

Research Article | Araştırma Makalesi

THE RELATIONSHIP BETWEEN GOOD COLLATERAL DEVELOPMENT AND MAGNESIUM/PHOSPHATE RATIOS IN CHRONIC TOTAL OCCLUSION

KRONİK TOTAL OKLÜZYONDA İYİ KOLLATERAL GELİŞİMİ İLE MAGNEZYUM/FOSFAT ORANLARI ARASINDAKİ İLİŞKİ

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ABSTRACT

Objective: Coronary collateral formation can be triggered by many acquired factors such as ischemia and growth factors, which ultimately manifests as differences in the quality of the coronary collateral circulation (CCC) in patients. Low magnesium (Mg) levels can increase endothelial cell dysfunction and potentially increase the risk of thrombosis and atherosclerosis. However, it has been reported that high serum phosphate (P) levels are correlated with the development of atherosclerosis and mortality. In this article, we aimed to reveal the relationship between CCC quality and Mg/P ratio in chronic total occlusion (CTO).

Methods: A total of 269 patients with detected CTO in coronary angiography between March 2014 and June 2018 were included in the study. The patients were divided into two groups as group I (127 patients) and group II (142 patients) according to the Rentrop classification. The study is a retrospective, observational study.

Results: In the multivariable regression analysis; smoking ($p=0.004$), triglyceride ($p<0.001$) and Mg/P ratio ($p<0.001$) parameters were independent predictors affecting CCC in CTO. Mg/P value was statistically lower in the group I (0.49 ± 0.17) than group II (0.62 ± 0.12) ($p<0.001$). The ideal Mg/P cut-off value was 0.56 that calculated by the Youden index had 69% sensitivity, and 64% specificity for collateral development of CTO.

Conclusion: Mg/P is a parameter that affects coronary collateral development. High Mg/P ratio level is associated with good collateral development in patients who had CTO.

Keywords: Coronary artery disease, chronic total occlusion, Mg/P ratio, collateral development

Öz

Amaç: Koroner kollateral oluşumu, iskemi ve büyüme faktörleri gibi birçok edinsel faktör tarafından tetiklenebilir bu da hastalarda koroner kollateral dolaşımın (KKD) kalitesinde farklılıklar olarak ortaya çıkar. Düşük magnezyum (Mg) seviyeleri endotel hücrelerinin fonksiyon bozukluğunu artırabilir ve potansiyel olarak tromboz ve ateroskleroz riskini artırabilir. Bununla birlikte yüksek serum fosfat (P) seviyelerinin ateroskleroz gelişimi ve mortalite ile ilişkili olduğu bildirilmiştir. Bu çalışmada kronik total oklüzyonda (KTO) KKD kalitesi ile Mg/P oranı arasındaki ilişkiyi araştırmayı amaçladık.

Yöntem: Temmuz 2014 ile Şubat 2018 tarihleri arasında koroner anjiyografide KTO saptanan toplam 269 hasta çalışmaya dahil edildi. Hastalar Rentrop sınıflamasına göre grup I (127 hasta) ve grup II (142 hasta) olarak iki gruba ayrıldı. Çalışma retrospektif, gözlemsel bir çalışmadır.

Bulgular: Çok değişkenli regresyon analizinde; sigara ($p=0,004$), trigliserid ($p<0,001$) ve Mg/P oranı ($p<0,001$) KTO'da KKD'ı etkileyen bağımsız prediktörlerdir. Mg/P değeri grup I'de ($0,49\pm 0,17$) grup II'ye ($0,62\pm 0,12$) göre istatistiksel olarak daha düşüktü ($p<0,001$). Youden indeksi ile hesaplanan ideal Mg/P cut-off değeri 0,56 olup, KTO'da iyi kollateral gelişimi için %69 duyarlılık ve %64 özgüllüğe sahiptir.

Sonuç: Mg/P oranı, koroner kollateral gelişimi etkileyen bir parametredir. Yüksek Mg/P oranı, KTO'su olan hastalarda iyi kollateral gelişim ile ilişkilidir.

Anahtar Kelimeler: Koroner arter hastalığı, kronik total oklüzyon, Mg/P oranı, kollateral gelişim

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Introduction

Coronary collateral circulation (CCC) protects the myocardial tissue from ischemia and provides its adaptation, thus restoring myocardial perfusion. Normal individuals have coronary collateral vessels between the main coronary arteries. Since they provide negligible blood circulation, they cannot be visualized in coronary angiography (CAG).¹ Coronary collateral formation can be triggered by many factors such as growth factors, pressure gradients, and ischemia.^{1,2} CCC plays an important role in reducing myocardial ischemia and possible infarction in patients with chronic total occlusion (CTO). Well-developed CCC is correlated with improved cardiac function and reduced cardiovascular (CV) mortality.³ Many non-congenital factors influence arterial remodeling, which ultimately manifests as differences in the development of CCC.

