Ann Med Res 2021;28(1):20-4

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.07.694

Original Article

Evaluation of the relationship between coronary slow flow phenomenon and serum magnesium levels

Mustafa Ozturk[1], Oguzhan Ekrem Turan[2], Gokhan Ceyhun[1], Emrah Aksakal[1], Kayihan Karaman[3], Oktay Gulcu[1], Selami Demirelli[4], Ali Fuat Korkmaz[1]

[1]Department of Cardiology, University of Health Sciences, Erzurum Education and Research Hospital, Erzurum,Turkey
[2]Department of Cardiology, Karadeniz Technical University, Faculty of Medicine, Trabzon, Turkey
[3]Department of Cardiology, Gaziosmanpasa University, Facultyof Medicine, Tokat, Turkey
[4]Department of Cardiology, University of Health Sciences, Kayseri Training and Research Hospital, Kayseri, Turkey

Abstract

Aim: Coronary slow flow phenomenon (CSFP) is a microvascular circulation disorder. It is known that serum magnesium has positive effects on anti-inflammation, vasodilatation and endothelial functions. This observational study investigated the association of serum magnesium levels with CSFP.

Materials and Methods: Patients who had undergone coronary angiography (CAG) after noninvasive testing were included in the study. CAG records were reassessed for CSFP and 100 patients were diagnosed as having CSFP. Control subjects (n = 80) had normal coronary flow. Serum Mg levels and other biochemical parameters such as glucose, creatinine, cholesterol levels and hemoglobin samples were collected before CAG. Serum Mg values were categorized into two groups: Mg levels equal/under and above 1.9 mg/dL.

Results: The mean patient age was 56.1±9.7 years; 68.9% of patients were men. Patient's hypertension, diabetes mellitus history and smoking habits rate were similar between groups. Biochemical tests revealed lower serum magnesium levels (1.87 vs 1.95mg/dL, p=0.02) for CSFP patients and controls, respectively. In multivariate regression analysis, a serum magnesium level under 1.9 mg/dL (OR:3.33, 95% CI:1.75-6.37, p<0.001) and male gender (OR:2.08, 95% CI: 1.016-4.34, p=0.04) were found to be independent predictors of CSFP.

Conclusion: Low serum magnesium levels were associated with CSFP. However, these results are not sufficient to fully determine the role of Mg levels in the mechanism of CSFP-related chest pain.

Keywords: Coronary slow flow phenomenon; endothelial functions; inflammation; magnesium; vasodilation

INTRODUCTION

Coronary slow flow phenomenon (CSFP) is defined as slow access of the radio-opaque contrast agent to the distal coronary bed during angiography in the absence of obstructive coronary artery disease (CAD) and is considered a coronary microvascular circulation disorder(1). CSFP is observed in 1–7% of patients undergoing coronary angiography (CAG) (2). CSFP has a wide spectrum of clinical features varying from chest pain to cardiac arrest (3). Although the etiology of CSFP is not yet fully understood, inflammation may be an important cause (4). Another hypothesis suggests that vasoconstriction by neurohumoral meditators may promote CSFP (5,6). Studies have identified high endothelin-1 concentrations along with low nitric oxide (NO) concentrations in the coronary sinus and this condition was associated with endothelial dysfunction (7-9).

Magnesium (Mg) is involved in many enzymatic reactions in the body. Mg affects muscle contraction, neuromuscular conduction, vasomotor tone, blood pressure regulation, cardiac excitability, and insulin metabolism (10). Mg is a natural calcium channel blocker and has positive effects on the cardiovascular system, including coronary vasodilation and improvement in endothelial function (11). Increased intracellular levels of Mg result in decreased intracellular free calcium, thus promoting vasodilation (12). The action of Mg as a calcium channel blocker may also help to reduce the release of calcium, therefore reducing vascular resistance (13). Experimental and in vivo studies have shown that Mg deficiency may cause increased inflammation (14,15). Also decreased Mg leads to the generation of reactive oxygen species. This continuous oxidative stress may cause numerous chronic diseases. Increasing dietary magnesium intake is inverted inflammatory markers (16). It is also known Mg

Received: 04.07.2020 **Accepted:** 30.09.2020 **Available online:** 22.01.2021
Corresponding Author: Mustafa Ozturk, Department of Cardiology, University of Health Sciences, Erzurum Education and Research Hospital, Erzurum,Turkey **E-mail:** mozturk81@yahoo.com

may play an important role in regulating arteriolar tone and blood flow (17). But it is not known whether lower serum Mg levels are related to impaired coronary blood flow. Moreover, the relationship of serum Mg levels and CSFP has not been investigated yet.

