THE SERUM CALCIUM TO MAGNESIUM RATIO IN PATIENTS WITH ACUTE CORONARY SYNDROME

MURAT CELIK*, MUSTAFA KOKLU*, EROL GUSOY*, MUTLU GUNGOR **, SALIM YASAR*, SUAT GORMEL*, ERKAN YILDIRIM*, YALCIN GOKOGLAN*, UYGAR CAGDAS YUKSEL *, HASAN KUTSI KABUL*, CEM BARCIN*
*Gulhane Military Medical Academy, Department of Cardiology, Ankara, Turkey - **Memorial Sisli Hospital, Service of Cardiology, Istanbul, Turkey

ABSTRACT

Introduction: *There is still uncertainty about the pathophysiological role of magnesium (Mg) in the course of acute coronary syndrome. Since Mg is considered to be natural physiologic 'calcium (Ca) antagonist', the balance between Ca and Mg seems to be more important to reflect its homoeostasis rather than the measurement of serum Mg level.*

Material and methods*: A total of 92 patients (67 male, mean age 61.19 ± 13.64 years) with the diagnosis of acute coronary syndrome were enrolled into this study. Patients were divided into 2 groups by non-ST-segment elevation myocardial infarction to ST-segment elevation myocardial infarction. Clinical and demographic characteristics, and the results of blood samples within 24 hour of admission were evaluated.*

Results: *The mean Ca/Mg ratio for the entire subject cohort on admission was 4.28 ± 0.53. Although serum Ca level was not statistically significantly different between two groups, the patients with ST-segment elevation myocardial infarction were found to have significantly low levels of serum Mg as compared to the non-ST-segment elevation myocardial infarction group (p = 0.004). Consistently, ST-segment elevation myocardial infarction was associated with higher Ca/Mg ratio as compared those with non-ST-segment elevation myocardial infarction. In multivariate linear regression analysis, acute coronary syndrome presentation (ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction) (Unstandardized Coefficients B = 0.262; 95%CI= 0.048 - 0.476; p= 0.017) and serum triglyceride (Unstandardized Coefficients B = -0.002; 95%CI= -0.001 – 0.000; p= 0.027) were found as independent predictors of serum Ca/Mg ratio.*

Conclusion*: The serum Ca/Mg ratio is higher in ST-segment elevation myocardial infarction patients compared those with non-ST-segment elevation myocardial infarction. This could be because of a greater decrease in the levels of Mg than in those of Ca.*

Key words*: Serum Ca/Mg ratio, acute coronary syndrome, ST-segment elevation myocardial infarction, and non-ST-segment elevation myocardial infarction*

DOI: 10.19193/0393-6384_2016_3_76

Received *June 30, 2015;* ***Accepted*** *January 02, 2016*

Introduction

Mg (Mg) is an activator of more than 300 enzymatic reactions in the human body and helps in continuing stable intra- and extracellular concentrations of serum electrolytes throughout its ion stabilizing effect[1]. Hypomagnesaemia is a common electrolyte abnormality, predominantly in the elderly and patients receiving diuretic therapy[2].

The frequency of hypomagnesaemia in hospitalized patients ranges from 8 to 30% and a higher incidence (60-65%) among patients in the intensive care unit[3]. Nonetheless, it has been shown that hypomagnesaemia present on admission to the intensive care unit was associated with prolonged hospitalization duration and increased mortality rate compared with normomagnesemic patients[2].

Mg deficiency is a well-rounded causative factor to cardiovascular diseases. Mg has β adrenoreceptor blocking action, antiplatelet action, reduces the release of Calcium (Ca) from and into the sarcoplasmic reticulum and protects the cells against Ca overload under conditions of ischemia and inhibitory effect on the cardiac conducting system (4). Through these effects, Mg provides to the regulation of vascular tone, heart rhythm, and platelet-activated thrombosis, and regarded as a cardio-protective element. Mg deficiency causes vascular endothelial injury, increases low-density lipoprotein concentration and oxidative modification, and therefore stimulates the development and progression of atherosclerosis[5]. Nonetheless, healthy subjects with the lowest serum Mg level had higher risk for coronary artery disease (CAD) compared to high Mg concentration, even after adjustment for traditional cardiovascular risk factors[6].

