The Study of Serum Calcium to Magnesium Ratio in Patients with Acute Coronary Syndrome in a Tertiary Hospital, Hubli, Karnataka

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ABSTRACT

BACKGROUND

Cardiovascular diseases are one of the leading causes of morbidity and mortality worldwide. High Ca levels and low Mg levels are associated with increased cardiovascular risk in the general population.[1] The balance between Ca and Mg seems to play an important role in homeostasis since Mg is considered as physiologic antagonist of Ca.[2] Hence Ca/Mg ratio was considered to study its association with acute coronary syndrome (ACS).

METHODS

This is a case control study conducted in Karnataka Institute of Medical Sciences, Hubli over a period of 2 years, February 2019 to December 2020. 200 cases and 150 controls were included in the study. The biochemical measurements including complete blood count (CBC), cardiac biomarkers, liver function tests, renal function tests (RFT), serum electrolytes and lipid profile were measured using standard laboratory methods. Student 't' test was used to compare the data. Optimum cut-offs for diagnosis of acute myocardial infarction was calculated using receiver operating characteristics (ROC) analysis. The association among markers was established by calculating Pearson's correlation.

RESULTS

Serum Ca/Mg ratio was significantly higher (p value < 0.001) in ACS when compared to control groups. It was also found that Ca/Mg ratio was significantly lower (p value < 0.001) in non-ST elevation myocardial infarction (NSTEMI) when compared to STEMI group. Serum Mg was significantly lower (p value < 0.001) in ACS group when compared to control group. Significant correlation (p value < 0.05) was found between serum Ca/Mg ratio and cardiac markers (CK-MB, Troponin-I). ROC analysis of Ca/Mg (4.19) ratios showed optimum cut-offs in diagnosis of AMI.

CONCLUSIONS

Serum Ca/Mg could be useful adjuvant marker in diagnosis of AMI. The ratio is higher in ST-segment elevation myocardial infarction when compared to non-ST-segment myocardial infarction, which could be due to greater decrease in Mg levels when compared Ca in ACS.

KEYWORDS

ST Elevation Myocardial Infarction (STEMI), Non ST Elevation Myocardial Infarction (NSTEMI), Calcium (Ca), Magnesium (Mg), Acute Coronary Syndrome (ACS), Creatine Kinase-MB (CK-MB).

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DOI: 10.14260/jemds/2021/644

How to Cite This Article:
Bande US, Eranaik KB, Hiremani MS, et al. The study of serum calcium to magnesium ratio in patients with acute coronary syndrome in a tertiary hospital, Hubli, Karnataka. J Evid Based Med Healthc 2021;8(32):3553-3558. DOI: 10.18410/jebmh/2021/644

Submission 23-09-2021,
Peer Review 29-09-2021,
Acceptance 22-10-2021,
Published 30-10-2021.

BACKGROUND

Cardiovascular diseases are one of the leading causes of morbidity and mortality worldwide. These cardiovascular diseases have been declared as 'Modern Epidemic' by World Health Organization (WHO). Acute coronary syndrome (ACS) is one among manifestation of cardiovascular diseases responsible for depletion of most of public health resources. It is the leading cause of morbidity and mortality worldwide. The prevalence of ACS among adults (based on clinical and ECG criteria) was estimated at 96.7 per 1000 population in the urban and 27.1 percent in rural areas in India.[3] Even then various mechanisms underlying the poor prognosis of ACS patients have not yet been clearly understood. Several factors might affect the prognosis, such as baseline characteristics and treatment before, during, and after hospitalization. Thus, it is still difficult to accurately identify the patients who might end up with poor outcomes.

Various metabolic changes are also seen in ACS, like increase in plasma concentrations of catecholamines, free fatty acids, glucose, glycerol, cortisol and cyclic-AMP. Changes in serum levels of various electrolytes have also been observed in ACS. These electrolytes play an important role in regulating cardiac and neurological functions, oxygen delivery, acid-base balance and fluid balance in the body. Important electrolytes in the body are sodium, potassium, calcium, magnesium, phosphorous etc.