In this study, we aim to evaluate the role of serum Mg levels as a marker of inflammation, vasodilation and endothelial function in patients with and without CSFP.

MATERIALS and METHODS

This study included patients who were admitted to our hospital with chest pain between February 2016 and May 2018 and who underwent CAG after noninvasive testing. Clinical characteristics and laboratory data of the patients were obtained from files and digital records. Patients with acute coronary syndrome (ACS), myocarditis-pericarditis, elevated troponin levels, ≥40% coronary stenosis, atrial fibrillation, nonsinusoidal rhythm or marked bradycardia, connective tissue disease, renal and hepatic insufficiency, and CAD patients with severe valve disease were excluded. After this exclusion, CAG images were evaluated by three experienced interventional cardiologists and the Thrombolysis in myocardial infarction (TIMI) frame count was calculated. CAG was recorded based on images obtained at 30 frames per second. The TIMI frame count is defined as the number of frames required for the contrast agent to reach the specified distal coronary artery point. The distal bifurcation, called the mustache or whale's tail, for the left anterior descending (LAD) artery, the end of the distal bifurcation for the circumflex artery (Cx), and the first lateral branch of the posterolateral artery (PL) for the right coronary artery (RCA) were selected as the distal points. The starting frame was defined as the frame in which the coronary artery ostium was completely filled with contrast material and the last frame was the frame in which the contrast material reached the distal branch. The difference between the first and last frames was the number of frames. A correction factor of 1.7 was used to eliminate the effect of differences in the length of the LAD artery and the adjusted TIMI frame count was calculated. We used TIMI frame counts to define CSFP and performed our evaluation as per the procedures described by Gibson et al. (18). The average TIMI frame count was obtained by dividing the sum of the RCA, Cx, and LAD TIMI frame counts by three. We considered 21.1±1.5 frames for LAD (adjusted), 22.2±4.1 frames for Cx, and 20.4±3 frames for RCA as reference values. In total, 100 patients were identified as having CSFP and 80 normal coronary flow (NCF) patients were randomly selected as a control group.

Serum Mg, creatinine, glucose, hemoglobin, white blood cell count, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglyceride samples were collected before the CAG procedure. Serum Mg levels were measured in a biochemical laboratory by using the Abbott/Architect c16000 auto-analyzer (Abbott Park, Illinois, U.S.A.). Mg levels were expressed in mg/dL. Serum Mg values were categorized into two groups: Mg levels equal/under and above 1.9 mg/dL. This study was approved by Erzurum Education and Research Hospital Ethic committee (Approved number: 2018/12-115 and date:18.06.2018), all participants provided informed consent.

Statistical analysis

All statistical analyses were performed using SPSS software (SPSS 20.0 for Windows Inc., Chicago, IL, USA). Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk's test) to determine whether or not they were normally distributed. Descriptive analyses were presented using medians and interquartile range (IQR) for non-normally distributed variables. Categorical variables are expressed as number (percentage). An independent sample T test was used to compare the differences for normally distributed parameters. Wilcoxon test was used to compare the difference for non-normally distributed parameters. Chi-square test was used to compare categorical variables. Spearman correlation test was used to compare serum magnesium and TIMI frame count values. For multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of CSFP. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. A 5% type-I error level was used to infer statistical significance. P-values less than 0.05 were considered statistically significant.

RESULTS

The study population consisted of CSFP (n=100) and NCF (n=80) patients. The mean patient age was 56.1±9.7 years and 68.9% of patients were men. Baseline patient demographic characteristics are shown in Table 1 and there was no statistically significant difference between the two groups except gender. In our study, 45.14% of patients had CSFP in a single vessel, 34.35% in two, and 20.51% in three. The TIMI frame count was higher for all three vessels in the CSFP group than in the NCF group ($p < 0.001$) (Table 1). Also the TIMI frame count values were negatively correlated with serum magnesium levels (r=0.3, p=0.01).