The term acute coronary syndrome (ACS) covers the spectrum of clinical conditions ranging from unstable angina to non–ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI). Although risk factors, in-hospital and long-term prognoses are quite similar, STEMI and NSTEMI are somewhat different from each other. Since they do not share the same pathophysiology, different therapeutic goals and approaches are required.

Although studies have documented significant decreases in serum Mg and other electrolytes in patients with ACS, there is still uncertainty about the pathophysiological role of Mg in the course of ACS. Nonetheless, since it should be noted that Mg and Ca compete with one another for the same binding sites on plasma protein molecules, Mg is considered to be natural physiologic 'Ca antagonist'[7]. Thus, the measurement of serum Mg, which commonly used in clinical practice, does not fully reflect its homoeostasis. Instead, the balance between Ca and Mg seems to be more important. The aim of the study was to investigate the status of serum Ca/Mg ratio as a means to understand the underlying pathophysiology of ACS.

Material and methods

We retrospectively investigated 151 patients, who admitted emergency department with chest pain and hospitalized in coronary intensive care unit with the diagnosis of ACS defined by the current guidelines. Among subjects with ACS, patients with a diagnosis of STEMI and NSTEMI were enrolled to this study. Clinical and demographic characteristics were obtained from the computerized hospital database. The results of blood samples which drawn from the antecubital vein within 24 hour of admission were evaluated. Complete blood count analysis and biochemical measurements including cardiac biomarkers, renal function, electrolytes and lipid panel were measured using standard laboratory methods. The estimated glomerular filtration rate values (ml/min/1.73m2) were calculated using the four variable MDRD (Modification of Diet in Renal Disease) equation. Exclusion criteria included diagnosis of unstable angina, active blood loss, excessive sweating, drug and/or alcohol abuse, certain chronic medication use such as loop diuretics and thiazides, aminoglycosides and steroids, liver cirrhosis, thyroid and parathyroid diseases, chronic gastrointestinal and renal diseases, and lack of biochemical and basal demographical data of patients. 59 patients were excluded and the final 92 patients were enrolled into this study.

Statistical analysis

The data were tested for normal distributions using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as percentages. Chi-square test was used for comparison of categorical data. Independent samples t test and Mann-Whitney U test were used to compare quantitative data with normal distribution and without normal distribution, respectively, between groups. Univariate correlation was performed with Spearman and Pearson's correlation coefficients. Following univariate correlations, a multivariate linear regression model with a backward selection process was applied. Differences were considered statistically significant when the p value was < 0.05. The Statistical Package for Social Sciences (SPSS, Chicago, Illinois, USA) version 20 was used for all calculations and statistical analyses.

Results

We included 92 patients with ACS (67 male, mean age 61.19 ± 13.64 years). The clinical features of patients are in Table 1 and the baseline demographic and clinical data were similar between two groups. As expected, there was a significant increase in the serum creatine kinase muscle-brain fraction (CK-MB) and Troponin-T levels in the

STEMI group. Mean serum Ca and serum Mg concentrations, were 9.04 ± 0.56 mmol/L and 2.14 ± 0.29 mmol/L, respectively.