Magnesium is second most abundant intracellular electrolyte after potassium. It is an essential mineral and it acts as a co factor for more than 300 enzyme systems in the human body,[4] importantly sodium potassium adenosine triphosphatase (Na-K ATPase). It has a predominant role in normal myocardial physiology.

Magnesium has β adrenoreceptor blocking action, anti-platelet 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.[5] Mg is thus regarded as a cardio protective element, as it provides to the regulation of vascular tone, heart rhythm and platelet activated thrombosis. Mg deficiency is associated with vascular endothelial injury, increase in low-density lipoprotein (LDL) concentration and oxidative modification, leading to accelerated atherosclerosis.[6] Healthy individuals with low serum Mg levels had increased risk for coronary artery disease compared to those with normal levels, even after adjustment for traditional cardiovascular risk factors.[7]

Serum calcium is one of the major electrolytes found extracellularly, with extracellular concentration being about 10,000 times higher than the intracellular concentration. It is associated with the electrophysiological properties of the myocardium. It is involved in various physiological and biochemical processes of heart like, heart electrophysiology and contraction, blood coagulation, neurotransmitter release, and regulation of enzyme activity and blood pressure. Hypercalcemia was found to be an independent predictor of poor long-term outcomes in stable coronary artery disease (CAD) patients in recent acute myocardial infarction (AMI).[8] Observation of another study was close association of hypocalcaemia with higher in hospital mortality in patients of acute STEMI.[9] These studies suggest calcium as a potential prognostic factor in CAD.

Magnesium is considered as a natural antagonist of calcium, as they both compete with one another for same binding sites on plasma proteins and calcium transporters. A study done in dialysis patients showed significant all cause and cardiovascular disease (CVD) mortality in those with high calcium and lower magnesium levels.[10] It has also been shown that high Ca-Mg ratio with lack of Mg in drinking water and diet is associated with increased risk of CAD.[11] Thus the balance between calcium and magnesium seems to be more important. The aim of the present study was to study Ca-Mg ratio as an adjuvant marker in the diagnosis of AMI.

Aims and Objectives

- To study Ca/Mg ratio as an adjuvant marker in the diagnosis of acute myocardial infarction.
- To compare Ca/Mg ratio in among various ACS.

METHODS

The study was conducted for a period of 2 years from February 2019 to December 2020 in Karnataka Institute of Medical Sciences, Hubli. The study was approved by research and ethical committee of the institution. It was a case control study with 200 ACS cases admitted in intensive coronary care unit and 150 age and sex appropriate controls. The ACS cases were enrolled for the study according to the European Society of Cardiology (ESC), the American College of Cardiology (ACC), the American Heart Association (AHA) Jointly. Among the ACS group, those with the diagnosis of STEMI and NSTEMI were enrolled to this study. The blood samples were drawn from antecubital vein within 12 hours of admission and results were evaluated. The biochemical measurements including complete blood count, cardiac biomarkers, renal function tests, liver function tests, serum electrolytes and lipid profile were measured using standard laboratory methods. All serum calcium levels for each patient were corrected for albumin and corrected calcium levels were used for analysis.

Inclusion Criteria

- Patients admitted in intensive cardiac care unit with the diagnosis of acute coronary syndrome in Karnataka Institute of Medical Sciences, Hubli.
- Among subject with acute coronary syndrome, patient with a diagnosis of STEMI and NSTEMI were enrolled to this study.

Exclusion Criteria

- Unstable angina.
- Active blood loss.
- Alcohol use.

- Chronic medication use such as Thiazides and loop diuretics, steroids.
- Chronic gastrointestinal and renal diseases.
- Liver cirrhosis.

Statistical Analysis

The data was analysed by using the Statistical Package for Social Sciences (SPSS) software, version 20. The values were expressed as mean and standard deviation. The independent "t" test was performed to compare the mean values between the cases and the controls. Pearson's correlation analysis was performed to assess the association between the various test parameters. A p value of < 0.05 is considered significant. Receiver operating curves (ROCs) were drawn to find the optimum sensitivity, specificity and the cut-off values.