Table 1. Baseline clinical and laboratory characteristics of the study population

Variables	CSFP (n=100)	NCF (n=80)	p-value
Age (years)	56.1 ±10.1	56.2 ±9.4	0.9
Sex (male),n%	76 (76)	48 (60)	**0.02**
Diabetes mellitus,n%	29 (29)	22 (27.5)	0.2
Hypertension, n%	37 (37)	29 (36.3)	0.6
Smoking, n%	61 (61)	49 (61.2)	0.3
WBC × 10^3mL	7.7 (6.6–9.3)	7.7 (6.9–9.5)	0.9
Neutrophil× 10^3mL	5.3 (4.2-6.2)	4.7 (4.3-6.8)	0.2
Lymphocyte× 10^3mL	2 (1.5-2.4)	2.2 (1.7-2.7)	**0.04**
NLR	2.6 (1.8-3.4)	2.1 (1.7-3.2)	**0.005**
Hemoglobin, g/dL	15.5 ±1.7	15.1 ±1.9	0.1
Serum creatinine, mg/dL	0.83±0.4	0.78±0.7	0.4

Glucose, mg/dL		109.6±37.3	108.2±32.3	0.7
Total Cholesterol, mg/dL		187.5 (150.5–217.5)	168.5 (151.7–198.5)	0.3
LDL-Cholesterol, mg/dL		125 (102–146)	121 (100–136)	0.4
HDL-Cholesterol, mg/dL		41.6±12.4	40.1±7	0.7
Triglyceride, mg/dL		167 (134–191)	116 (76.5–162.5)	0.08
Magnesium, mg/dL		1.87 (1.75–2)	1.95 (1.8–2)	**0.02**
Magnesium≤1.9 mg/dL, n %		58 (58)	25 (31.3)	**<0.001**
TFC	LAD (Corrected)	22.86±3.52	34.62 ±9.04	**<0.001**
	Cx	19.74±3.14	31.74 ±7.44	**<0.001**
	RCA	20.64±3.4	32.66 ±8.33	**<0.001**
	Mean TFC	21.08±3.04	33 ±6.93	**<0.001**

CSF- Coronary Slow Flow; Cx- Circumflex Artery; HDL- High-Density Lipoprotein; LAD-Left Anterior Descending Artery; LDL- Low-Density Lipoprotein; NCF- Normal Coronary Flow; NLR: Neutrophil to Lymphocyte Ratio; RCA- Right Coronary Artery; TFC- TIMI Frame Count; WBC- White Blood Cell Count

Biochemical test results revealed that mean serum Mg levels for all patients were 1.9 (1.78-2.01) mg/dL. CSFP patients had lower serum Mg levels than controls (1.87 vs 1.95 mg/dL, p=0.02 respectively) (Figure 1). Pre-CAG creatinine levels were found to be similar for both groups (0.83±0.4 vs 0.78±0.7 mg/dL, p=0.4 respectively). Also CSFP patients had similar serum glucose (109.6±37.3 vs 108.2±32.3 mg/dL, p=0.7), total cholesterol (187.5 vs 168.5 mg/dL, p=0.3), LDL cholesterol (125 vs 121 mg/dL, p=0.4) and HDL cholesterol (41.6±12.4 vs 40.1±7 mg/dL, p=0.7), triglyceride (167 vs 116 mg/dL, p=0.08) levels than controls. Moreover CSFP patients had similar hemoglobin (15.5 ±1.7 vs 15.1 ±1.9 g/dL, p=0.1) and white blood cell count (7.7 vs 7.7 × 10^3mL, p=0.9) than controls. Patients with CSFP had higher neutrophil to lymphocyte ratio (NLR) value than NCF group (2.6 vs 2.1, p=0.005). The distribution of biochemical variables levels according to groups is shown in Table 1.

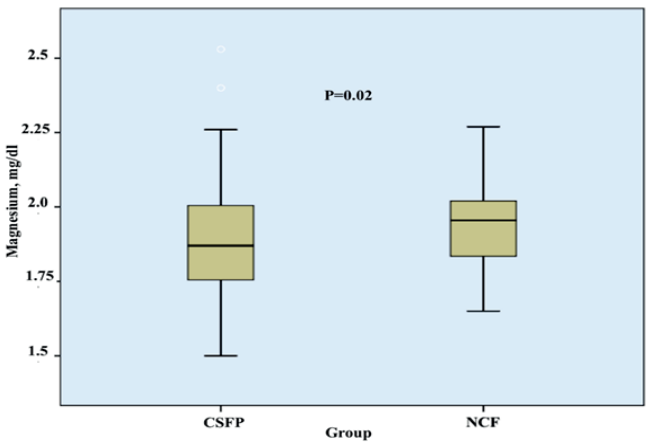

Figure 1. Serum Mg levels of normal (NCF) and coronary slow flow phenomenon (CSFP) patients

The parameters that were significant in the single-variable analysis were included in regression analysis and independent predictors of CSFP were investigated. A serum Mg level ≤1.9 mg/dL (OR 3.33, 95% CI: 1.75-6.37, p<0.001) and male gender (OR 2.08, 95% CI: 1.016-4.34, p=0.045) were independent predictors of CSFP (Table 2).