	All population (n=92)	NSTEMI (n= 49)	STEMI (n=43)	P value
Male, n (%)	67 (72.8)	35 (71.4)	32 (74.4)	0.466
Age, years	61.19 ± 13.64	62,53 ± 14,69	59,67 ± 12,33	0.319
SBP, mmHg	131.50 ± 23.87	132.61 ± 21.06	130.23 ± 26.91	0.636
DBP, mmHg	81.44 ± 13.68	81.22 ± 14.54	81.69 ± 12.78	0.870
Previous history of CAD, n (%)	42 (45.7)	25 (51)	17 (39.5)	0.186
Diabetes mellitus, n (%)	19 (20.7)	10 (20,4)	9 (20.9)	0.576
Hypertension, n (%)	44 (47.8)	26 (53.1)	18 (41.9)	0.194
Hyperlipidemia, n (%)	14 (15.2)	10 (20,4)	4 (9.3)	0.117
Hospitalization duration, (days)	5 (5)	5 (7.50)	5 (4)	0.880*
In-Hospital mortality, n (%)	5 (5.4)	4 (8,2)	1 (2.3)	0.224
Fasting Glucose, (mg/dL)	123.50 (62.25)	116.00 (55.00)	131.00 (60.00)	0.148*
eGFR (mL/min/1.73m^2)	77.47 (32.69)	76.92 (30.21)	81.15 (36.18)	0.268*
Serum Uric Acid, (mg/(dL)	6.04 ± 2.07	6.30 ± 2.19	5.75 ± 1.91	0.200
LDL-C, (mg/dL)	126.72 ± 43.96	132.53 ± 52.91	120.11 ± 30.05	0.407
HDL-C, (mg/dL)	42.59 ± 20.90	44.65 ± 27.22	40.25 ± 9.44	0.802
Total Cholesterol, (mg/dL)	195.50 (62.75)	196.00 (68.50)	195.00 (57.00)	0.471*
Triglyceride, (mg/dL)	120.50 (80.25)	128.00 (124.50)	112.00 (76.00)	0.173*
Neutrophil / Lymphocyte Ratio	3.07 (3.19)	2.58 (2.88)	3.67 (3.01)	0.043*
Hemoglobin, (g/dL)	13.70 ± 2.24	13.57 ± 2.24	13.84 ± 2.26	0.577
Platelet count, (10^3 µL)	237.51 ± 72.17	230.40 ± 66.80	245.60 ± 77.85	0.316
Mean platelet volume, (fL)	9.48 ± 1.28	9.42 ± 1.16	9.54 ± 1.42	0.646
Red Cell Distributed Width (%)	25.47 ± 14.83	26.28 ± 14.84	24.95 ± 15.04	0.300
hs-CRP, (mg/L)	23.98 ± 32.16	25.28 ± 35.78	23.03 ± 28.19	0.691
Peak serum CK-MB (IU/L)	66.50 (142.50)	44.00 (99.00)	128.00 (164.00)	0.003*
Peak serum Troponin-T	30.46 (48.61)	9.15 (49.10)	50.00 (38.53)	< 0.001*
LVIDd, (mm)	47.00 (7.75)	47.00 (8.00)	47.00 (6.00)	0.875*
IVSd, (mm)	10.39 ± 1.78	10.39 ± 1.88	10.38 ± 1.68	0.970
LVEF, (%)	50.00 (17.75)	55.00 (15.00)	45.00 (15.00)	< 0.001*

Table 1: Baseline demographical, clinical and laboratory data of patients with acute coronary syndrome according to clinical presentation at admission.

*SBP: systolic blood pressure; DBP: diastolic blood pressure; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; hs-CRP: high sentsitive C-reactive protein; CK-MB: creatine kinase muscle-brain fraction; LVIDd: left ventricular end-diastolic internal dimension; IVSd: interventricular septal end diastolic dimension; LVEF: left ventricular ejection fraction. Data are presented as mean ± SD, median (interquartile range) or n (%). *Mann-Whitney U test was used to compare quantitative data without normal distribution between groups*

The mean Ca/Mg ratio for the entire subject cohort on admission was 4.28 ± 0.53, significantly higher than the normal range published in the previous studies[4, 8].

For further analysis, patients were divided into 2 groups by the type of ACS: NSTEMI and STEMI. Although serum Ca level was not statistically significantly different between two groups, the patients with STEMI were found to have significantly low levels of serum Mg as compared to the NSTEMI group (p = 0.004). Nonetheless, the Ca/Mg ratio was differed by clinical presentation. STEMI was associated with higher Ca/Mg ratio as compared those with NSTEMI (Table 2). Also, the K to Mg and the Na to Mg ratios were significantly higher in the STEMI patients compared to those with NSTEMI (Table 2).

	All population (n=92)	NSTEMI (n= 49)	STEMI (n=43)	P value
Serum Na, (mEq/L)	140.00 (3.00)	141.00 (3.00)	140.00 (3.00)	0.151*
Serum K, (mEq/L)	4.03 (0.63)	3.98 (0.64)	4.08 (0.66)	0.757*
Serum PO4, (mg/dL)	3.58 (1.35)	3.83 (1.66)	3.56 (1.04)	0.255*
Serum Ca, (mg/dL)	9.04 (0.50)	9.11 (0.54)	9.03 (0.44)	0.340*
Serum Mg, (mg/dL)	2.12 (0.28)	2.17 (0.28)	2.05 (0.25)	0.004*
Ca / Mg ratio	4.31 (0.54)	4.18 (0.50)	4.40 (0.48)	0.015*
K / Mg ratio	1.90 (0.39)	1.85 (0.36)	1.97 (0.37)	0.019*
Na / Mg ratio	66.11 (8.64)	65.09 (8.33)	67.63 (8.77)	0.012*
Na / K ratio	34.62 ± 4.42	34.74 ± 4.77	34.48 ± 4.04	0.776

Table 2: . Comparison of serum electrolytes, Ca/Mg, K/Mg, Na/K ratios between cases with NSTEMI and STEMI.

