ORIGINAL ARTICLE

Comparison of Serum Magnesium Levelin Diabetes Mellitus (DM) Patientswith or without Acute Coronary Syndrome (ACS)

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ABSTRACT

Introduction: Until now, cardiovascular complications are still the highest cause of death and disability in DM patients.Hypomagnesemia in DM accelerate atherosclerosis and can cause instability and plaque rupture which lead to acute coronary syndrome.
Methods: Design of this study was observational analytic using a “case control” study involved 76 patients of DM patients, consisting of 38 patientswith ACS(+) and 38 patientswith ACS(-). Subjects of this study were all DM patients in the period of July to December 2018 in the Emergency Room(ER) and Outpatient Installation of Endocrine,which fulfill the criteria for inclusion and exclusion.Demographic data and clinical characteristics are presented descriptively.If data is normally distributed then an unpaired T test is carried out and if the data is not normally distributed with Mann Whitney test is performed.The statistical test was stated to be significant if p <0.05. The association between hypomagnesemia and the incidence of ACS a multivariate logistic regression test was performed, the risk number was in the form of odds ratios (OR).
Results: This study involved 76 patientswith diabetes mellitus with SKA and non SKA of 38patients. The mean serum magnesium level in the ACS group was lower than non ACS (1.9 mg/dL vs. 2.1 mg/dL), hypomagnesemia cut-off of <2.08 mg/dL. In this study hypomagnesemia as a risk factor for the incidence of ACS in DM patients with OR 2.8 (CI 1.1-7.6; p = 0.039).
Conclusion: Magnesium levels in the ACS group were lower than the non ACS group. Hypomagnesemia increasesthe incidence of acute coronary syndrome in diabetes mellitus patients.

Introduction

Cardiovascular complications are still the highest cause of death and disability in diabetes mellitus (DM) patients.An estimated 17.9 million people died from cardiovascular disease in 2016, representing 31% of all global death.[1] Diabetes mellitus can trigger a variety of pathological processes that can accelerate the occurrence of atherosclerosis and heart failure.[2] Decrease serum magnesium levels/hypomagnesemia is one of the chronic effects of DM patients who can increase cardiovascular complications.

Evaluation of serum magnesium levels in the blood in patients with DM will reduce the risk of complications of ACS.Hypomagnesemia, as seen in the study by Mhaskar et al., (2013) and Sugunakar et al., (2014), related to ACS and the incidence of arrhythmias.[3,4] As many as 10 out of 37 (27%) study samples of Sugunakar et al., (2014) experienced death from myocardial infarction.This proves that hypomagnesaemia is a chronic effect of DM and is associated with increased risk of ACS.

Hypomagnesemia and DM are a circulus vitiosus which can increase the risk of complications and mortality.Poorly regulated diabetes mellitus can cause hypomagnesemia through a variety of methods including decreased magnesium (Mg) intake due to nausea, food restriction, and gastroparesis, gastrointestinal Mg loss due to autonomic dysfunction, and kidney loss, both due to the hyperfiltration process in DM patients, as well as due to impaired Mg reabsorption due to insulin resistance.[5,6] Hypomagnesemia can trigger insulin resistance because Mg is needed in the activity of tyrosine kinase in the insulin receptor.[7]

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Low magnesium levels in DM patients will increase the risk of thrombus and ACS. The researchers try to examine the association between serum magnesium levels and the incidence of ACS in DM patients that given the number of cases that occur in RSUD Dr. Soetomo General Hospital Surabaya.The study can be used for administration of magnesium therapy in DM patients and can reduce the incidence of ACS in DM patients.This study will look for the role of hypomagnesemia as a risk factor in the incidence of ACS in DM patients.

Methods

This research was observational analytic with case control study conducted at Dr. Soetomo General Hospital Surabaya from July to December 2018. The population of this studywas DM patients treated at ER and Outpatients Installation of Endocrine atDr. Soetomo General Hospital Surabaya. This study was conducted by consecutive sampling, accordance with the inclusion and exclusion criteria.

