International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 10, 2020
ISSN: 1475-7192

Serum Magnesium Level Relationship With Coronary Artery Ectasia

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Abstract

Background:*Coronary artery ectasia (CAE) without specific symptoms is the localised or diffuse swelling of the epicardial coronary arteries to at least 1.5 times the adjacent normal coronary segment. Magnesium, the second most abundant intracellular cation, is an essential element that plays a crucial role in cardiac and vascular functions. The aim of the study is to assess the vasodilatory effect of (Mg2+) in the pathogenesis of Ectasia.****Methods:****This case control study was carried out in zagazig university hospital from December 2018 to May 2019 included 84 selected patients who were admitted to coronary care unit for Diagnostic coronary angiography.Study patients were divided into 4 groups sample each group 21 patients. Laboratory investigations including complete blood cell count, RBS, lipid profile and serum creatinine and (MG2+) level were measured.* ***Results:****There was statistically non-significant difference regarding Hypertension, DM, dyslipidemia, smoking and family history of coronary artery disease with the four groups. When comparing serum creatinine in-between the four groups, it was of no statistically significant difference. Meanwhile as regarding serum Magnesium between the four groups, it was of high statistically significant difference with mean and SD of 1.69 ± 0.14, 2.06 ± 0.18, 1.7 ± 0.15 and 1.84 ± 0.14 receptively. 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.****Conclusion:*** *(Mg2+) level is highly predictive in the development of coronary artery ectasia in both obstructive and non obstructive coronary lesion*

Key words: *Serum Magnesium Level- Coronary Artery Ectasia – diagnosis.*

I. Introduction:

Coronary artery ectasia (CAE) without specific symptoms is the localised or diffuse swelling of the epicardial coronary arteries to at least 1.5 times the adjacent normal coronary segment. It is congenital or acquired and several studies have reported its incidence at 0.3–5**%.** **(1)**

The basic pathogenic mechanism is destruction of the musculo-elastic layers of the arterial tunica media, and the accumulation of collagen in place of elastin, leading to thinning of the arterial wall**.** **(2)**

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Injury of the media causes decreased stress tolerance of the vessel wall to intraluminar pressure, leading to progressive dilatation and ectasia formation**.** [1]

Atherosclerosis, congenital factors, and inflammatory or connective tissue disorders may play a role in the aetiology, however, the aetiopathogenesis remains unclear despite some molecular, cellular and vascular mechanisms being defined in previous studies**.** [3]

In several studies, other vascular structures were shown to be involved in CAE patients. In previous studies, aortic aneursym, dilatations in lower-extremity varicose veins, basillary artery aneurysm and varicocele were reported to be more frequent in isolated ectasia patients**.** [4]

These findings propose that positive remodelling in the vessel wall, which is not common in the atherosclerotic process, plays a role in the aetiopathogenesis of CAE, which indicates CAE is a vascular disease and not localised to the coronary arteries. Therefore factors other than atheroscleosis may play a role in its aetiopathogenesis.[4]

Magnesium, the second most abundant intracellular cation, is an essential element that plays a crucial role in cardiac and vascular functions.

Magnesium regulates contractile proteins, modulates transmembrane transport of calcium (Ca2+), sodium (Na+) and potassium (K+), acts as a co-factor in the activation of ATPase, controls regulation of energy-dependent cytoplasmic and mitochondrial metabolism, and influences DNA and protein synthesis at the subcellular level**.** [5]

Small changes in concentration of extracellular and/or intracellular free (Mg2+) have important effects in cardiac excitability, vascular tonus,contractibility, reactivity and growth. Low levels of intracellular (Mg2+) lead to abnormal vascular cell growth, inflammation, fibrosis and contraction, resulting in negative vascular remodelling. Dosing with (Mg2+) was found to cause vasodilatation and to have anti-inflammatory effects. [6]

The study aimed tostudy the vasodilatory effect of (Mg2+) in the pathogenesis of ectasia

II. Patients and Methods

This case control study was carried out in Zagazig University Hospital in the period from December 2017 to May 2019 included 84 selected patients who were admitted to coronary care unit for elective coronary intervention.