Na: sodium; K: potassium; PO4: phosphate; Ca: calcium; Mg: magnesium; Data are presented as mean ± SD or median (interquartile range).

** Mann-Whitney U test was used to compare quantitative data without normal distribution between groups*

There were significant correlations of the Ca/Mg ratio with ACS presentation (STEMI or NSTEMI), left ventricular ejection fraction, serum triglyceride and total cholesterol as has been described in univariate correlation analysis (p values of <0.05) (Table 3). Then, we performed a backward multivariate linear regression analysis to determine the independent variables likely to affect the Ca/Mg ratio including variables, which were clinically important, found significant in univariate correlation analysis and significantly differed between two groups. ACS presentation (STEMI or NSTEMI) (Unstandardized Coefficients B = 0.262; p= 0.017) and serum triglyceride level

(Unstandardized Coefficients B = -0.002; p= 0.027) continued significant association with Ca/Mg ratio in multivariate analysis (Table 3).

	Univariate analysis		Multivariate analysis	
	r	P value	Unstandardized Coefficients B (95% CI)	P value
Clinical presentation (NSTEMI or STEMI)	0.28	0.007	0.262 ((0.048) - (0.476))	0.017
In-hospital mortality	0.04	0.704	0.051 ((-0.463) - (0.565))	0.844
LVEF	-0.254	0.015	-0.007 ((-0.018) - (0.003))	0.166
eGFR	0.069	0.511	0.003 ((-0.002) - (0.007))	0.141
Triglyceride	-0.264	0.011	-0.001 ((-0.001) - (0.000))	0.027
Total Cholesterol	-0.212	0.043	0.000 ((-0.003) - (0.002))	0.85
Neutrophil / Lymphocyte Ratio	0.19	0.07	0.014 ((-0.012) - (0.041))	0.294
Peak CK-MB	0.111	0.291	0.000 ((-0.001) - (0.001))	0.93
Peak Troponin T	0.139	0.185	0.000 ((-0.005) - (0.005))	0.895

Table 3: The variables significantly correlated with Ca/Mg ratio in univariate and multivariate analyses.
NSTEMI: non–ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; CK-MB: creatine kinase muscle-brain fraction

Discussion

The main finding of our study is that serum Ca/Mg ratio was significantly higher in ACS patients and this increase seems to be due to a greater decrease in the levels of Mg rather than increase in Ca level. Nonetheless, higher serum Ca/Mg ratio was significantly associated with the clinical presentation of ACS, as higher in STEMI patients compared to NSTEMI.

The pathogenesis of ACS involves a multifaceted interaction among the endothelium, the lipid and tissue factor content of the plaque, the inflammatory cells, and the thrombogenicity of the blood[9].

Since it regulates hundreds of enzyme systems, Mg may also play a critical role in the pathophysiology of ACS[3]. The data showing the potential importance of Mg in acute myocardial infarction (AMI) patients is mostly based on observations in Mg deficient animals. In animal models, experimental hypomagnesemic state induces an exaggerated pro-inflammatory response marked by elevations in C-reactive protein, leukocyte and macrophage activation, release of inflammatory cytokines, acute phase proteins and nuclear factor kappa B[10, 11]. Mg deficiency also promotes oxidative stress throughout the release of free oxygen radicals and impairs the release of nitric oxide (NO) from coronary endothelium[12]. Since NO is a potent endogenous vasodilator and inhibitor of platelet aggregation and adhesion, hypomagnesemia may promote vasoconstriction and platelet-dependent coronary thrombosis, for possible involvement in the setting of AMI[13]. Nonetheless, low Mg level affects endothelial fibrinolytic activity by overexpressing of plasminogen activator inhibitor-1[14]. Ravn et al.[15] proposed that the increased arterial thrombus formation in patients with low Mg levels is related to effects on platelet activity rather than to effects on the coagulation cascade. Consequently, this hypomagnesemic state disrupts the endothelium, and promotes thrombosis and contributes to consequent influences on plaque vulnerability throughout impairing the balance between extracellular matrix production and degradation[16, 17]. On the contrary, some Mg reduction in the acute phase of AMI has been mainly attributed Mg binding to free fatty acids released by catecholamines, and thereby, it has been suggested that lower blood concentrations of Mg may be a result of AMI[18].

