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Original Article

Association of Serum Magnesium Level with Major Risk Factor, Thrombolysis and Echocardiography in Patients with Acute Coronary Syndrome

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ABSTRACT

Megnesium depletion plays a key role in the pathphysiologic features of diabetes mellitus, hypertension, thrombosis, arrhythmias and coronary artery disease. Whether the depletion is related to the Echocardiographic parameters in an acute phase of acute coronary syndrome is not known. The objective of the study is to explore the status of serum magnesium in acute coronary syndrome patients. To investigated the association of serum magnesium levels with major risk factor, fibrinolysis and echocardiography in Patients with acute coronary syndrome. The 68 patients with were divided into three groups: STEMI, NSTEMI and unstable angina. The 24 healthy individuals matched as a control group. Serum Mg was measured in all patients groups and control group, the analysis is performed in an atomic absorption spectrophotometer (Schmiadzu AA5646). Estimation of serum glucose, urea, creatinine, lipid profile was done by colorimetric method. The mean ±SD value of serum Mg levels in patients with ACS was significantly lower than those in normal controls. ANOVA test revealed there was non significant difference in the value of serum Mg mean ±SD levels among three types of acute coronary syndrome, t- test revealed there was non significant difference in the value of serum Mg mean±SD levels in the presence or absente of diabetes millitus, Dyslipidemia, Hypertension, Smoking, Obesity and fibrinolytic treatment. The mean (±SD) value of serum Mg levels was non-significantly associated with mitral regurgitataion (MR) severity and diastolic dysfunction stages. There was non-significant correlation between the serum Mg concentration and the value of Isovolumic relaxation time, E (left ventricular inflow velocity) / e (tissue doppler velocity) ratio and Decceleration time, Age, Diameter of left atrium and Left Ventricular Ejection Fraction (LVEF). Decreases Serum magnesium level indicate ischemia severity in acute coronary syndrome patients, Serum magnesium level non significantly associated with major risk factor, fibrinolytic treatment and Echocardiographic parameter in acute phase of disease.

Key Words: Magnesium, ACS, Echocardiographic

INTRODUCTION

Disruption of vulnerable or high-risk plaques is the common pathophysiological substrate of the acute coronary syndromes that comprise a spectrum of myocardial ischemia. Patients with an acute coronary syndrome include those whose clinical presentations cover the following range of diagnoses: unstable angina, MI without ST elevation (NSTEMI), and MI with ST elevation (STEMI) [**1-3]**.

Patients with STEMI have a high likelihood of a coronary thrombus occluding the infarct artery. Patients presenting with persistent ST-segment elevation are candidates for reperfusion therapy (either pharmacological or catheter-based) to restore flow promptly in the occluded epicardial infarct-related artery. Patients presenting without ST-segment elevation are not candidates for immediate pharmacological reperfusion but should receive anti-ischemic therapy and catheter-based therapy [**4, 5]**. Magnesium (Mg) is the second most common intracellular electrolyte after potassium (K) [6]. Mg is a cofactor in more than 300 enzyme systems in human cells and it has a predominant role in normal myocardial physiology. Mg is an essential co-factor for sodium potassium adenosine triphosphatase (Na-KATPase) [7].

The mechanisms by which magnesium might exert a beneficial effect in myocardial infarction are obviously multiple, and include effects on both normal and abnormal automation, on intracellular calcium and, perhaps on factors such as coronary tone [8].