This study included (84) patients (57 males “67.85%” and 27 females “32.14%” their age ranged between 49 years and 70 years, with mean age 57.5 ± 5.69years, divided into four groups, according to their coronary angiography **:**

-Group (1): CAD patients without ectasia.

-Group (2): Isolated ectasia patients.

-Group (3): Normal coronary angiography patients.

-Group (4): CAD patients with ectasia.

Each group includes 21 patients who were admitted for elective coronary intervention.

All patients gave an informed consent to participate in the study

Inclusion criteria:

- Patients with stable coronary angina going to do elective coronary angiography.

Exclusion criteria:

- . Patients with renal failure.
- Patients with moderate to severevalvular heart disease.
- Patients with poor lt ventricular systolic function.
- Patients with neoplastic disease.
- Patients with chronic systemic illness.
- Patients with Addisons disease.
- Patients with hypothyroidism.

Methods:

All patients were subjected to:

A) **Full history taking**: with special emphasis on:

1. Demographic criteria including Age, sex.
2. A detailed medical and cardiac history including cardiovascular risk factors:

B) Physical Examination:

Thorough clinical examination including:

- Pulse and blood pressure.
- Neck veins.
- Edema of lower limbs.
- Chest and abdominal examination.
- Cardiac examination including inspection, palpation and auscultation.

C) Electrocardiography

ECG was done on admission at a paper speed of 25mm/s and amplification of 10mm/mv.

Depicted ECG changes were either:

- ST depression > 0.5 mm in 2 contiguous leads

- T wave inversion
- Pathological Q waves
- Normal ECG (no ST deviation)

D) Transthoracic Echo Doppler study

Detailed transthoracic echocardiography was performed to all patients using GE Vivid 9.

The conventional Echo was performed by experienced echo cardiographer in accordance with the recommendations of the American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE). The mean of three measurements was used in the analysis.

The echocardiogram was performed with the patient breathing quietly and lying in the left lateral position.

Left ventricular dimensions: -

From parasternal long axis view, we assessed the linear measurement of LV.

At the level of mitral valve tip or immediately below it perpendicular line taken left parasternal long axis view that view internal dimensions were calculated by (2DE) guided M-mode approach**.**

These measurements included the following:

- Inter-ventricular septum thickness (IVST)
- left ventricular posterior wall thickness (LVPWT)
- LV End diastolic diameter (LVEDD).
- LV End systolic diameter (LVESD).
- LV Ejection Fraction (EF) by M-Mode

Pulsed-wave (PW) Doppler was performed in the apical 4-chamber view to obtain mitral inflow velocities to assess LV filling.

E) Laboratory investigations including

1. Serum creatinine and blood urea: detected by Cobas 6000 C501 electrochemiluminescentassay.
2. Complete blood cell count using Sysmex S. F3000 automated analyzer.
3. Random blood sugar level and HBA1C.
4. Lipid profile: This included total cholesterol, low-density lipoproteins, high-density lipoproteins, and triglycerides using Cobas Integra instrument – spectrophotometry method.
5. Serum magnesium level; detected by spectrophotometry method, it required (12 hours fasting).

G) Coronary angiography

Invasive coronary angiography was done. Left and right guiding catheters introduced through the sheath in right femoral artery (trans-femoral approach).

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 arterie to at least 1.5 times the adjacent normal coronary segment.

The results of coronary intervention were: -

- Normal coronary arteies.
- One& two vessels with coronary lesions.
- One& two&multivessels with ectasia.

One & two& multi ecstatic vessels with also coronary lesions with them.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 25 (IBM, USA).

Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- **Chi-square (X^2) test** of significance was used in order to compare proportions between qualitative parameters.
- **ANOVA (F) test** of significance was used in order to compare proportions between quantitative parameters.

The following regarding ROC curve were done:

- **Receiver** operating characteristic (ROC) curve analysis was used to identify optimal cut-off values. Area Under Curve (AUC) was also calculated, criteria to qualify for AUC were as follows: 0.90 – 1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair; 0.60-0.70 = poor; and 0.50-0.6 = fail. The optimal cutoff point was established at point of maximum accuracy by Younden index.