The normal adult total body Mg content is approximately 25g[7]. Almost 60% of Mg in bones, 35% is located in high metabolic tissues such as muscles, brain, heart, kidneys and liver. Simply 1% of total body Mg is present in extracellular fluids, and only 0.3% of total body Mg is found in serum[7]. Serum Mg concentration is strictly continued within the physiological range in healthy individuals and is valuable for rapid assessment of acute changes in clinical medicine[7]. However, individuals still may have a deficit in total body Mg, even when serum Mg levels are within the reference range[19]. On the contrary, some individuals have low serum Mg levels but a physiological Mg body content[19]. Since most Mg is found intracellular, the measurement of serum Mg cannot completely reveal its homoeostasis. In addition, serum Mg should be measured more than once, because of variations in Mg levels depending upon diet, medication and physical activity[20].

Although the intracellular Mg concentration reflects the total Mg status more exactly compared to the serum Mg levels, measuring the intracellular Mg is inconvenient, as this is a very sophisticated and time-consuming method. Consequently, for this reasons, many studies could not ascertain the exact

role of the serum Mg measurement in the setting of AMI.

Mg has complicated effects on myocardial ion fluxes such as Ca channels and the Na-K-ATPase pump[21]. Therefore, the status of intracellular Mg is closely linked to the cellular ionic balance through its association with Ca, sodium (Na), and potassium (K). The Mg deficiency caused by the reduction of the Na/K ATPase activity is leading to Na accumulation in the myocytes[4]. Elevated myocardial Na levels would yield the reverse of the Na+/K+ exchange and a increase in the intracellular Ca levels[21]. Although Mg and Ca share similar chemical properties, they compete with each other for the same binding sites on plasma protein molecules, depending on their concentrations[1]. Mg acts as a mild physiological Ca blocker, primarily through mainly the L-type and N-type Ca channels[22]. Thus, a deficiency in Mg will lead to an increase in intracellular Ca level.

The mechanisms by which Mg might protect the myocardium in the setting of ischemia and infarction are not fully elucidated. Recent some experimental studies on animal models of AMI have demonstrated that Mg can inhibit the formation of thrombi by reducing platelet aggregation and prolonging blood-clotting time, rescue the physiological activities of endothelial cells by increasing NO production and decrease free radical formation[17, 23, 24]. These favorable effects of Mg somewhat might be a consequence of its competition with Ca ions. Since Ca promotes coagulation, Mg inhibits Ca-induced coagulation process[7]. The formation and destruction of blood clots is accepted as healthy when Ca and Mg are balanced at a ratio below 4-to-1, whereas pathological blood clot formation results when the ratio is above 4-to-1[25]. Since platelet activation is a key element in the pathogenesis of STEMI, checking the ratio of serum Ca/Mg rather than only serum Mg level seems to be more important for assessing the bioavailability of Mg. Speich et al.[26] demonstrated an alteration in the serum Ca/Mg ratio in heart muscles after an AMI. Ramasamy et al.[4] investigated the levels of Mg with those of other routine electrolytes. They found that Ca/Mg, the K to Mg and the Na to K ratios were comparatively higher in the AMI patients than in the control groups, and the Ca/Mg and the K to Mg ratios showed significant correlations with other established cardiac markers such as CK-MB and troponin. They stated that the optimum cut-off of 3.43 for the Ca/Mg ratio had a sensitivity of 96% and a specificity of 78% for the diagnosis of AMI[4]. Similar to these studies, we found that serum Ca/Mg ratio was 4.28 ± 0.5, which is significantly higher than the value indicated in the previous studies, and it was higher in STEMI patients rather than NSTEMI patients. We suggested that this elevation could be primarily because of a greater decrease in the levels of serum Mg level than in those of Ca. Although benefits of Mg therapy in AMI patients have been investigated over two decades, no firm guidelines do not support the routine use of oral Mg in patients with AMI. However, treatment strategies for maintaining the serum Ca/Mg ratio within the physiological range through increasing the intracellular Mg levels might theoretically prevent endothelial dysfunction and pathological formation of blood clots in the course of STEMI/NSTEMI. Future studies should address this issue.