Magnesium (Mg) and phosphate (P) are important minerals in the pathophysiology of atherogenesis. Mg plays an important role in many conditions that regulate CV functions, such as endothelial function, regulation of vascular tone, and myocardial excitability.^{4,5} It has been shown that high circulating Mg values and Mg intake are correlated with a slight reduction in the risk of CV disease, including coronary artery disease (CAD).^{6,7} Low plasma Mg levels can increase endothelial cell dysfunction and potentially increase the risk of thrombosis and atherosclerosis.⁸ It has been stated that even high serum P values in the reference range in patients without renal failure are associated with the occurrence of atherosclerosis and mortality.^{9,10}

So, in this study, we aimed to investigate the relationship between good coronary collateral development and Mg/P ratios in patients with CTO.

Methods

This trial was planned as a retrospective study. In line with this purpose, it was planned to include patients who applied to Dicle University Medicine Faculty Department of Cardiology. A total of 269 patients with detected CTO in coronary angiography between March 2014 and June 2018 were included in the study. There were 2 groups formed according to coronary collateral development: Rentrop 0-1 group I (127 patients), Rentrop 2-3 group II (142 patients).

Our study was designed in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the local ethics committee of our hospital before starting the study.

Patients with a history of coronary artery bypass graft and/or percutaneous coronary intervention, severe renal impairment, severe hepatic impairment, moderate or severe heart valve disease, evidence of ongoing infection or inflammation, active malignancy, and patients in whom optimal angiographic examination cannot be performed were excluded. Since the plasma Mg and P levels may change in acute conditions such as

dehydration and diarrhea, patients with acute general condition disorder, dehydration and diarrhea were excluded from the study. In addition, patients with serious comorbid diseases such as peripheral artery disease, hematological disorders, aortic dissection and pulmonary embolism were excluded from the study.

Coronary Angiography

CAG was performed via femoral or radial access using 6F or 7F catheters with the Judkins technique. The level of stenosis in the coronary arteries was determined according to the angle at which the highest stenosis was observed. CCC was classified semi-quantitatively between 0 and 3 according to the Rentrop classification.^{11,12} The patients were divided into 2 groups according to the degree of collateral vessel formation: poor collateral (Rentrop 0-1), good collateral (Rentrop 2-3).^{11,12} The highest Rentrop level was considered in the presence of two or more coronary artery lesions and coronary collateral.

Statistical Analysis

IBM SPSS Statistics 25.0 program was used to perform and evaluate all statistical analyzes. Normally distributed numerical parameters were analyzed using the Kolmogorov-Smirnov test. Numerical parameters are presented with mean and standard deviation values. To compare the numerical parameters between the two groups; the independent sample T test was used if it was normally distributed, and the Mann-Whitney U test was used if it did not show normal distribution. Categorical parameters were specified as numbers (n) and percent (%). The relationship between categorical parameters was analyzed based on Pearson's chi-square or Fisher's exact tests. ROC (Receiver Operating Characteristic) analysis was used to determine the cut-off value of Mg/P. For all hypotheses, the significance level of the p value was taken as <0.05.

Results

The 269 patients included in the study were divided into two groups as Group I (Rentrop 0-1) and Group II (Rentrop 2-3). The mean age of the patients included in the study was 60.9±10.6 years, and the mean age was statistically significantly higher group II than group I (62.1±11.1 vs. 59.5±9.7 years, p=0.046). Male gender comprised 72.5% of the study population. There was no significant difference between the groups in terms of gender (male sex ratio 71.7% vs. 73.2%, p=0.771).

The rate of smoking was higher in poor collateral development group than good collateral group (53.5% vs. 26.8%, p<0.001). Between the two groups; hypertension (HT) (40.9% vs. 34.5%, p=0.276) and previous myocardial infarction (MI) (19.7% vs. 15.5%, p=0.366) rate were similar. The rate of diabetes mellitus (DM) was higher in group I than group II (38.6%, 23.2%, p=0.006). There was no significant difference between the groups in terms of the medical treatments used by the patients before the

procedure. Demographic data and comorbid diseases of the study population, and medical treatments that used by the patients before the procedure are given in Table 1.