The sample size in this study was 76 patients divided by 38 sample group cases and 38 control groups. Inclusion criteria DM with ACS (case) was DM patients who came to the ER at Dr. Soetomo General Hospital Surabaya, with a diagnosis of ACS based on typical angina complaints, ECG shows a picture of ST elevation, ST depression, T inversion, accompanied by an increase in markers, aged between 18-60 years, and willing to take part in the study.The inclusion criteria for DM without SKA (control) was DM patients who came to the Outpatients Installation Endocrine at Dr. Soetomo General Hospital Surabaya, without complaints of angina with a normal ECG, aged 18-60 years, and willing to take part in the study. Exclusion criteria for case and control groups was patients who had gastrointestinal disease, metabolic syndrome, nephrotic syndrome, pregnant and lactating women, impaired renal function eGFR ≤60, immobilization, autoimmune, malignancy, history of alcohol, loop diuretics, cyclosporine/tacrolimus, aminoglycosides, and medicine containing magnesium consumption.

All subjects were subjected to venous blood sampling according to the procedure to determine serum magnesium levels and then record and analyze data.

Sample Collection

Taking blood serum as much as 3cc with Li-Heparin anticoagulant, turning back slowly until homogeneous and then let stand for 30-45 minutes until the blood is frozen and then in the centrifuge 1000g (around 3000 rpm) for 15 minutes then the serum is immediately separated.Blood samples were then processed with a Roche/Hitachi Cobas C 311/501 system with TRIS[a]/6-aminocaproic acid buffer and xylidyl blue reagents through the calorimetric method.

Serum Magnesium Level

Examination of serum magnesium levels with a Roche machine/Hitachi Cobas C 311/501 system was done in Prodia Clinical Laboratory. Normal serum magnesium levels were 1.8-2.4 mg/dL .[8]

Statistical Analysis

The data before analysis were tested for normality Kolmogorov Smirnov. If data is normally distributed then an unpaired T test is carried out and if the data is not normally distributed with Mann Whitney test is performed. The relationship between magnesium levels and the incidence of ACSwith multivariate logistic regression test was performed, the risk numbers were odds ratios (OR), statistical tests were significant if $p < 0.05$. SPSS 22 software was used for data collection, recording and calculation.

Results

Most groups with ACS were mostly male as much as 55.3% while in the group of non ACSpatients the majority were female as many as 57.9%.These results indicate that there were no significant differences between groups of patients with gender ($p = 0.359$). Patients with ACS and non ACS have relatively the same age average of 53.1 years and 52.2 years. This is confirmedby statistical tests that p-value equals to 0.555.

Most of the patients with ACS and non ACS had dyslipidemia in the negative category, ACS (52.6%) and non ACS (60.5%). The condition shows that there is no difference in dyslipidemia between the ACS and non ACS groups. Most of the ACS group had hypertension (55.3%) while in the non ACS group mostly had no history of hypertension (57.9%), Based on this description, the results of the statistical tests also showed no significant differences. Patients with smoking habits in the non ACS group (13.2%) and (36.8%) in the ACS group, this showed a significant difference.Based on the BMI data of this study sample, the mean BMI in the ACSgroup 25.3 ± 2.7 and the non ACS group was 23.7 ± 2.3.Patients with ACS have greater laboratory results than non ACS on average in the HbA1c, RPG, BUN, creatinine serum parameters,data of demographic and clinical characteristic was shown in Table 1.

The results of the medical record magnesium levels are known that patients with ACS have a smaller average value compared with patients with non ACS with a ratio of 1.9mg/dL and 2.1mg/dL.The results of the comparative test also showed that there were significant differences in serum magnesium levels in the ACS and non ACS groups ($p = 0.005$) (Table 2). The researchers determine the cut off value for magnesium levels on the basis of normal magnesium values in this study with the receiver operating characteristic (ROC) method (Figure 1). The cut off of serum magnesium levels in this study was 2.08 (Table 3).

Association between Serum Magnesium Levels and Incidence of ACS in DM Patients

Sample size was calculatedfor all independent variables before being included in the model.Following is a summary of the sample size calculation using z statistics on dichotomous variables such as hypomagnesemia, obesity, smoking, and RPG controls, namely 66; 64; 150; 84.Smoking variables and RPG controls were not included in the model because they requires a larger sample size. The variables obesity and hypomagnesemia deserves were included in the model which analyzed bivariate.The results of bivariate analysis of factors that cause the incidence of ACS in DM patients using logistic regression analysis concluded that hypomagnesemia and obesity variables with p-value <0.25; 0.023 and 0.004 appropriate multivariate analysis (Table 4).