RESULTS

A total of 350 subjects were studied, with division into two groups. One group being acute coronary syndrome patients and the other being control group. In the study overall, majority of the subjects were males 223 (63.7 %) and females were 127 (36.28 %). In the control group, there were 96 males and 54 females. And in ACS group, there were 127 males and 77 females. Following tables shows the demographical, clinical and laboratory data collected in the study.

Parameters	All Population (350)	Controls (150)	ACS (200)	'P' Value
Age	60.04 +/- 9.41	60.09 +/- 9.62	60.01 +/- 9.28	0.34
Male	223 (63.7%)	96 (64%)	127 (63.5%)	0.92
HbA1c	6.810 +/- 1.33	6.861 +/- 1.22	6.72 +/- 1.42	0.53
DM	164 (46.9%)	70 (46.7%)	94 (47%)	0.94
HTN	184 (52.6%)	84 (56%)	100 (50%)	0.32
S. Urea (mg/dL)	28.78 +/- 9.52	28.44 +/- 9.63	29.04 +/- 9.45	0.56
S. Creatinine (mg/dL)	0.960 +/- 0.21	0.955 +/- 0.21	0.96 +/- 0.21	0.70
S.Na (mEq/L)	136.74 +/- 2.63	138.89 +/- 1.21	135.12 +/- 2.22	<0.001
S.K (mEq/L)	3.7711 +/- 0.15	3.87 +/- 0.13	3.69 +/- 0.12	<0.001
S. Calcium (mg/dL)	8.816 +/- 0.19	8.85 +/- 0.18	8.790 +/-.1981	<0.01
S.Mg (mg/dL)	2.0553 +/- 0.17	2.19 +/- 0.10	1.94 +/- 0.13	<0.001
CK-MB (IU/L)	57.75 +/- 52.64	7.77 +/- 2.68	95.23 +/- 39.50	<0.001
Trop I (ng/ml)	1.08 +/- 0.50	<0.012	1.08 +/- 0.50	<0.001
Total Chol (mg/dL)	174.95 +/- 36.14	161.76 +/- 37.876	184.84 +/- 37.51	<0.001
Triglycerides (mg/dL)	169.33 +/- 55.72	154.24 +/- 45.74	180.65 +/- 59.81	<0.001
HDL-C (mg/dL)	42.97 +/- 11.68	49.53 +/- 10.42	38.06 +/-10.06	<0.001
LDL-C (mg/dL)	110.6 +/- 21.669	104.04 +/- 20.68	115.52 +/- 21.13	<0.001
Hb (g/dL)	12.19 +/- 1.77	12.2 +/- 1.86	12.14 +/- 1.71	0.62
Plt (103µL)	2.6501 +/- 0.91	2.65 +/- 0.84	2.64 +/- 0.96	0.90
EF (%)	51.50 +/- 8.78	60.00 +/- 0.0	45.12 +/- 6.320	<0.001

Table 1. Demographical, Clinical Data and Laboratory Data of all the Subjects in Study, along with Comparison between ACS Group and Control Group

Age, sex, co-morbidities such as diabetes and hypertension, S. Urea, S. Creatinine, haemoglobin, platelet count were not significantly different between the groups. S. Sodium, S. Potassium, S. Magnesium, S. Calcium and high density lipoprotein (HDL-C) were significantly higher (< 0.001) in control group when compared to ACS group. CK-MB and Trop-I significantly higher (< 0.001) in ACS group when compared to control group. There was significant difference (< 0.001) in Total cholesterol, triglycerides, LDL-C in ACS group when compared with control group.

