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ORIGINAL ARTICLE.

The relationship between serum magnesium level and coronary artery ectasia.

Ahmed Attia Abd-elhameed El-ghoribi, [1], **Waleed Salem Elawady**, [2], **Manar Mostafa Elzaky**[2], **Kamal Saad Mansour**[2].

1 Mahalla Cardiac Center, Gharbia, Egypt.

2 Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

Corresponding author:
Ahmed Attia Abd-Elhameed El-ghorib
Mahalla cardiac center,
Gharbia, Egypt.
E-mail:
Ahmedelghoribi@gmail.com

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ABSTRACT

Background: Magnesium is an essential element that plays a crucial role in cardiac and vascular functions. Low levels of intracellular (Mg2+) lead to abnormal vascular cell growth, inflammation, fibrosis resulting in negative vascular remodelling, finally results in CAE.

Objective: The aim of this study was to measuring serum magnesium level among patients going to have elective coronary angiography for comparing its level in O- CAD patients, and CAE patients, and the relationship between serum magnesium level and CAE.

Methods: A case control study was conducted on 84 patients were admitted for elective CA for suspected ischemic heart disease. The patients were divided into 4 groups according to CA results. All patients were subjected to detailed history, physical examination, electrocardiography, conventional echocardiography, laboratory investigations and coronary angiography.

Results: 84 patients divided into 4 groups, patients with obstructive coronary artery disease (group I), isolated coronary artery ectasia (group II), normal coronaries (group III) and patients with coronary artery ectasia and obstructive coronary artery disease (group IV). A significant correlation was found as regarding serum Mg in between the 4 group with significant p values, except for comparing group I (obstructive coronary artery disease) with group III (normal coronaries) there was no statistically significant correlation in between them with p value 0.984, with best cut-off value considering prediction of CAE >1.8 with 80.95% sensitivity and 71.43% specificity.

Conclusion: (Mg2+) level is highly predictive in suspecting coronary artery ectasia disease in both obstructive and non-obstructive coronary lesions.

Key words: Coronary artery Ectasia, Obstructive coronary artery disease, Mg2+.

INTRODUCTION

Coronary artery ectasia (CAE) is the diffuse dilatation of the epicardial coronary arteries to at least 1.5 times the normal coronary segment. It is congenital or acquired and many studies have announced its incidence at 0.3–5%. (1) Positive remodeling in the vessel wall, that is not frequent in the atherosclerotic process, plays an important role in the aetiopathogenesis of CAE, which demonstrates CAE is a vascular disease and not confined to the coronary arteries. Accordingly, factors other than atherosclerosis can also play a role in its aetiopathogenesis. (2) Magnesium, which is the second most generous intracellular cation, is a crucial element that plays an essential role in cardiac and vascular functions. It controls contractile proteins, balances transmembrane transport of calcium (Ca2+), sodium (Na+) and potassium (K+), serves as a co-factor in the process of activation of ATPase, manages adjustment of energy-dependent cytoplasmic and mitochondrial metabolism, and forces DNA and protein synthesis at the subcellular level. (3) minute changes in the concentration level of extracellular and/or intracellular free (Mg2+) have crucial effects in cardiac excitability, vascular tonicity, contractibility, reactivity and also growth. Small levels of intracellular (Mg2+) motivates abnormal vascular cell growth, inflammation, fibrosis and also contraction, resulting in negative vascular remodeling. Administration of (Mg2+) was found to cause vasodilatation and to have anti-inflammatory effects. (4)**Material and methods:**

Patient population: This study is a case control study conducted on a convenient sample of 84 patients were admitted at Zagazig University Hospital for elective coronary angiography. The patients were classified into 4 groups according to presentation into group I, 21 patients with

O_CAD and group II, 21 patients with isolated CAE, 21 patients represent control group III and group IV, 21 patients with O_CAD and CAE.

The study protocol was formally reviewed and approved by the ethics committee for human research at Zagazig Faculty of Medicine with informed consent obtained from all participants prior to commencement of the study after thorough explanation of the study objectives.

Inclusion Criteria Adult male or female >18 years old with stable coronary angina going to do elective coronary angiography.

Exclusion Criteria Patients with, renal failure, moderate to severe valvular heart disease, left ventricular ejection fraction less than 50%, neoplastic disease, chronic systemic illness, Addison disease and hypothyroidism were excluded from our study.After exclusion of non-responders, drop out participants and those with exclusion criteria, 84 subjects completed the study (this number was considered suitable enough sample for statistical analysis with significant results and correlations).