While Ca is accepted as a powerful 'death trigger', Mg has anti-apoptotic activity in mitochondrial permeability transition and antagonizes Ca-overload-triggered apoptosis[7]. Also, hypomagnesaemia may adversely effect the re-endothelialization of vascular injuries and result in deferred or insufficient angiogenesis and collateral development, and infarct expansion[27].

In our study, we found a statistically significant correlation between left ventricular ejection fraction and serum Ca/Mg ratio in univariate analysis. However, the value was not statistically significant in multivariate linear regression analysis likely possibly due to the small sample size of the study.

Mg is an important cofactor of two enzymes that are essential in lipid metabolism: lecithin-cholesterol acyltransferase and lipoprotein lipase[28]. Therefore, hypomagnesaemia induces a proatherogenic lipid profile by decreasing HDL (high-density lipoprotein) and increasing total serum cholesterol, LDL (low-density-lipoprotein) and triglycerides, especially in diabetic patients[29]. However, Niemela et al.[30] showed that intracellular platelet Mg levels significantly inversely correlated with serum total cholesterol level. Similarly, we found statistically significant inverse correlations between serum triglyceride level and serum Ca/Mg ratio in univariate and multivariate analyses.

Limitations

The present study has a number of limitations. First, this study was limited by its modest size and retrospective design, which may affect the study

generalizability. Second, we did not attempt to clarify the factors affecting serum concentrations of Mg or serum Ca/Mg ratio in ACS patients. Third, Ueshima et al.[8] showed that recovery of serum Mg concentration was relatively rapid in the acute phase of STEMI compared with NSTEMI. However, we measured Mg and Ca only within 24 h of admission and did not evaluate the time course of serum Mg and Ca levels. These could be the scope of future studies, to further document the utility of Ca/Mg ratio in the day-to-day management of ACS. Fourth, although serum Mg level plays a pivotal role in platelet dependent thrombosis, we did not assess it using an ex vivo model. Despite these limitations, our results propose a need for further studies with larger numbers of patients.

In conclusion, we found that serum Ca/Mg ratio is higher in ACS patients compared to the normal range published in the previous studies. Nonetheless, the serum Ca/Mg ratio is higher in STEMI patients compared those with NSTEMI, probably due to the effect of serum Ca/Mg ratio on platelet-dependent coronary artery thrombosis. This could be because of a greater decrease in the levels of Mg than in those of Ca. This study is already a preliminary report, and we strongly believe that the results will be more accurate when we reach a higher number of patients.

References

1) Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. *Magnesium. An update on physiological, clinical and analytical aspects*. Clin Chim Acta, 2000; 294: *1-26*.

2) Rubeiz GJ, Thill-Baharozian M, Hardie D, Carlson RW. *Association of hypomagnesemia and mortality in acutely ill medical patients*. Crit Care Med, 1993; 21: *203-9*.

3) Tong GM, Rude RK. *Magnesium deficiency in critical illness*. J Intensive Care Med, 2005; 20: *3-17*.

4) Ramasamy R, Murugaiyan SB, Gopal N, Shalini R. *The prospect of serum magnesium and an electrolyte panel as an adjuvant cardiac biomarker in the management of acute myocardial infarction*. J Clin Diagn Res, 2013; 7: *817-20*.

5) Shivakumar K. *Model of cardiovascular injury in magnesium deficiency*. Med Hypotheses, 2001; 56: *110-3*.

6) Liao F, Folsom AR, Brancati FL. *Is low magnesium concentration a risk factor for coronary heart disease?* The Atherosclerosis Risk in Communities (ARIC) .Study. Am Heart J, 1998; 136: *480-90*.

7) Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J, 2012; 5: i3-i14

8) Ueshima K, Tachibana H, Suzuki T, Hiramori K. *Factors affecting the blood concentration of ionized magnesium in patients in the acute phase of myocardial infarction*. Heart Vessels, 2004; 19: *267-70*.

9) Kumar A, Cannon CP. *Acute coronary syndromes: diagnosis and management, part I*. Mayo Clin Proc, 2009; 84: 917-38

10) Mazur A, Maier JA, Rock E, Gueux E, Nowacki W, et al. *Magnesium and the inflammatory response: potential physiopathological implications*. Arch Biochem Biophys, 2007; 458: 48-56

11) King DE. *Inflammation and elevation of C-reactive protein: does magnesium play a key role?* Magnes Res, 2009; 22: *57-9*.