Parameters	ACS (150)	NSTEMI (67)	STEMI (133)	'P' Value
Age	60.01 +/- 9.28	59.40 +/- 8.22	60.32 +/- 9.78	0.21
Male	127 (63.5%)	41 (61.2 %)	86 (64.7%)	0.74
HbA1c	6.72 +/- 1.42	6.74 +/- 1.3	6.78 +/- 1.4	0.82
DM	94 (47%)	33 (49.3%)	61 (45.9%)	0.76
HTN	100 (50%)	34 (50.7%)	66 (49.6%)	0.88
Serum Urea (mg/dL)	29.04 +/- 9.45	30.87 +/- 11.42	28.11 +/- 8.18	0.08
Serum Creatinine(mg/dL)	0.96 +/- 0.21	0.96 +/- 0.20	0.96 +/- 0.21	0.96
Serum Na (mEq/L)	135.12 +/- 2.22	135 +/- 2.17	135.19 +/- 2.26	0.54
Serum K (mEq/L)	3.69 +/- 0.12	3.65 +/- 0.11	3.71 +/- 0.12	<0.001
S. Calcium (mg/dL)	8.790 +/- 0.19	8.74 +/- 0.18	8.81 +/- 0.20	0.01
Serum Mg (mg/dL)	1.94 +/- 0.13	2.06 +/- 0.06	1.88 +/- 0.12	<0.001
Serum CK-MB (IU/L)	95.23 +/- 39.50	45.75 +/- 10.08	120.16 +/- 20.8	<0.001
Serum Trop I (ng/ml)	1.08 +/- 0.50	0.49 +/- 0.08	1.37 +/- 0.33	<0.001
Total Chol (mg/dL)	184.84 +/- 37.51	186.52 +/- 29.08	183.98 +/- 41.18	0.65
Triglycerides (mg/dL)	180.65 +/- 59.81	184.1 +/- 51.39	178.92 +/- 63.75	0.61
HDL-C (mg/dL)	38.06 +/- 10.06	37.91 +/- 9.14	38.14 +/- 10.53	0.88
LDL-C (mg/dL)	115.52 +/- 21.13	122.94 +/- 18.6	111.78 +/- 21.401	0.30
Hb (g/dL)	12.14 +/- 1.71	11.74 +/- 1.40	12.34 +/- 1.82	0.36
Platelet count (10^3µL)	2.64 +/- 0.96	2.50 +/- 0.71	2.71 +/- 1.05	0.11
EF (%)	45.12 +/- 6.320	48.12 +/- 5.7	43.6 +/- 6.0	<0.001

Table 2. Comparison of Various Parameters among ACS Group, between STEMI and NSTEMI

Age, sex, co-morbidities such as diabetes and hypertension, S. Urea, S. Creatinine, haemoglobin, platelet count were not significantly different between the groups. There was no significant difference in total cholesterol, HDL-C, LDL-C between these groups. CK-MB and Trop-I were significantly higher in STEMI group than NSTEMI group. Serum magnesium was found to be significantly lower (< 0.001) in STEMI group when compared to NSTEMI group.

Parameters	Controls	ACS	P - Value
Serum Na (mEq/L)	138.89 +/- 1.21	135.12 +/- 2.22	< 0.001
Serum K (mEq/L)	3.87 +/- 0.13	3.69 +/- 0.12	< 0.001
S. Calcium (mg/dL)	8.85 +/- 0.18	8.790 +/- 0.19	< 0.001
Serum Mg (mg/dL)	2.19 +/- 0.10	1.94 +/- 0.13	< 0.001
Ca/Mg	4.03 +/- 0.19	4.53 +/- 0.32	< 0.001
K/Mg	1.76 +/- 0.10	1.90 +/- 0.15	< 0.001
Na/Mg	63.33 +/- 3.12	69.71 +/- 5.30	< 0.001
Serum CK-MB (IU/L)	7.77 +/- 2.688	95.23 +/- 39.50	< 0.001
Serum Trop I (ng/ml)	< 0.0120	1.08 +/- 0.50	< 0.001

Table 3. Comparison of Serum Electrolytes, Ca/Mg, K/Mg, Na/Mg Ratios between Control Group and ACS Group

As compared to the control group, ACS patients were found to have significantly low levels of serum sodium, serum potassium, serum magnesium and serum calcium, with p value of < 0.001.

ACS group had significant increase in CK-MB, Troponin – I with p value of < 0.001. There was also a significant difference between Ca/Mg, K/Mg and Na/Mg levels between the two groups, with higher ratios in ACS group when compared to control groups.