Table 2. Univariate and multivariate analysis of predictors of coronary slow flow phenomenon

Variables	OddsRatio, 95 CI%	Univariate p value	OddsRatio, 95 CI%	Multivariate p value
Male gender	2.13 (1.018-4)	**0.022**	2.08 (1.016-4.34)	**0.045**
Magnesium ≤1.9, mg/dL	0.33 (0.178-0.61)	**0.016**	3.33 (1.75-6.37)	**<0.001**
NLR	1.2 (0.95-1.5)	**0.005**	1.16 (0.88- 1.5)	0.292

NLR: Neutrophil to Lymphocyte Ratio

DISCUSSION

We investigated the association of serum magnesium levels with CSFP, which has not been previously evaluated. Our results indicate that serum Mg levels were lower in patients with CSFP.

CSFP is defined as the slow delivery of radio-opaque material to the distal coronary bed during angiography(1). The phenomenon of CSF, an important cardiac cause of hospital admission for chest pain, can also lead to considerably negative cardiac consequences. The mean prevalence of CSFP is 1–7% in patients who undergo coronary angiography for suspected ischemic chest pain and/or ACS (2). The clinical presentation may be chest pain with exertion and/or rest, or as ACS (19). A number of hypotheses have been proposed for the mechanism of CSFP, whose etiology is not yet fully clarified. Mangieri et al. identified vascular wall thickening, mitochondrial abnormalities, and decreased glycogen content as causing a decrease in the vessel lumen diameter in the histopathological evaluation of left ventricular biopsies of CSFP patients (20). The authors also reported that coronary slow flow is improved by dipyridamole administration. In light of this, it was thought that functional obstruction and existing histopathological abnormalities at the microvascular level may increase flow resistance. In another study, mibefradil, a T-type calcium channel blocker, improved slow flow, reduced the frequency of angina complaints, and reduced the need for sublingual nitrate administration (21).

Mg is a cofactor of the rate-limiting step in the synthesis of prostaglandin E1 and consequently has a vasodilatory effect, which is also mediated by increasing NO release (22). Oral Mg intake acts as a natural calcium channel blocker, increases endothelial function, and induces both direct and indirect vasodilation (23). Specifically, increases in Mg levels lead to decreased vascular resistance and

vasodilation, while decreases in Mg levels reduce vessel luminal diameter because of increased inflammation and oxidative stress, resulting in medial hypertrophy, increased vascular tone after vascular remodeling, and vasoconstriction (13). The inverse relationship between dietary Mg levels, inflammation, and endothelial dysfunction was demonstrated by a study in healthy women (24). NLR, defined as an inflammatory marker, was found higher in CSFP group than in NCF group. Çetin et al. demonstrated that NLR may play an inflammation-mediated role in the pathogenesis of CSFP (25). Our study results supported these findings. In this context, the higher rate of CSFP development in patients with low serum Mg levels may be related to endothelial dysfunction and inflammation. In our study, the serum Mg level, a marker of inflammation, vasodilation and endothelial function, was also lower in the CSFP group than in the NCF group. In multivariate analysis, male gender and lower (less than 1.9 mg/dL) serum Mg levels were the only predictors of CSFP. The etiological relationship between gender association CSFP is not known, and other studies yielded results similar to ours (26,27).

LIMITATIONS

Despite the convincing results, this study had some limitations. The first is its retrospective design. The heart rate of patients was obtained from their ECGs on file. Failure to obtain heart rate data during CAG can be considered a limitation. Another limitation was that the diagnosis of CSFP was made based on a visual interpretation of CAG images. We attempted to obtaining more quantitative results using the TIMI frame count. However, intravascular ultrasound or dynamic pressure measurement methods, which provide more accurate measurements of actual coronary flow, were not used. Prospective studies involving more patients may give more statistically significant results.

CONCLUSION

Based on the results of our study, we have shown that Mg levels are lower in patients with CSFP than in a patient with NCF. However, these results are not sufficient to fully determine the role of Mg levels in the mechanism of CSFP-related chest pain. In light of these data, we think that prospective studies should be performed by increasing the Mg level in the diets of patients or administering oral Mg supplementation to control chest pain in CSFP patients.

Conflict of interest : The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: This study was approved by Erzurum Education and Research Hospital Ethic committee (Approved number: 2018/12-115 and date:18.06.2018), all participants provided informed consent.