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PATIENTS AND METHODS

The study was conducted in Baghdad Teaching hospital and Al- shahed ghaze al-harere Hospital. The 68 patients with ACS aged (34.00-76.00) year (52 male and 16 female) diagnosed on the base of clinical features, Electrocardiography, and Echocardiography, they were divided into three groups. Group I included 40 patients with STEMI aged (34.00-76.00) year, group II included 8 patients with NSTEMI aged (50.00-75.00) year, and group III included 20 patients with Unstable angina aged (45.00-68.00) year. 24 healthy individuals matched as a control group. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (BMI =weight/(height)^2), patients were obese if Body mass index > 25 kg/m^2 . Prevalent diabetes was defined as a fasting serum glucose 126 mg/dl or current use of any diabetes medication. Prevalent hypertension was defined as seated diastolic blood pressure 90 mmHg, systolic blood pressure 140 mmHg, or use of anti-hypertensive drugs. Dyslipidemia was defined as Atherogenic Index > 3.2. Current smokers were defined as self-reported regular smoking. Each serum sample was analyzed for urea and creatinin to exclude kidney diseases. Serum Mg were measured in all patients groups and control group. Any correlated diseases that can cause hypo or hypermagnesia are excluded from the study, about 2 milliliters of blood was aspirated from patients and healthy individuals then transferred to plane tube, left to clot in room temperature and then centrifuged for 10 min. many times, the clear serum was stored at -20 C ° until used for measuring Mg+2 . The serum was diluted 1:50 with 0.3 M HCL containing 0.5 per cent (w/v) lanthanum chloride, and the analysis is performed in an atomic absorption spectrophotometer (Schmiadzu AA5646). Estimation of serum glucose, urea, creatinine, lipid profil were done by colorimetric method.

Statistic: Statistical analysis were performed by using SPSS version 14.0 the results were expressed as mean ± SD. t-test for analysis data and comparison between group mean. Correlation coefficient used to find the correlation between studied markers by using Pearson correlation. The significance level was set as p>0.05. A p-value less than 0.05 were considered statistically significant (S), p-value greater than 0.05 considered non-significant (NS).

RESULTS

The (68) patients with ACS divided into three groups. First group (40) patients with STEMI (30 males & 10 females), Second group (8) patient with NSTEMI (4 males & 4 females) and and Third group (20) patients with Unstable angina (16 males & 4 females) compared with (24) healthy individuals (12 male &12 female) as a control group. The mean value of patients age was significantly higher when compared with the mean value of healthy control age ($p \leq 0.05$), as shown in (table 1). The mean±SD of age was (64.25 ± 11.50) years for the patients with NSTEMI, (59.80 ± 10.48) years for the patients with STEMI and (56.30 ± 7.87) years for the patients with Unstable angina (UNSA)**.** Analysis of Variance (ANOVA) revealed non-significant difference in the mean±SD of age among three groups ($p > 0.05$). The results of current study showed that the mean ±SD value of serum Mg levels in patients with ACS was significantly lower than that in normal controls ($p \leq 0.01$), (Table 3). The ANOVA test revealed there was non-significant difference ($p > 0.05$) in the value of serum Mg mean±SD levels among three types of acute coronary syndrome(ACS), (Table 4). The t- test revealed there was non-significant difference ($p > 0.05$) in the serum Mg mean ±SD levels in the presence(**YES**) or absente(NO) of diabetes millitus, Dyslipidemia, Hypertension, Smoking, Obesity and fibrinolysis treatment (Actilyse), (Table 5). Table (6) shows the mean(±SD) value of serum Mg levels according to diastolic dysfunction stages, 56 patients had diastolic dysfunction, the mean(±SD) values of serum Mg levels of patients in stage 3 were non-significantly higher than that in stage 1 and 2 (p-value = 0.93), (Table 6).

The table 7 show distribution of serum Mg level by mitral regurgitataion (MR) echocardiographic Finding. There was non-significant difference in mean (± SD) values of serum Mg levels among MR severity groups, (P-value=0.902). The study showed that there was non-significant positive correlation between the serum Mg concentrations and the values of Isovolumic relaxation time (r = 0.17) (P= 0.33), E (left ventricular inflow velocity) / e (tissue doppler velocity) ratio (r = 0.002) (P = 0.99) and Decceleration time (r = 0.22) (P = 0.20). However, there was non-significant negative correlation with Age (r = - 0.071) (P = 0.689), Diameter of left atrium(r = - 0.032) (P = O.860) and Left Ventricular Ejection Fraction (LVEF) (r = -0.176) (P = 0.319).

Table 1: Distribution of the studied sample according to the age:

Age	Number of subjects (n)	Minimum	Maximum	Mean	Std. Deviation
patients	68	34.00	76.00	59.29	9.90
control	24	20.00	58.00	37.62	14.56
P- value				0.023 *	

Means compared using Student's unpaired't' test; * (P≤0.05) Significant.