Parameters	NSTEMI	STEMI	P - Value
Ca/Mg	4.23 +/- 0.11	4.68 +/- 0.29	< 0.001
K/Mg	1.77 +/- 0.07	1.97 +/- 0.14	< 0.001
Na/Mg	65.47 +/- 2.11	71.84 +/- 5.14	< 0.001
Serum CK-MB (IU/L)	45.75 +/- 10.08	120.16 +/- 20.8	< 0.001
Serum Trop I (ng/ml)	0.49 +/- 0.08	1.37 +/- 0.33	< 0.001

Table 4. Comparison of Serum Electrolytes, Ca/Mg, K/Mg, Na/Mg Ratios among ACS Group, between NSTEMI and STEMI

It was found that Ca/Mg, K/Mg, Na/Mg ratios were lower in NSTEMI when compared to STEMI, with p values of < 0.001. Serum CK-MB and serum Troponin-I were significantly higher in STEMI group than NSTEMI group with p value < 0.001.

Parameters and Ratios		Biochemical Parameters Serum. CK-MB	Serum Troponin-I
Ca/Mg	r (Pearson's correlation)	0.515	0.454
	p Value	< 0.001	< 0.001
K/Mg	r (Pearson's correlation)	0.426	0.383
	p Value	< 0.001	< 0.001
Na/Mg	r (Pearson's correlation)	0.466	0.417
	p Value	< 0.001	< 0.001

Table 5. Correlation Analysis of Serum Ca/Mg, K/Mg, Na/Mg Ratio with Other Biochemical Parameters

There was significant correlation between serum Ca/Mg, K/Mg, Na/Mg ratios with CK-MB and Trop I levels with p value of < 0.001.

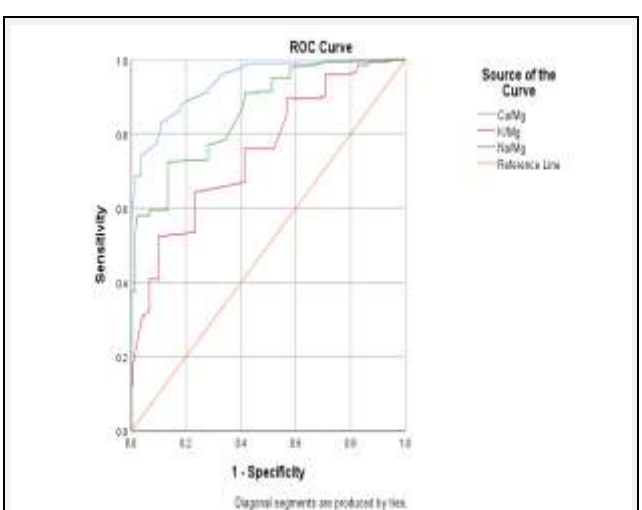

Table 6. ROC of Serum Ca/Mg, K/Mg, Na/Mg Ratio with Acute Coronary Syndrome

Parameters	Optimum Cut-Off	Sensitivity	Specificity	AUC
Ca/Mg ratio	4.19	88 %	82 %	0.941
K/Mg ratio	1.79	76 %	59 %	0.752
Na/Mg ratio	65.85	77 %	72 %	0.861

The receiver operating characteristic curve of Ca/Mg ratio showed sensitivity of 88 % and specificity of 82 % at cut off of 4.19 with significant area under the curve.

DISCUSSION

Mg content of normal adult body is approximately 25 g.[12] Out of which 60 % is found in bones, 35 % in high metabolic tissues such as heart, brain, kidneys, liver. Remaining just 1% is found in extracellular fluids and of which only 0.3 % of total body Mg is found in serum. This shows the more intracellular presence of Mg. To overcome this problem, the ratios of serum Mg and other electrolytes were considered to look for their relevance in acute myocardial infarction.

Mg deficiency causes endothelial dysfunction, hypercoagulability and increases lipids concentration in atheromatic lesions.[13] Further reduction of Mg levels is associated with hyper reactivity of coronary arteries to vasoconstrictive stimuli (neurohormonic, electrolytic), whereas Mg levels normalization has a protective role against angina and peripheral vasoconstriction.[14]

Mg can also inhibit the thrombi formation by reducing platelet aggregation and prolonging blood-clotting time. It increases NO production thereby rescuing physiological activities of endothelial cells and also decrease free radical formation.[15] These favourable effects of Mg might be seen as a consequence of its competition with Ca ions. Calcium promotes coagulation whereas Mg inhibits Ca-induced coagulation process.[16] As key to pathogenesis of STEMI is platelet activation, considering Ca/Mg ratio rather than only serum Mg seems important as Mg is physiological antagonist of Ca.[17] Any decrease in Mg levels is associated with increased action of Calcium. In addition, these ratios may be more indicative of homeostasis than measurement of serum magnesium and calcium alone.