P-value $\leq$0.05 was considered significant.

III. Results:

This is a case control study included 84 patients (57 males and 27 females) divided into 4 groups each of them includes 21 patients. Patients with obstructive coronary artery disease (group I) ,isolated coronary artery

ectasia (group II) Patients with normal coronaries (group III),), and patients with coronary artery ectasia and obstructive coronary artery disease (group IV).

Demographic data:

- **Comparison between the studied groups regarding the demographic data**

As regarding gender distribution between the four groups there were no statistically significant difference between them with(**p value 0.426)**. The mean value of **age** distribution for control group(normal coronary angiography)was 58.3 ± 6.35 years ,and the mean value of age distribution for CAE group was 57.6 ± 5.33 years ,and the mean value of age distribution for O-CAD with ectasia was 57.1 ± 5.44 years ,and the mean value of age distribution for obstructive coronary group was 57.5 ± 5.69 years, with no statistically significant difference in between them, with (**p value 0.936)**.

According to weight,the mean value of weight distribution for control group(normal coronary angiography) was 85.2 ± 8.21 kg,and the mean value of weight distribution for CAE group was 84 ± 9.92 kg,and the mean value of weight distribution for O-CAD with ectasia group was 83.7 ± 9.02 kg,and the mean value of weight distribution for obstructive coronary group was 86.2 ± 9.56 kg with no statistically significant difference between the four groups with , (**p value 0.822).**

Table (1) Comparison between the studied groups regarding the demographic data

	Group (1) **O-CAD**	Group(2) **CAE**	Group(3) **NORMAL CORONARIES**	Group(4) **O-CAD With ectasia**	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		

Risk factors:

- **Comparison between the studied groups regarding the risk factors**

As regarding risk factors, there were no statistically significant difference between the four groups. As regarding **Hypertension** there was no significant correlation differences with the four groups with (**p value0.811)** , As regarding DM there was no significant correlation differences with the four groups with (**p value0.644)** , As regarding dyslipidemia there was no significant correlation differences with the four groups with (**p value0.824)** ,As regarding smoking there was no significant correlation differences with the four groups with (**p value0.914)** and as regarding family history of coronary artery disease was all non-significantly correlated with the four groups with(**p value 0.801)** receptively.

As shown in **figure 4,hypertension** represents 57.1% of group (I) O-CAD , 61.9% of group (II) CAE , 52.4% of group (III) NORMAL coronariesand 47.6% of group (IV)) O-CAD with ectasia . **DM** represents 52.4% of O-CAD group , and 42.9% of CAE group ,and 47.6% of NORMAL coronariesgroupand 61.9% of the O-CAD with ectasia group . As regarding **dyslipidemia**, it represents 57.1% of O-CAD group ,and 47.6% of CAE group ,and 47.6% of NORMAL coronariesgroupand 42.9% of O-CAD with ectasia group receptively. Meanwhile for **smoking** it represents 57.1% of O-CAD group, 52.4% of CAE group ,and 47.6% of NORMAL coronariesgroup and 47.6% of O-CAD with ectasia group receptively. Finally, for **family history** of coronary artery disease it represents 33.3% of O-CAD group , 42.9% of CAE group , 33.3% of NORMAL coronariesgroup and 28.6% of O-CAD with ectasia group receptively.

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

RISK FACTORS	Group I O-CAD	Group II ECTASIA	Group III NORMAL coronaries	Group IV O-CAD with ECTASIA	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

Laboratory data:

- **Comparison between the studied groups regarding serum creatinine.**

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 coronariesgroup and 0.93 ± 0.1 for O-CAD with ectasia group with (**p value 0.276).**

Table (3): Comparison between the studied groups regarding serum creatinine.