Table 2: The mean of age for the studied sample according to type of acute coronary syndrom(ACS):

TACS	Number of subjects	Minimum	Maximum	Mean of age(year)	Std. Deviation
STEMI	40	34.00	76.00	59.80	10.48
NSTMI	8	50.00	75.00	64.25	11.50
UNSA	20	45.00	68.00	56.30	7.87
p-value				0.099 NS	

Results are mean ± SD, data were subjected to one way Analysis of Variance (ANOVA) Mean were significantly different at $p \leq 0.05$ at 95% confidence limit. NS: Non-significant ($p > 0.05$).

Table 3: The mean ±SD level of serum Mg (mgldl) in patients with acute coronary syndrome (ACS) and Control:

Group	Mean of serum Mg (mgldl)	Std. Deviation
Control	1.72	0.31
patients	1.06	0.18
P-Value	0.002**	

Results expressed as Mean (± SD). ** (P≤0.01)

Table 4: Distribution of the mean±SD level of serum Mg (mgldl) according to type of acute coronary syndrome (ACS):

Type of acute coronary syndrome	Number	Minimum	Maximum	Mean of serum Mg (mgldl)	Std. Deviation
STEMI	40	0.70	1.61	1.16	0.23
NSTMI	8	0.79	1.58	1.21	0.34
Unstabeangina	20	0.70	1.55	1.23	0.28
P-Value				0.7 **NS**	

- Results expressed as Mean (± SD). NS: Non-significant ($p > 0.05$).
- (ANOVA) Mean were significantly different at $p \leq 0.05$ at 95% confidence limit. NS: Non-significant ($p < 0.05$).

Table 5: Effect of risk factor and fibrinolysis treatment (Actilyse) on serum magnesium level:

Risk factor		Number	Mean of serum Mg (mgldl)	Std. Deviation	P-Value
Diabetes millitus	**NO**	32	1.24	0.23	0.2
	YES	36	1.13	0.27	NS
Dyslipidemia	**NO**	58	1.21	0.25	0.18
	YES	10	1.04	0.22	NS
Hypertension	**NO**	30	1.14	0.22	0.27
	YES	38	1.13	0.27	NS
Obsity	**NO**	40	1.23	0.253	0.26
	YES	28	1.25	0.25	NS
Smoking	**NO**	48	1.26	0.26	0.27
	YES	20	1.16	0.23	NS
Actilys	**NO**	50	1.17	0.27	0.36
	YES	18	1.24	0.19	NS

Results expressed as Mean (± SD). NS: Non-significant (p > 0.05).

Table (6) The mean(±SD) of serum Mg levels (mg/dL) according to diastolic dysfunction Stages:

Diastolic dysfunction Stages(DDS)	Number of patients=68	Mean ± SD of serum Mg(mg/dL)
NO D.D.	12	1.16 ± 0.25
1	32	1.21 ± 0.25
2	16	1.14 ± o.27
3	8	1.22 ± o.30
P-value	----	0.86 NS

Results expressed as Mean (± SD). NS: Non-significant (p > 0.05); (ANOVA) Mean were significantly different at p ≤ 0.05 at 95% confidence limit. NS: Non-significant (p >0.05).

Table 7: Distribution of serum Mg concentrations by mitral regurgitataion (MR) echocardiographic Finding:

Mitral regurgitataion (MR)severity	Number	Minimum	Maximum	Mean of serum Mg (mgldl)	Std. Deviation
NO	42	o.70	1.61	1.18	0.27
Mild	22	o.97	1.44	1.22	0.17
Moderate	4	0.70	1.46	1.08	0.53
P-value				0.90 NS	

Results expressed as Mean (± SD). NS: Non-significant (p > 0.05); (ANOVA) Mean were significantly difference at p ≤ 0.05 at 95% confidence limit. NS: Non-significant (p >0.05).