The hypomagnesemia logistic regression

coefficient 1.040 with OR value of 2.8.These results indicate a positive influence between hypomagnesemia and the incidence of ACS in DM patients.In this study, hypomagnesemia and the incidence of ACS in DM patients

Table 1. Demographic and clinical data of research subjects

Characteristic	ACS			Non ACS			p-value
	n	%	Mean ± SD	n	%	Mean ± SD	
Sex							
Male	21	55.3		16	42.1		0.359
Female	17	44.7		22	57.9		
Age			53.1 ± 7.0			52.2 ± 2.3	0.555
Dyslipidemia							
Positive	18	47.4		15	39.5		0.644
Negative	20	52.6		23	60.5		
Hypertension							
Positive	21	55.3		16	42.1		0.359
Negative	17	44.7		22	57.9		
Smoking							
Positive	14	36.8		5	13.2		0.032
Negative	24	63.2		33	86.8		
BMI			25.3±2.7			23.7±2.3	0.006
HbA1c			8.2±1.1			7.7±1.3	0.106
RPG			282.±82.8			240.1±89.2	0.034
BUN			13.1±4.9			12.5 ± 4.5	0.612
Plasma creatinine			0.93 ± 0.2			0.91 ± 0.2	0.701
Potassium			4.1 ± 0.5			4.3 ± 0.5	0.100

Table 2. Mean Serum Magnesium Levels

Serum Magnesium Levels	Mean ± SD		p-value
	ACS	Non ACS	
Magnesium Serum	1.9 ± 0.2	2.1 ± 0.2	0.005

Table 3. Cross Tab Serum Magnesium Levels

	Category	ACS	Non ACS	Total
	Hypomagnesemia (< 2.08)	24 (63.2%)	14 (36.8%)	38 (100%)
	Normal (> 2.08)	14 (36.8%)	24 (63.2%)	38 (100%)
Total			38 (100%)	38 (100%)

Table 4. Bivariate Logistic Regression Analysis

Variable Independent/ Predictor	p-value	OR	95% CI	
			Lower	Upper
Hypomagnesemia	0.038	2.9	1.1	7.6
Obesity	0.023	4.8	1.6	14.1

Table 5. Multivariate Logistic Regression Analysis

Variable Independent/ Predictor	β	p-value		OR	CI	
Constanta	-0.980	0.013				
Hypomagnesemia	1.040	0.039	Significant	2.8	1.0	7.6
Obesity	1.537	0.007	Significant	4.6	1.5	14.1

Area Under the Curve		
Test Result Variable(s): Mg		
Area		
		.658
The test result variable(s): Mg has at least one tie between the positive actual state group and the negative actual state group and the negative actual state group. Statistics may be biased		

Coordinate of the Curve		
Test Results Variable(s): Mg		
Positive if Greater Than or Equal To[a]	Sensivity	1-Specificity
.5200	1.000	1.000
1.6100	1.000	.974
1.7300	1.000	.921
1.7650	1.000	.895
1.7750	1.000	.868
1.7900	1.000	.816
1.8100	.895	.789
1.9300	.895	.763
1.8500	.895	.711
1.8700	.895	.689
1.8900	.895	.658
1.9050	.789	.632
1.9150	.789	.605
1.9300	.789	.579
1.9500	.789	.553
1.9700	.789	.526
1.9900	.789	.500
2.0050	.632	.474
2.0250	.632	.447
2.0450	.632	.421
2.0550	.632	.395
2.0800	.632	.368
2.1100	.395	.316
2.1250	.395	.289
2.1600	.395	.263
2.1950	.395	.237
2.2050	.263	.211
2.2200	.263	.158
2.2350	.263	.132
2.2500	.263	.105
2.2800	.263	.053
2.3050	.211	.053
2.3250	.211	.026
2.3550	.211	.000
2.3850	.184	.000
2.4500	.158	.000
3.5000	.000	.000

The test results variable(s): Mg has at least one tie between the positive actual state group and the negative actual state group.
a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

Figure 1. A. Receiver Operating Characteristic Method (ROC)

concluded to be significant with a p-value of 0.039 (Table 5).