REFERENCES

1. Tambe AA, Demany MA, Zimmerman HA, et al. Angina pectoris and slow flow velocity of dye in coronary arteries--a new angiographic finding. Am Heart J 1972; 84:66-71.
2. Singh S, Kothari SS, Bahl VK. Coronary slow flow phenomenon: an angiographic curiosity. Indian Heart J 2004;56:613-7.
3. Cesar LA, Ramires JA, SerranoJunior CV, et al. Slow coronary run-off in patients with angina pectoris: clinical significance and thallium-201 scintigraphic study. Braz J Med Biol Res 1996;29:605-13.
4. Xia S, Deng SB, Wang Y, et al. Clinical analysis of the risk factors of slow coronary flow. Heart Vessels 2011;26:480-6.
5. Larkin SW, Clarke JG, Keogh BE, et al. Intracoronary endothelin induces myocardial ischemia by small vessel constriction in the dog. The American journal of cardiology 1989;64:956-8.
6. Clarke JG, Davies GJ, Kerwin R, et al. Coronary artery infusion of neuropeptide Y in patients with angina pectoris. Lancet 1987;1:1057-9.
7. Camsarl A, Pekdemir H, Cicek D, et al. Endothelin-1 and nitric oxide concentrations and their response to exercise in patients with slow coronary flow. Circ J 2003; 67:1022-8.
8. Pekdemir H, Cicek D, Camsari A, et al. The relationship between plasma endothelin-1, nitric oxide levels, and heart rate variability in patients with coronary slow flow. Ann Noninvasive Electrocardiol 2004;9:24-33.
9. Pekdemir H, Polat G, Cin VG, et al. Elevated plasma endothelin-1 levels in coronary sinus during rapid right atrial pacing in patients with slow coronary flow. Int J Cardiol 2004;97:35-41.
10. Grober U, Schmidt J, Kisters K. Magnesium in Prevention and Therapy. Nutrients 2015;7:8199-226.
11. Shechter M. Magnesium and cardiovascular system. Magnes Res 2010;23:60-72.
12. Griendling KK, Rittenhouse SE, Brock TA, et al. Sustained diacylglycerol formation from inositol phospholipids in angiotensin II-stimulated vascular smooth muscle cells. J Biol Chem 1986;261:5901-6.
13. Sontia B, Touyz RM. Role of magnesium in hypertension. Arch Biochem Biophys 2007;458:33-9.
14. Nielsen FH. Magnesium deficiency and increased inflammation: current perspectives. J Inflamm Res 2018;11:25-34.
15. Libako P, Nowacki W, Rock E, et al. Phagocyte priming by low magnesium status: input to the enhanced inflammatory and oxidative stres responses. Magnes Res 2010;23:1-4.
16. Dibaba DT, Xun P, He K. Dietary magnesium intake is inversely associated with serum C-reactive protein levels: meta-analysis and systematic review. Eur J Clin Nutr 2014;68:510-6.
17. Altura BM, Altura BT. Magnesium and vascular tone and reactivity. Blood Vessels 1978;15:5-16.
18. Gibson CM, Cannon CP, Daley WL, et al. TIMI framecount: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879-88.
19. Oktay V, Arat Ozkan A. Coronaryslowflow. Turk Kardiyol Dern Ars 2016;44:193-5.

20. Mangieri E, Macchiarelli G, Ciavolella M, et al. Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Cathet Cardiovasc Diagn1996;37:375-81.
21. Beltrame JF, Turner SP, Leslie SL, et al. The angiographic and clinical benefits of mibefradil in the coronary slow flow phenomenon. J Am Coll Cardiol 2004;44:57-62.
22. Kostov K, Halacheva L. Role of Magnesium Deficiency in Promoting Atherosclerosis, Endothelial Dysfunction, and Arterial Stiffening as Risk Factors for Hypertension. Int J MolSci 2018;19.
23. Houston M. The role of magnesium in hypertension and cardiovascular disease. J Clin Hypertens (Greenwich) 2011;13:843-7.
24. Song Y, Li TY, van Dam RM, et al. Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women. Am J ClinNutr 2007;85(4):1068-74.
25. Cetin M, Kiziltunc E, Elalmis OU, et al. Predictive Value of Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio in Patients with Coronary Slow Flow. Acta Cardiol Sin. 2016;32(3):307-312.
26. Elamragy AA, Abdelhalim AA, Arafa ME, et al. Anxiety and depression relationship with coronary slow flow. PLoS One 2019;14.
27. Sadr-Ameli MA, Saedi S, Saedi T, et al. Coronary slow flow: Benign or ominous? Anatol J Cardiol 2015;15:531-5.