Table (8) The correlation (r) between serum Mg (mgldl) with Age, left atrium diameter, E/e, Isovolumic relaxation time, and LVEF% for patients groups:

parameters	Age (year) (r)	Diameter of left atrium(cm) (r)	Isovolumic relaxation time(ms) (r)	E/e	Deccelera-tion time(ms)	LVEF%
Mg(mg/dl)	0.071 P=0.68 NS	-0.032 P=O.86 NS	0.177 P=0.33 NS	0.002 P=0.99 NS	0.228 P=0.20 NS	-0.176 P=0.31 NS

- **NS: Non-significant (p > 0.05).**
- **E/e = (left ventricular inflow velocity) / (tissue doppler velocity) ratio**

DISCUSSION

Magnesium depletion seems to be involved in onset, morbidity and mortality from myocardial infarction. In experimental animals the degree of atherosclerotic disease is inversely related with dietary magnesium intake. Deficiency causes endothelial dysfunction, hypercoagulopathy and increases lipids concentration in atheromatic lesions. Further depletion seems to be related with hyperreactivity of coronary arteries to vasoconstrictive stimuli (neurohormonic, electrolytic), whereas Mg levels normalization plays a role in protection against angina and peripheral vasoconstriction [9]**.** Animals with magnesium deficiency have significantly shorter prothrombin time than healthy animals [10].

The results of current study showed that the mean ±SD value of serum Mg levels in patients with ACS was significantly lower than that in normal control ($p \leq 0.05$). The present study result agree with following studies:

Maciejewski P et al. reported that hypomagnesemia is often present in patients with ACS. The former is associated with dangerous ventricular arrhythmias [11]. Reza Hassanzadeh Makoui in his study reported that: 43 cases (23.6%) were suffering from hypomagnesaemia and 139 cases (76.4%) were with normalmagnesium level [12].

Singh et al make brief reference to the relationship of increased catecholamine levels, found in AMI patients, and accept the premise that the reduction of serum Mg they observed in their arrhythmic patients might have been caused by a shift of circulating Mg to ischemic cells, caused by their increased metabolic requirements for Mg[13].

Adenosine is a major cardioprotective substance in ischemia. Ischemic myocardium is salvaged by administration of adenosine or by inhibition of adenosine breakdown. The main pathway of adenosine synthesis in ischemic myocardium is decomposition of adenosine monophosphate by ecto-5-nucleotidase. Interestingly, magnesium is an important co-factor of 5-nucleotidase. Therefore we hypothesized that magnesium potentiates 5-nucleotidase activity and protects ischemic myocardium [14].

ANOVA test revealed there was non-significant difference in the serum Mg mean±SD value among three types of acute coronary syndrome (ACS), ($p > 0.05$). Serum Mg mean ±SD value in STEMI > NSTEMI and Unstable angina, the explanation for this result may be that NSTEMI occurs by developing a complete occlusion of a minor coronary artery or a partial occlusion of a major coronary artery previously affected by atherosclerosis. This causes a partial thickness damage of heart muscle [15]. STEMI occurs by developing a complete occlusion of a major coronary artery previously affected by atherosclerosis. This causes a full thickness damage of heart muscle [15]. There were no previous studies in this section to be relied on for comparison.

The present study result showed the mean (± SD) value of serum Mg concentrations was non-significantly higher in non-diabetic group than diabetic group as shown in table (5). Diabetes mellitus, both type I and type II, are said to be the commonest causes of magnesium deficiency, with 25–39% of patients being affected [16]**.** A decrease in total, ultrafiltrable, ionised, red cell and white cell magnesium have been found [17,18]**.** The decrease in serum magnesium concentration is correlated with fasting blood glucose, glycated haemoglobin, albumin excretion and the duration of diabetes [19]**.** Magnesium depletion is due to increased magnesium excretion brought about by osmotic diuresis; there may additionally be a specific tubular defect [20]. Magnesium depletion, via its effect on inositol transport, has been suggested to be of pathogenic significance in the development of diabetic complications [21].

The present study result showed the mean (± SD) value of serum Mg concentrations was non-significantly higher in non Dyslipidemic group than Dyslipidemic group as shown in table (5). Magnesium deficiency may contribute to the progression of atherosclerosis by its effects on lipid metabolism, platelet aggregation and blood pressure. Experimental magnesium deficiency is characterised by increased triglycerides, cholesterol, VLDL, LDL, apolipoprotein B and triglyceride-rich lipoproteins and a reduced HDL, apolipoprotein A1 and plasma lecithin-cholesterol acyltransferase activity[22]. Peroxidation of lipoproteins due to free radical production and increased platelet aggregation may also contribute to the development of atherosclerosis. Magnesium supplementation of hyperlipidaemic subjects has been shown to cause a reduction in total and LDL cholesterol and apolipoprotein B, and an increase in HDL cholesterol and triglycerides [23].