In biochemical and hemogram parameters; there was a statistically significant difference between the two groups in terms of platelet ($p=0.020$), fasting blood glucose ($p=0.007$), total cholesterol ($p=0.001$), triglyceride ($p<0.001$), high density lipoprotein (HDL) cholesterol ($p<0.001$), Mg ($p<0.001$) and P ($p<0.001$). Left ventricular ejection fraction (LVEF) was similar in the two groups ($48.5 (\pm 8.3)$ vs. $49.6 (\pm 11.0)$, $p=0.366$) (Table 2).

In the univariable regression analysis performed among the collateral influencing factors in CTO; age (OR: 1.02; 95% CI: 1.0-1.05, $p=0.047$), DM (OR: 0.48; 95% CI: 0.28-0.82, $p=0.007$), smoking (OR: 0.32; 95% CI: 0.19-0.53, $p<0.001$), platelet (OR: 1.00; 95% CI: 0.99-1.00, $p=0.025$), fasting glucose (OR: 1.00; 95% CI: 0.99-1.00, $p=0.009$),

triglyceride (OR: 0.99; 95% CI: 0.98-0.99, $p<0.001$), total cholesterol (OR: 0.99; 95% CI: 0.98-1.00, $p=0.001$), HDL (OR: 1.06; 95% CI: 1.02-1.09, $p=0.001$) and Mg/P ratio (OR: 3.94; 95% CI: 2.37-6.54, $p<0.001$) were a predictor.

In the multivariable regression analysis, we found that; smoking (OR: 2.43; 95% CI: 0.19-0.72, $p=0.004$), triglyceride (OR: 0.99; 95% CI: 0.98-0.99, $p<0.001$) and Mg/P ratio (OR: 4.56; 95% CI: 2.50-8.32, $p<0.001$) were independent predictors for good coronary collateral development (Table 3).

The mean value of the Mg/P ratio is $0.56 (\pm 0.16)$. The Mg/P ratio was statistically significantly higher in group II than group I (0.62 ± 0.12 vs. 0.49 ± 0.17 , $p<0.001$). Magnesium/phosphorus ratio >0.56 , with 69% sensitivity and 64% specificity (ROC area under curve: 0.721, 95% CI: 0.658-0.784, $p<0.001$), is associated with good collateral development in patients with CTO (Figure 1).

Table 1. Demographic and clinical characteristics

	Grup I (n=127)	Grup II (n=142)	Total (n=269)	p value
Age (year), mean \pm std	59.5 \pm 9.7	62.1 \pm 11.1	60.9 \pm 10.6	0.046
Male gender, n (%)	91 (71.7)	104 (73.2)	195 (72.5)	0.771
Smoking, n (%)	68 (53.5)	38 (26.8)	106 (39.4)	<0.001
Hypertension, n (%)	52 (40.9)	49 (34.5)	101 (37.5)	0.276
Diabetes mellitus, n (%)	49 (38.6)	33 (23.2)	82 (30.5)	0.006
Previous MI, n (%)	25 (19.7)	22 (15.5)	47 (17.5)	0.366
Success of interventional procedure, n (%)	104 (81.9)	119 (83.8)	223 (82.9)	0.677
Betablockers, n (%)	36 (28.3)	34 (23.9)	70 (26.0)	0.411
ACEi, n (%)	60 (47.2)	56 (39.4)	116 (43.1)	0.197
CCB, n (%)	23 (18.1)	15 (10.6)	38 (14.1)	0.076
Long-acting nitrate, n (%)	16 (9.4)	12 (8.4)	28 (10.4)	0.266
Statine, n (%)	24 (18.9)	30 (21.1)	54 (20.0)	0.649
ASA, n (%)	24 (18.9)	21 (14.8)	45 (16.7)	0.367
Clopidogrel, n (%)	6 (4.7)	11 (7.7)	17 (6.3)	0.309

ACEi: Angiotensin converting enzyme inhibitor, ASA: Acetyl salicylic acid, CCB: Calcium channel blocker, MI: Myocardial infarction