METHODS

The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. All patients were subjected to detailed history, including CAD risk factors, physical examination, Electrocardiography (ECG) and laboratory investigations included, complete blood picture, liver and kidney function. Some patients -who did not have history of CAD- performed a stress imaging test to diagnose CAD. Conventional Echocardiography was performed by experienced echo cardiographer in accordance with the recommendations of the American Society of Echocardiography (ASE). The mean of three measurements was used in the analysis measure of the left ventricle geometry (LVEDD, LVESD, IVSd, PWDd and EF by m-Mode) as recommended by American Society of Echocardiography and Pulsed-wave (PW) Doppler was performed to obtain mitral inflow velocities to assess LV filling.(5) Blood samples were collected before cardiac catheterization. Patients fasted for >12 hours before cardiac catheterization. Blood was collected either from the antecubital vein or indwelling catheter into Two 3.2% trisodium citrate tube after discarding the initial 3 ml of blood. Serum was separated by centrifugation at 2000g for 15 minutes and stored at -70°C. CBC, Liver and renal function, RBS, HbA1C, lipid profile and serum Mg2+ levels were measured by spectrophotometry method. The normal range for blood magnesium level is 1.7 to 2.2 mg/dL (0.85 to 1.10 mmol/L). (6) Elective coronary angiography was performed using the percutaneous femoral approach by Sildenger technique. Right and left coronary angiography were performed using multiple projections and analysis was done by professional interventionists who were blind to the cases. Lesion was considered significant if epicardial coronary artery was 70% luminal stenosis or >50% in case of left main stenosis. Ectasia was considered if swelling of the epicardial coronary arteries at least 1.5 times the adjacent normal coronary segment. (1)

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for The Social Sciences Version 22 (IBM Corp., Armonk, NY, USA). Quantitative data are expressed as means and standard deviations. P-Value $\leq$ 0.05 was considered to indicate significance. Correlation analysis assesses the strength of association between two variables. Multiple logistic regression analysis was used.

RESULTS

The difference in between the studied groups as regarding demographic data (age, gender and weight) was Statistically non_significant **table 1**.

In **table 2, figure 1**, there were no statistically significant difference between the four groups. As regarding Hypertension there was no significant differences with the four groups with (p value 0.811), as regarding DM there was no significant differences with the four groups with (p value 0.644), as regarding dyslipidemia there was no significant differences with the four groups with (p value 0.824). For smoking, there was no significant differences with the four groups with (p value 0.914) and finally, family history of coronary artery disease was all non-significantly correlated with the four groups with (p value 0.801) receptively. **Table 3**, when comparing serum creatinine in-between the four groups, it was of no statistically significant difference with mean and SD values of 0.95 ± 0.10 for O-CAD group, and 0.91 ± 0.11 for CAE group, and 0.97 ± 0.1 for normal coronaries group and 0.93 ± 0.1 for O-CAD with ectasia group with (p value 0.276) As we compared each group with the other one as regarding serum Magnesium, we found a significant correlation in between one another with significant p values as shown in **table 4, fig 2**, except for comparing group I (obstructive coronary artery disease) with group III (normal coronaries) there was no statistically significant difference in between them with (p value 0.984), **table 5.** As regarding the correlation between serum (Mg2+) and demographic data there was no statistical significant correlation for age with (p value 0.545), weight with (p value 0.605) and gender with (p value 0.897) respectively, **table 6**

Table (1): Demographic data among the studied groups

	Group I	Group II	Group III	Group IV	Test	P value
Age (y)						
Mean± SD	57.5 ± 5.69	57.6 ± 5.33	58.3 ± 6.35	57.1 ± 5.44	F = 0.139	0.936
Range	49 – 69	50 - 69	49 – 70	50 – 68		
Gender						
Male	16 (76.2%)	16 (76.2%)	12 (57.1%)	13 (61.2%)	X2 = 2.786	0.426
Female	5 (23.8%)	5 (23.8%)	9 (43.9%)	8 (38.1%)		
Weight (kg)						
Mean	86.2 ± 9.56	84 ± 9.92	85.2 ± 8.21	83.7 ± 9.02	0.305	0.822
Range	70 – 100	70 - 100	70 - 100	70 – 99		

Table (2): Comparison between the studied groups regarding the risk factors.