The present study result showed the mean (± SD) value of serum Mg concentrations was non-significantly higher in nonsmoker group than smoker group as shown in table (5). Guipeng An et al. Reported that high frequency of smoking (P= 0.001) and diabetes (P, 0.05) was associated with low Mg level. However, Mg level was lower for patients with than without diabetes (P= 0.03) and smoking versus not smoking (P= 0.01) [24].

Howard et al. [25] suggested that the effects of smoking on the progression rate of atherosclerosis may be both cumulative and irreversible.

The mean (± SD) value of serum Mg concentrations was non-significantly lower in hypertensive group than non-hypertensive group, table (5). Magnesium has a direct effect upon the relaxation capability of vascular smooth muscle cells!'. When magnesium is deficient in these cells, they are unable to relax. Vasodilation becomes hindered, and hypertension is one result. In addition to this direct result, magnesium deficit can impact the cellular placement of other cations important to blood pressure regulation-cellular sodium: potassium (Na: K) ratio and intracellular calcium, thus effecting hypertension indirectly. When sodium becomes too high and potassium too low, high blood pressure is one result [26]. Epidemiological studies show an increased incidence of hypertension in areas where the magnesium content of water is low [27]. Furthermore, magnesium supplementation was associated with a significant decrease in blood pressure in 10 out of 15 studies [28]**.** Magnesium deficiency increases angiotensin II induced plasma aldosterone concentration and production of thromboxane and vasoconstrictor prostaglandins [29]. Insulin resistance caused by magnesium deficiency also increases vascular tone. Changes in cytosolic free calcium produced by magnesium deficiency may increase vascular reactivity even further. Magnesium supplementation can reduce the pressor effect of angiotensin II and stimulate the production of the vasodilator prostaglandin I2 [27]**.** Magnesium may also influence the release of nitric oxide and its effects on vascular tone [30].

The table 7 show distribution of serum Mg level by mitral regurgitataion (MR) echocardiogaphic Finding (Development of MR during ACS may be due to ischaemic injury of the papillary muscle apparatus and/or dilation of the left ventricle and has been linked to death and development of heart failure in patients with acute MI independently of LVEF and clinical confounders) [31]. There was non-significant difference in mean (± SD) values of serum Mg level among MR severity groups, (P-value=0.90), the association between MR grade and Mg level was linear.

There was non-significant negative correlation between serum Mg level with Age (r = - 0.07) (P = 0.68), this result disagree with An G et al. [31].

There was no association between serum Mg level and grade of diastolic dysfunction. The study showed that there was non-significant positive correlation between the serum concentrations of Mg and the value of Isovolumic relaxation time, E/e and Decceleration time. However, there was non-significant negative correlation with Diameter of left atrium and Left Ventricular Ejection Fraction (LVEF).

The explanation for this result may be that Magnesium is a potent vasodilator, and plays an important role in muscle contraction, Magnesium deficiency cause contraction of heart muscle which has been reported previously. If myocardial relaxation is delayed, severe diastolic dysfunction is also termed restrictive filling and can be present in severe coronary artery disease, acute severe aortic regurgitation (AR), and constrictive pericarditis. Early rapid diastolic filling into a less compliant left ventricle causes a rapid increase in early LV diastolic pressure, with rapid equalization of LV and LA pressures producing a shortened DT. Atrial contraction increases LA pressure, but A velocity and duration are shortened because LV pressure increases even more rapidly. When LV diastolic pressure is markedly increased, there may be diastolic MR during mid-diastole or with atrial relaxation. Therefore, restrictive filling with severe diastolic dysfunction is characterized by increased E velocity, decreased A velocity (markedly less than E) with an E/A ratio higher than 2, and

shortened DT (<160 milliseconds) and IVRT (<70 milliseconds). Systolic forward flow velocity in the pulmonary vein is decreased because of increased LA pressure and decreased LA compliance [32]. There were no previous studies in this section to be relied on for comparison.

Conclusions: Decreases Serum magnesium level indicate ischemia severity in all five types of acute coronary syndrom(ACS) patients, Serum magnesium level non significantly associated with major risk factor, fibrinolytic treatment and Echocardiographic parameter in acute phase of disease.

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