Table 2. Biochemical and imaging findings

	Group I (n=127)	Group II (n=142)	Total (n=269)	p value
Creatinine, mg/dl	1.08 (\pm 0.64)	1.09 (\pm 0.99)	1.09 (\pm 0.84)	0.927
WBC, $\times 10^9$ /L	9.33 (\pm 2.82)	8.81 (\pm 2.65)	9.05 (\pm 2.74)	0.124
Hemoglobin, g/dl	13.66 (\pm 2.36)	13.80 (\pm 1.88)	13.73 (\pm 2.12)	0.586
Platelet, $\times 10^9$ /L	265.31 (\pm 97.12)	240.95 (\pm 73.54)	252.5 (\pm 86.2)	0.020
Fasting glucose, mg/dl	153.98 (\pm 78.36)	131.28 (\pm 57.89)	142.1 (\pm 69.1)	0.007
Total cholesterol, mg/dl	177.47 (\pm 47.52)	158.97 (\pm 43.03)	167.7 (46.1)	0.001
Triglyceride, mg/dl	200.51 (\pm 103.54)	127.92 (\pm 63.10)	162.2 (\pm 91.9)	<0.001
HDL, mg/dl	39.97 (\pm 8.87)	43.69 (\pm 7.65)	41.9 (\pm 8.4)	<0.001
LDL, mg/dl	92.52 (\pm 38.67)	92.25 (\pm 33.62)	92.4 (\pm 36.0)	0.951
Sodium, mEq/L	136.64 (\pm 2.71)	137.45 (\pm 3.31)	137.1 (\pm 3.1)	0.031
Potassium, mmol/L	4.44 (\pm 0.38)	4.39 (\pm 0.45)	4.41 (\pm 0.42)	0.278
Calcium, mg/dl	9.23 (\pm 0.69)	9.12 (\pm 0.57)	9.17 (\pm 0.63)	0.182
Magnesium, n (%)	1.82 (\pm 0.35)	2.05 (\pm 0.20)	1.94 (\pm 0.31)	<0.001
Phosphate, n (%)	3.97 (\pm 0.97)	3.41 (\pm 0.57)	3.67 (\pm 0.83)	<0.001
Mg/PO4 ratio	0.49 (\pm 0.17)	0.62 (\pm 0.12)	0.56 (\pm 0.16)	<0.001
LVEF, %	48.51 (\pm 8.31)	49.60 (\pm 11.00)	49.09 (\pm 9.82)	0.366

HDL: High density lipoprotein; LDL: Low density lipoprotein; LVEF: Left ventricular ejection fraction; Mg: Magnesium; PO4: phosphate; WBC: White blood cell
*The values in the table are shown as mean (\pm std).

Table 3. Univariable and multivariable regression analysis for determine predictor of CTO collateral development

Variables	Univariate, OR (95% CI)	p value	Multivariate, OR (95% CI)	p value
Age	1.02 (1.00-1.05)	0.047	0.98 (0.95-1.01)	0.174
DM	0.48 (0.28-0.82)	0.007	0.73 (0.32-1.67)	0.459
Smoking	0.32 (0.19-0.53)	<0.001	2.43 (0.19-0.72)	0.004
Platelet	1.00 (0.99-1.00)	0.025	1.00 (0.99-1.00)	0.261
Fasting glucose	1.00 (0.99-1.00)	0.009	1.00 (0.99-1.00)	0.609
Triglyceride	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	<0.001
Total cholesterol	0.99 (0.98-1.00)	0.001	1.00 (0.99-1.00)	0.371
HDL	1.06 (1.02-1.09)	<0.001	1.03 (0.99-1.07)	0.207
Mg/PO4 ratio	3.94 (2.37-6.54)	<0.001	4.56 (2.50-8.32)	<0.001

CI: Confidence interval; DM: Diabetes mellitus; HDL: High density lipoprotein; OR: Odds ratios

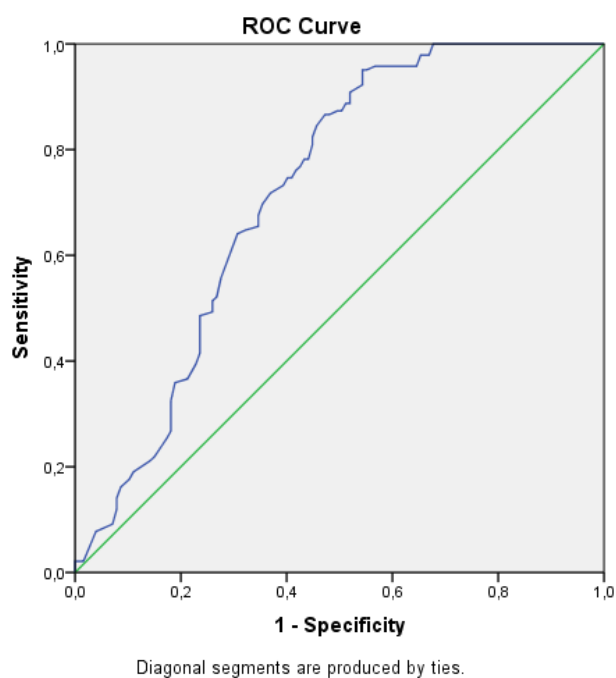


Figure 1. ROC analysis of the sensitivity and specificity of Mg/P ratio to good collateral development in patients with chronic total occlusion.