RISK FACTORS	Group I	Group II	Group III	Group IV	X2 Test	P value
Hypertension	12 (57.1%)	13 (61.9%)	11 (52.4%)	10 (47.6%)	0.961	0.811
DM	11 (52.4%)	9 (42.9%)	10 (47.6%)	13 (61.9%)	1.668	0.644
Dyslipidemia	12 (57.1%)	10 (47.6%)	10 (47.6%)	9 (42.9%)	0.905	0.824
Smoking	12 (57.1%)	11 (52.4%)	10 (47.6%)	10 (47.6%)	0.524	0.914
Family History	7 (33.3%)	9 (42.9%)	7 (33.3%)	6 (28.6%)	1.001	0.801

Table (3): Serum create. among the studied groups.

creatinine	Group I	Group II	Group III	Group IV	Test	P value
Mean ± SD	0.95 ± 0.10	0.91 ± 0.11	0.97 ± 0.1	0.93 ± 0.1	F = 1.314	0.276
Range	0.8 - 1.2	0.7 - 1.12	0.8 - 1.2	0.8 - 1.2		

Table (4): Serum Mg2+ among the studied groups

Serum (Mg2+)	Group I	Group II	Group III	Group IV	Test	P value
Mean ± SD	1.69 ± 0.14	2.06 ± 0.18	1.7 ± 0.15	1.84 ± 0.14	F = 5.282	**<0.001***
Range	1.5 - 1.9	1.8 - 2.4	1.5 – 2	1.6 - 2.1		

Table (5): Comparison between each group with the other as regarding serum (Mg2+)

GI-GII	**<0.001***
GI-GIII	**0.984**
GI-GIV	**0.011***
GII-GIII	**<0.001***
GII-GIV	**<0.001***
GIII-GIV	**0.014***

Table (6): Correlation between (Mg2+) level and demographic data and risk factors

Risk factors.	serum (Mg2+) level	P value
Age^{+}	-0.067	0.545
Weight^{+}	-0.057	0.605
Gender^{++}	-0.014	0.897
Hypertension^{++}	0.032	0.77
DM^{++}	-0.1	0.364
Dyslipidemia^{++}	-0.051	0.647
Smoking^{++}	-0.068	0.542
Family history^{++}	0.019	0.865

Table (7): Serum Magnesium as predictors for CAE & OCAD; ROC curve analysis

Cutoff	Sensitivity	Specificity	PPV	NPV
>1.8	80.95%	71.43%	75.00%	90.63%
>1.9	71.43%	92.06%	48.57%	91.84%

DISCUSSION

CAE is swelling of the coronary arteries to at least 1.5 times of the normal caliber of the vessel, and the basic way to understand the mechanism of formation is destruction of the musculo-elastic layers of the arterial tunica media, and the accumulation of collagen and elastin, leading to thinning of the arterial wall. **(1)** (Mg2+) enhances nitric oxide release, which has a very strong vasodilator effect, from the endothelium. It is a co-factor for the delta-6-desaturase enzyme, which plays a crucial role in the formation of prostaglandin E1 (it has vasodilator and antiplatelet effects) from linoleic acid. **(7)** In our study as regarding gender, age and weight between the four groups there was no statistically significant difference between them. In a study done by *Tin et al,* they noticed an inverse relationship in between serum magnesium and incidence of CHD in women and less strongly in men. There was also found a weak inverse association between dietary magnesium intake and incident CHD in men only. These associations were present after adjustment for multiple external factors, including sociodemographic characteristics and waist/hip ratio **(8)**

Our results showed that hypertension, DM, dyslipidemia, smoking and family history of coronary artery disease were all non-significantly different in the four groups.

In **contrast** to our results, a study done by *Kostov and Halacheva* about the etiopathogenesis of hypertension, a (Mg2+) deficiency was issued to have hypertensive effects, and dietary (Mg2+) intake is in a link with hypotension, showing the reverse positive relationship between blood pressure and serum (Mg2+) levels **(4).**

A relationship between diabetes mellitus and (Mg2+) deficiency has been issued in humans. They reported that, in insulin-treated diabetic patients, serum (Mg2+) corresponds inversely with both fasting blood glucose and the urinary glucose excretion rate; urinary (Mg2+) excretion rate corresponds directly with the same variables. Their data recommended that the net tubular reabsorption of (Mg2+) is diminished in diabetic patients in the presence of hyperglycemia, leading to hypermagnesuria and hypomagnesemia.(9)

