticosteroid			Hyperglycemia		Total
				Yes	No	
Yes[1)]		Yes	n	4	1	5
			%	80,00%	20,00%	100,00%
		No	n	20	14	34
			%	58,80%	41,20%	100,00%
	Total		n	24	15	39
			%	61,50%	38,50%	100,00%
No[2)]		Yes	n	15	0	15
			%	100,00%	0,00%	100,00%
		No	n	5	31	36
			%	13,90%	86,10%	100,00%
	Total		n	20	31	51
			%	39,20%	60,80%	100,00%

4. Discussion

This study included 90 research subjects: 44 non-diabetic hyperglycemic subjects and 46 non-diabetic subjects without hyperglycemia, with a mean age of 53.5 years in the non-diabetic hyperglycemia group and 57.7 years in the non-hyperglycemia group. This is in line with the study of Perez et al regarding the prevalence of hyperglycemia in hospitals, which found 94 samples with hyperglycemia in the age range of 52 ± 20 years (12).

Based on gender, it was found that male subjects had hyperglycemia (46.3%). This is in line with the study of Temez, et al., with male subjects who likely experienced hyperglycemia more, namely 54% (12). In the BMI category, the percentage of non-diabetic hyperglycemic subjects who were obese was (34.1%). A study on obesity has also been reported by Laura F Defina et al, in which the prevalence of hyperglycemia in non-diabetic subjects was 40.7% (15).

In this study, a prevalence of dyslipidemia of 46.9% was also found in non-diabetic subjects with hyperglycemia, this is in line with the study of Anna, et al., with the prevalence of dyslipidemia in non-diabetic subjects with hyperglycemia of 48.6%, which shows the occurrence of hyperglycemia in subjects with hyperglycemia. dyslipidemia is not greater than without dyslipidemia. (17)

Non-diabetic subjects with hypertension who experienced hyperglycemia were 61.5%. Tsimihodimos, et al. Hypertension was initially an independent predictor of the occurrence of hyperglycemia and diabetes. (57) Subjects with a history of parenteral nutrition were 4 out of 90 subjects, 3 (three) subjects with hyperglycemia were non-diabetic. Other subjects with a history of fasting, oral intake, and enteral (via NGT). Pasquel et al. Have previously reported that hyperglycemia is associated with increased complications during hospitalization and mortality, especially in subjects receiving total parenteral nutrition. (58)

In this study, it was found that the prevalence of hyperglycemia in non-diabetic subjects receiving corticosteroid therapy was 95%. This is in line with the study of Donihi, et al, which found an increase in the occurrence of hyperglycemia in both subjects with diabetes and without a history of diabetes. (59) Harris, et al in their study also reported the prevalence of hyperglycemia due to corticosteroid use in subjects without a history of diabetes. (22)

Based on the category of diagnosis of diseases that cause ICU hospitalization, there are 3 (three) disease categories, namely CHD, stroke, and other diseases including infection, trauma, tumors or malignancy and post-surgery, with the prevalence of hyperglycemia respectively 36.8%, 58, 8%, and 57.7%. The prevalence of subjects with a diagnosis of CHD was 36.8%, in a previous study by Pieralli, et al. it was found out 34% of subjects with a diagnosis of CHD without a history of diabetes with hyperglycemia. (18) The prevalence of subjects with a diagnosis of stroke was 58.7%, when compared with previous studies by Bilal, et al. in 150 non-diabetic subjects with a diagnosis of acute stroke, the prevalence of hyperglycemia was 21.33%. (19)

In other disease categories which include infection, trauma, tumors, and post-surgery, the prevalence was 57.7%. Wernly, et al. Reported that out of 522 subjects, the prevalence of sepsis with hyperglycemia in subjects without diabetes was 66%. 21) Huang, et al reported the prevalence of hyperglycemia in malignancy, from 185 non-diabetic subjects, was 1.6% (61). Postoperative hyperglycemia in non-diabetic subjects has previously been reported by Greco et al with a prevalence of 36%. (62)

In this study, there was no significant relationship between age, sex, metabolic risk factors (obesity, dyslipidemia), history of parenteral nutrition, and diagnosis of intensive care

disease with hyperglycemia in non-diabetes (p> 0.05). There was a significant difference between the history of corticosteroid use and hyperglycemia in non-diabetes (p <0.001), where the percentage of occurrence of hyperglycemia was higher in subjects using corticosteroids than in non-taking subjects, namely 95.0% versus 35.7%.

In the multivariate analysis, there were 2 variables that were significantly associated with hyperglycemia, namely the history of corticosteroid use and hypertension. In non-hypertensive subjects, there was a significant relationship between the use of corticosteroids and hyperglycemia in non-diabetes (p <0.001), where the percentage of occurrence of hyperglycemia was significantly higher (6 times higher) in subjects using corticosteroids than in subjects who did not use corticosteroids, namely 100% compared to 14%.

4.1 Limitation

This research was a retrospective descriptive study using secondary data whose validity cannot be analyzed.

5.Conclusion

History of corticosteroid medicine use is associated with the occurrence of hyperglycemia in non-diabetic patients who are admitted to the intensive care unit. Data on dose and duration of administration of corticosteroids and further observational studies are needed to determine the role of corticosteroids in the occurrence of non-diabetic hyperglycemia.

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