Discussion

In this study most of the subjects in the ACS group were male of 21 patients (55.3%), and female of 17 patients (44.7%); while the male and female subjects in the non ACS group were male of 16 patients (42.1%) and female of 22 patients (57.9%). The study conducted byHartopo et al.,(2016) also showed that there were more men than women (307:68) and the research conducted by Moreno et al., (2013) also showed a comparison of men and women (97:22).[9,10] These results are in accordance with the theory and epidemiological data that men are more likely to develop ACS than women.[11] In this study, the mean age of subjects with ACS was 53.1 ± 7.0 while in non ACS subjects it was 52.2 ± 6.5 with no significant difference (p=0.555). The study conducted by Al Saif et al., (2011) showed that the average age of subjects with ACS was 58.01 ± 12.92 while the study conducted by Moreno et al., (2013) showed that the average age of subjects with ACS was 60.62 ± 9.2. According to this study, the average age of subjects with ACS is more than 50–60 years old.[10,12] These results are in accordance with epidemiological data that the incidence of ACS increases above the age of 40 years old.[11] Traditional risk factors such as dyslipidemia, hypertension, smoking, and HbA1c data were also analyzed in this study.In this study the category of dyslipidemia and smoking were higher in the ACS group than non ACS. Dyslipidemia in ACS (47.4%) and non ACS (39.5%), no significant differences between the number of people with dyslipidemia and hypertension in the ACS and non ACS groups. The two comparative studies are in accordance with this study and prove the theory that dyslipidemia and hypertension are risk factors for ACS.[13] The mean BMI in the group of subjects with ACS was 25.3 ± 2.7, significantly higher (p=0.006) than the mean BMI of the non ACS subject group (23.7 ± 2.3). The study conducted by Hartopo et al., (2016) with ACS subjects had mean BMI of 23.9 ± 3.2, it is almost the same as this study.[9] This study and the comparative research prove the theory that high BMI reflects the metabolic syndrome which is a risk factor for ACS.[10] HbA1c levels in the ACS group were higher (8.2) than in the non ACS group (7.7), but not significant (p=0.106).The study conducted by Chen et al., (2017) showed that the mean HbA1c levels in the CHD group were significantly higher than not CHD (5.91 ± 0.34 and 5.77 ± 0.36 with p = 0.012).[13] In this study it was found that the incidence of STEMI was higher, where the inferior STEMI (47.4%; 18 patients) was more than the anterior STEMI (28.9%; 11 patients), anteroseptal (13.2%; 5 patients) and NSTEMI (10.5%; 5 patients).The study conducted by Merza et al., (2016) stated that from the sample of 68 people, there were 40 STEMI samples.[14]

In this study, mean magnesium in the ACSgroup is lower than in the non ACS group, cut off hypomagnesemia <2.08. Several other studies examined magnesium and its role as a risk factor for SKA and mortality in CHD. The study conducted by Kieboom et al., (2013) of magnesium levels and association to the risk of CHD mortality showed that the average magnesium content of all subjects was 0.84 and patients with hypomagnesemia had a higher risk of CHD mortality (HR 1.36; p <0.05).[15] The comparative research is in accordance with this study and emphasizestheoretical basis of the association between ACS and hypomagnesemia.

The results of bivariate analysis of factors that cause the incidence of ACS in DM patients using logistic regression analysis concluded that the hypomagnesemia and obesity factors with p-value <0.25 that is 0.023 and 0.004 had appropriate test results to be carried out in the effect multivariate test. In this study, hypomagnesemia could be a prognostic factor for the incidence of ACS after interacting with other variables through multivariate analysis (OR 2.8; CI 1.1-7.6; p = 0.039).Furthermore, from the positive influence it can be interpreted if the patient hashypomagnesemia then the possibility of the patient will have the opportunity to experience the incidence of Acute Coronary Syndrome (ACS) of 2.8 times compared with patients with normal magnesium.In this study, obesity was significant (p=0.007) with (OR 4.7; CI 1.5-14.1) after interacting with other variables.Furthermore, from the positive influences it can interpreted that the obese patients are likely to have the opportunity to experience an incidence of Acute Coronary Syndrome (ACS) of 4.7 times compared to patients who are not obese.

Conclusion

The mean serum magnesium level is lower in ACS patients compared to non ACS.The result of this study revealedthe association between serum magnesium levels and the incidence of acute coronary syndrome in DM patients. Hypomagnesemia has a risk of having ACS of 2.8 times compared to patients without hypomagnesemia.

Conflict of Interest

The author stated there is no conflict of interest

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