Serum creatinine	Group I O-CAD	Group II ECTASIA	Group III NORMAL Coronaries	Group IV O-CAD with ECTASIA	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		

Comparison between the studied groups regarding serum (Mg2+)

Meanwhile as regarding **serum Magnesium** between the four groups, it was of **high** statistically significant difference with mean and SD of 1.69 ± 0.14 for O-CAD group ,and 2.06 ± 0.18 for CAE group ,and 1.7 ± 0.15 for NORMAL coronariesgroup and 1.84 ± 0.14 for O-CAD with ectasia group receptively with(**p value less than 0.001).**

Table (4): Comparison between the studied groups regarding serum (Mg2+).

Serum (Mg2+)	Group I O-CAD	Group II ECTASIA	Group III NORMAL coronaries	Group IV O-CAD with ECTASIA	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		

- **Comparison between each group with the other as regarding serum (Mg2+).**

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 5,** 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): 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***

- GI represents O-CAD group.
- GII represents isolated ectasia group.
- GIII represents normal coronaries group.
- GIV represents O-CAD with ectasia group.

- **Correlation between serum (Mg2+) level and demograghic data and risk factors.**

As regarding the correlation between serum (Mg2+) and demographic data there was no statistical significant difference for age with **(p value 0.545)** ,also there was no statistical significant difference for weight with **(p value 0.605)** and also there was no statistical significant difference for gender with **(p value 0.897)** respectively.

Also for the risk factors there was no significant ststistical differences for hypertention with **(p value 0.77)** , and there was no significant ststistical differences for DM with **(p value0.364)** , and there was no significant ststistical differences for dyslipedemia with **(p value 0.647)** , and there was no significant ststisticaldifferences for smoking with **(p value 0,542)** and also there was no significant ststistical differences for family history with **(p value 0.865)** respectively

Table (8): Correlation between serum (Mg2+) level and demograghic data and risk factors.

Demographic data and 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

[+:] Pearson's correlation, [++]: Spearman's correlation

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

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.**

Table (6): Serum Magnesium as predictors for CAE & OCAD; ROC curve analysis

Area under the ROC curve (AUC) (95% Confidence interval)	0.896 (0.81 - 0.952)
P value	<0.001