In a study by *Randell* and colleagues, HDL cholesterol levels were found to be positively connected with (Mg2+) levels. Our results are opposite to this study, showing higher (Mg2+) and HDL cholesterol levels in isolated ectasia and lower levels in CAD patients, announcing that there was no smash of this correlation on our results.**(10)** In our study when comparing **serum creatinine** in-between the four groups, it was of no statistically significant difference in between the four groups. In agreement with our results, the review by *Cunningham and colleagues*, reported that in the initial stages of renal failure, there was no difference in (Mg2+) metabolism but in the end stage, (Mg2+) levels were affected. Therefore, normal creatinine levels in our study groups doubtless did not affect the (Mg2+) balance. ***(11)*** *Mustafa et al* in contrast to our results reported that serum creatinine levels were in the normal range in a study by *Mustafa et al,* there was a statistically significant difference between the groups, due possibly to small differences in creatinine levels. **(1)** As we compared each group with the other one as regarding serum Magnesium, we found a significant correlation in between one another with significant p values, except for comparing group I (control group) with group III (obstructive coronary artery disease) there was no statistically significant difference in between them with p value 0.984. The best cut-off value considering prediction of CAE in reference to normal control group for serum (Mg2+) is >1.8 with 80.95% sensitivity and 71.43% specificity. Meanwhile, sensitivity decreases to 71.43% and specificity increases to 92.06% when the cut-off value increased to >1.9.

In agreement to our results, *Mustafa et al,* stated that serum (Mg2+) levels were statistically greater in isolated ectasia patients than in the NCA and CAD groups. (Mg2+) levels were minimum in the CAD group. (Mg2+) levels in the CAD + CAE group were more advanced than in the NCA group but lower than in the isolated ectasia group. The higher levels of (Mg2+) in the CAD + CAE than in the CAD group reached statistical significance.**(1)** *Zheltova et al*, had obtained preparatory data illustrating that culturing endothelial cells in low (Mg2+) medium, for 5-7 days, resulted in lightly lower glutathione levels. However, when cells were subjected to free radical stress, the glutathione decreased much more briskly in the (Mg2+)-deficient cells compared to the (Mg2+) sufficient cells. The fast loss of glutathione in (Mg2+) deficient cells is consistent with a bigger level of peroxide formation and subsequent increased consumption of intracellular glutathione.(12)

Peacock et al., founded a contrary association between dietary magnesium and CHD incidence in men proposes that habitually high intake of foods rich in magnesium may administers protection against CHD, either by expanding magnesium levels or by other means. This study advocates that low levels of serum (Mg2+) may be acritical predictor of SCD. Further research into the efficacy of (Mg2+) for those considered to be at high risk for SCD is warranted. **(13)**

Stronger evidence for a CVD-(Mg2+) relationship is the lower (Mg2+) level found in the myocardium of victims of abrupt coronary deaths, as matched with accident victims, in most but not all studies, although here a different interpretation may be post infarction (Mg2+) loss. In ARIC, mean serum (Mg2+) levels were unquestionably lower in those with prevalent CVD than in disease-free participants. **(14)** Barbagallo *et al,* demonstrated that oral (Mg2+) supplementation significantly promotes brachial artery endothelial function in elderly diabetic hypertensive patients. The present results boost the use of oral (Mg2+) supplementation in elderly subjects with diabetes and hypertension in which (Mg2+) deficiency is a familiar condition and in whom circulating ionized (Mg2+) is frequently low.**(15)** Ramasamy et al, said that the Receiver Operating Characteristics curve (ROC) of Na/(Mg2+) showed an excellent cut off at 40.9 with 100% sensitivity and 90% specificity, with a significant area under the curve. The K/(Mg2+) ratio showed an optimum cut off at 2.74 with 89% sensitivity and 80% specificity, with a significant area under the curve (AUC=0.924) in the Acute Myocardial Infarction patients **(16).**

Limitations: In our study, the definition of coronary arteries disease was based on angiographic views y 2D X-ray, we did not use IVUS or FFR which may interfere with the decision of the interpretation of coronary angiography and sample size needed to be more in further studies.

CONCLUSION

(Mg2+) level is highly predictive in suspecting the finding of coronary artery ectasia in both obstructive and non-obstructive coronary lesions.

Recommendations: Larger sample size studies are recommended to consolidate our findings. Longer follow up periods to determine validity of (Mg2+) level in predicting longer term clinical outcome. This study recommends using (Mg2+) level to predict development coronary ectasia.

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