Discussion

In this study, we found that coronary collateral development is relatively good in patients with coronary chronic total occlusion who had high Mg/P levels. These results shed light on the fact that magnesium supplementation or phosphate-lowering treatments may be effective methods in the development of good collateral in patients with CTO and low Mg/P ratio. And it may lead to future studies on this subject.

It is known that Mg regulates vascular tone and acts as a cofactor for acetylcholine-induced endothelium-dependent vasodilation.¹³ The roles of Mg in regulating smooth muscle cells and endothelial function are well known. In addition, it is thought that nitric oxide (NO) may change vascular tone by taking part in the classical pathway. In an animal experiment study, it was shown that Mg increases the production of prostacyclin and NO, which provoke endothelium-independent and endothelium-dependent vasodilation.¹⁴ Mg has been shown to potentially protect against CAD by increasing endothelium-induced vasodilation and reducing vascular resistance, oxidative stress, oxidized lipids, inflammation, and thrombosis.¹⁵

It has been stated that low Mg levels are a serious factor in the development of CVD and thrombosis in the general population, and are also important in the pathogenesis of CVD.⁵ It was stated that after controlling for standard CV risk factors, low serum Mg values significantly increased cardiac mortality during follow-up.⁶

In addition, even if serum P levels are within the normal limits, it has been reported that its elevation is closely correlated with the development of systemic

atherosclerosis.¹⁶ Due to the negative effects of P on the NO synthesis pathway, it may lead to chronic ischemic heart diseases by impairing endothelium-dependent vasomotor functions.¹⁷ In addition, it has been shown that endothelial cells faced with high P levels have high oxygen radical formation, resulting decrease NO synthesis and increase apoptosis rate.¹⁰

In the light of this information, Mg/P ratio was used in our study to emphasize the practical importance of these two elements that play a role in endothelial functions. It was investigated whether this ratio was correlated with collateral development in CTO. In this study, we observed a positive correlation between the Mg/P ratio and good collateral development. This result shows that these elements, which are detected by a simple and rapid blood test, are actually of great clinical importance.

Coronary collateral development is an important factor in the nutrition of the myocardium in the CTO region. Good CCC development can reduce the infarct area and preserve left ventricular systolic function in case of CTO.¹⁸

In a study in which 216 patients who underwent primary PCI for STEMI were analyzed, normal coronary artery flow could not be achieved (no reflow) in 15.7% of the patients. The high rate of patients who could not achieve normal coronary artery blood flow in this study makes us think that CCC development is important to protect the heart from the harmful effects of ischemia.¹⁹

Many acquired factors can cause differences in the quality of the CCC.²⁰ In a study, the relationship between the development of CTO and oxidative stress parameters in patients with chronic coronary syndrome was investigated.²¹ In this context, 29 CTO cases and 29 control group patients were included.²¹ As a result of the study, it was stated that low serum vitamin A and C values and low vitamin C/vitamin E values may be determinative in estimating the risk of CTO.²⁰ In another study involving 176 patients with CTO and acute coronary syndrome, smoking, HT, and LVEF were not found to be significantly associated with collateral development.¹² In our study, we did not observe an important difference between the two groups in terms of mean LVEF value and HT frequency. However, in our regression analysis, smoking was statistically significantly higher in group I than group II.

In conclusion, Mg/P ratio is a parameter that affects coronary collateral development. High Mg/P ratio is associated with good collateral development in patients who had CTO. We think that our study will lead to controlled studies that can be done to determine whether low Mg/P ratio treatment is a predictive of clinical events in patients with coronary CTO.

Study Limitations

Our study has some limitations. Since the healthy control group was not arranged, it would not be correct to generalize the results to all patients with CAD. Another one is that angiographically visualized collaterals constitute only a fraction of the total collateral arteries development, because very small collateral arteries cannot be visualized. Despite these limitations, it is the

first study in the literature to show that the Mg/P ratio is directly related to collateral development in CTO.

Compliance with Ethical Standards

Ethics committee approval of the study was obtained from the Izmir Bakircay University Clinical Research Ethics Committee (Decision no: 618, Date: 01.06.2022). Signed voluntary consent was obtained from all patients included in the study.

Conflict of Interest

The author declares no conflicts of interest.

Author Contribution

MK, TG: Study idea, hypothesis, study design; TG, OŞ: Material preparation, data collection and analysis; MK: Writing the article; MK, OŞ: Critical review and publication process

Financial Disclosure

None

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