12) Wolf FI, Trapani V, Simonacci M, Ferre S, Maier JA. Magnesium deficiency and endothelial dysfunction: is oxidative stress involved? Magnes Res, 2008; 21: 58-64

13) Pearson PJ, Evora PR, Seccombe JF, Schaff HV. Hypomagnesemia inhibits nitric oxide release from coronary endothelium: protective role of magnesium infusion after cardiac operations. Ann Thorac Surg, 1998; 65: 967-72

14) Maier JA, Malpuech-Brugere C, Zimowska W, Rayssiguier Y, Mazur A. *Low magnesium promotes endothelial cell dysfunction: implications for atherosclerosis, inflammation and thrombosis*. Biochim Biophys Acta, 2004; 1689: *13-21*.

15) Ravn HB, Lassen JF, Bergenhem N, Kristensen AT. *Intravenous magnesium does not influence the activity of the coagulation cascade*. Blood Coagul Fibrinolysis, 2001; 12: *223-8*.

16) Ferre S, Baldoli E, Leidi M, Maier JA. *Magnesium deficiency promotes a pro-atherogenic phenotype in cultured human endothelial cells via activation of NFkB*. Biochim Biophys Acta, 2010; 1802: 952-8.

17) Shechter M. Magnesium and cardiovascular system. Magnes Res, 2010; 23: 60-72

18. Flink EB, Brick JE, Shane SR. *Alterations of long-chain free fatty acid and magnesium concentrations in acute myocardial infarction*. Arch Intern Med, 1981; 141: *441-3*.

19. Elin RJ. *Assessment of magnesium status for diagnosis and therapy*. Magnes Res, 2010; 23: *S194-8*.

20. Fletcher GF, Sweeney ME, Fletcher BJ. *Blood magnesium and potassium alterations with maximal treadmill exercise testing: effects of beta-adrenergic blockade*. Am Heart J, 1991; 121: *105-10*.

21) Agus ZS, Morad M. *Modulation of cardiac ion channels by magnesium*. Annu Rev Physiol, 1991; 53: *299-307*.

22) Shimosawa T, Fujita T. *(Magnesium and N-type calcium channel)*. Clin Calcium, 2005; 15: *239-44*.

23) Maier JA, Bernardini D, Rayssiguier Y, Mazur A. *High concentrations of magnesium modulate vascular endothelial cell behaviour in vitro*. Biochim Biophys Acta, 2004; 1689: *6-12*.

24) Dong JF, Cruz MA, Aboulfatova K, Martin C, Choi H, et al. *Magnesium maintains endothelial integrity, up-regulates proteolysis of ultra-large von Willebrand factor, and reduces platelet aggregation under flow conditions*. Thromb Haemost, 2008; 99: 586-93.

25) Orrenius S, Zhivotovsky B, Nicotera P. *Regulation of cell death: the calcium-apoptosis link*. Nat Rev Mol Cell Biol, 2003; 4: *552-65*.

26) Speich M, Bousquet B, Nicolas G. *Concentrations of magnesium, calcium, potassium, and sodium in human heart muscle after acute myocardial infarction*. Clin Chem, 1980; 26: *1662-5*.

27) Weisman HF, Bush DE, Mannisi JA, Weisfeldt ML, Healy B. *Cellular mechanisms of myocardial infarct expansion*. Circulation, 1988; 78: *186-201*.

28) Rosanoff A, Seelig MS. *Comparison of mechanism and functional effects of magnesium and statin pharmaceuticals*. J Am Coll Nutr, 2004; 23: 501S-505S.

29) Barbagallo M, Dominguez LJ. *Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance*. Arch Biochem Biophys, 2007; 458: *40-7*.

30) Niemela JE, Csako G, Bui MN, Elin RJ. *Gender-specific correlation of platelet ionized magnesium and serum low-density-lipoprotein cholesterol concentrations in apparently healthy subjects*. J Lab Clin Med, 1997; 129: *89-96*.

Corresponding author
MURAT CELIK, M.D.
Associate Professor of Cardiology
Department of Cardiology
Gulhane Military Medical Academy
06018 Etlik-Ankara
(Turkey)