In the present study, the serum Calcium–Magnesium ratio was higher in ACS patients when compared to controls. There was comparatively lower levels of Mg in ACS group when compared to controls. Thus higher serum calcium magnesium ratio was associated with clinical presentation of ACS, with higher values in STEMI when compared to NSTEMI.

The study also supports hypothesis that serum electrolyte alterations are associated with pathological events in CAD. There was lower levels of serum magnesium, calcium, sodium and potassium levels when compared to control group. In the present study, Ca/Mg, K to Mg, Na to Mg ratios were higher in ACS compared to controls which was similar to Ramaswamy et al. study.[18] Thus significant correlation was noticed between Ca/Mg ratio and ACS presentation and Ca/Mg ratio differed by clinical presentation with STEMI having higher Ca/Mg ratio when compared to NSTEMI.

Comparison of Ca/Mg, K/Mg and Na/Mg ratio in our study with Ramaswamy et al. study.[18]

	Our Study		Ramaswamy et al. Study [18]		
Parameters	Controls	ACS	Controls	ACS	P - Value
Ca/Mg	4.03 +/- 0.19	4.53 +/- 0.32	3.27± 0.44	4.1± 0.67	<0.001
K/Mg	1.76 +/- 0.10	1.90 +/- 0.15	2.46± 0.36	3.2 ± 0.47	<0.001
Na/Mg	63.33 +/- 3.12	69.71 +/- 5.3	35.5± 2.1	49.8± 0.37	<0.001

In the present study, Ca/Mg, K to Mg, Na to Mg ratios were higher in STEMI compared to NSTEMI which was similar to Celik et al. study.[19]

	Our Study		Celik et al.[19]		
Parameters	NSTEMI	STEMI	NSTEMI	STEMI	P - Value
Ca/Mg	4.23 +/- 0.11	4.68 +/- 0.29	4.18+/- 0.5	4.4+/- 0.48	<0.001
K/Mg	1.77 +/- 0.07	1.97 +/- 0.14	1.85+/- 0.36	1.97+/- 0.37	<0.001
Na/Mg	65.47 +/- 2.11	71.84 +/- 5.1	65.09+/- 8.33	67.63+/-8.77	<0.001

Study by Shimoswa et al. showed that with lower magnesium levels, the normal vascular tone will be lost, worsening the event of myocardial infarction.[20]

A study by Singh et al. stated that low serum Mg levels where observed in the patients with ACS who had arrythmias.[21] The electrical instability in the hearts of Mg deficient individuals was explained by Theory of Seelig and Heggtveit which states that Mg deficient status and altered electrolyte concentration is caused by reduced Na/K ATPase activity. Reduced Na/K ATPase activity leads to Na accumulation in the myocytes, which intern leads to increased intracellular calcium levels because of reversal of Na/K exchange. Thus deficiency in Mg will lead to increase in intracellular Calcium levels.[22] A study by Speich et al. demonstrated that there was an alteration in serum Ca/Mg ratio in heart muscles after an AMI.[23]

CONCLUSIONS

Serum Ca/Mg ratio could be considered as an adjunct marker in the diagnosis of AMI. The ratio is higher in ACS patients when compared to controls. Higher in STEMI than NSTEMI group attributable to greater decrease in magnesium levels than calcium levels.

Limitations of the Study

Ours was a single centred study. Causal relationship between Ca/Mg ratio and risk of mortality was not drawn in our study. No data was collected regarding dietary Mg intake and urinary Mg excretion, which is thought to be better indicator of dietary Mg intake. The study cannot fully for any possible confounders which might be associated with serum magnesium and calcium levels and their ratio. Nevertheless this study proposes a need for further studies with larger subjects.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

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