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%

PPV: Positive predictive value, NPV: Negative predictive value

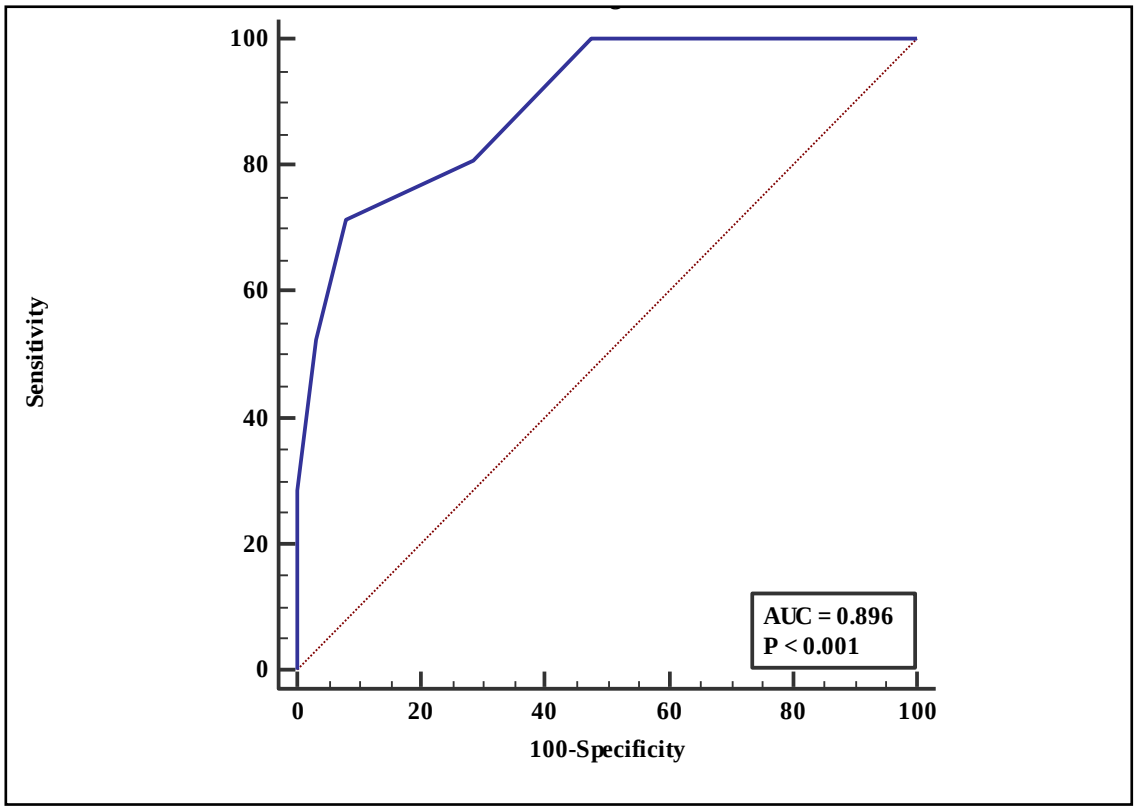

Figure (1): ROC curve analysis regarding serum (Mg2+) and CAE & OCAD

IV. Discussion

In our study as regarding gender distribution between the four groups there was no statistically significant difference between them with p value 0.426. The mean age distribution for control group, CAE, O-CAD and ectatic& obstructive group was 57.5 ± 5.69,57.6 ± 5.33, 58.3 ± 6.35 and 57.1 ± 5.44 receptively, with no statistically significant difference in between them, p value 0.936.

According to weight, there was no statistically significant difference between the four groups with mean values 86.2 ± 9.56, 84 ± 9.92, 85.2 ± 8.21 and 83.7 ± 9.02 receptively, p value 0.822.

In a study done by *Tin et al*, they observed an inverse relation between serum magnesium and incidence of CHD in women and less strongly in men. There was also a weak inverse association between dietary magnesium and incident CHD in men only. These associations were present after adjustment for multiple confounding factors, including sociodemographic characteristics and waist/hip ratio [(7)].

In our study as regarding risk factors, there were no statistically significant difference between the groups. **Hypertension**, DM, dyslipidemia, smoking and family history of coronary artery disease were all non-significantly correlated with the four groups with **p values 0.811, 0.644, 0.824, 0.914, 0.801** receptively.

In contrast to our results, a study done by *Kostov and Halacheva* about the etiopathogenesis of hypertension, a (Mg2+) deficiency was reported to have hypertensive effects, and dietary (Mg2+) intake was related to hypotension, showing the reverse positive relationship between blood pressure and serum (Mg2+) levels [(6)].

In our study when comparing **serum creatinine** in-between the four groups, it was of no statistically significant difference with mean and SD of 0.95 ± 0.10, 0.91 ± 0.11, 0.97 ± 0.1 and 0.93 ± 0.1 receptively with **p value 0.276.**

Although 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)***

In our study, serum Magnesium between the four groups was of high statistically significant difference with mean and SD of 1.69 ± 0.14, 2.06 ± 0.18, 1.7 ± 0.15 and 1.84 ± 0.14 receptively with p value less than 0.001.

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.

Mustafa et al, stated that serum (Mg2+) levels were statistically higher in isolated ectasia patients than in the NCA and CAD groups. (Mg2+) levels were lowest in the CAD group. (Mg2+) levels in the CAD + CAE group were higher 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)***

They also said that (Mg2+) in the extracellular fluid constitutes only 1% of the total body (Mg2+) concentration. However, our findings suggest that chronically higher levels of serum (Mg2+), with its anti-inflammatory effects, play a crucial role in the pathogenesis of ectasia by leading to vasodilation and negative remodeling. They proposed that factors other than atherosclerosis may play an important role in ectasia formation. They concluded that serum (Mg2+) levels were found to be statistically higher in ectasia patients with or without CAD.***(1)***

V. Conclusion:

(Mg2+) level is highly predictive in the development of coronary artery ectasia in both obstructive and non-obstructive coronary lesion

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