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Comparison of Coronary Artery Calcium Score and Serum Calcium, Phosphorus, and Gamma-Glutamyl Transferase Levels in Patients with Coronary Artery Imaging by Multi-Sectional Computed Tomography with Chronic Ischemic Heart Disease Prediagnosis

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ABSTRACT

Introduction: Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. Calcification of the coronary artery wall is a definite indicator of coronary atherosclerosis. Calcium scores in coronary arteries (CAC) can be detected by multidetector computed tomography (MDCT) before any cardiac event occurs. Gamma-glutamyl transferase (GGT) is a biomarker for oxidative stress and a proatherogenic marker for its indirect contribution to the biochemical process resulting in low-density lipoprotein cholesterol oxidation. Studies have shown that serum inorganic phosphorus levels are an independent risk factor for cardiovascular mortality. In our study, we evaluated the correlation between MDCT, CAC score, and the risk of coronary events predicted by evaluating this score according to age, gender, and serum GGT, calcium, and phosphorus levels.

Methods: In this retrospective study, 190 patients with a prediagnosis of CAD, laboratory investigations and MDCT were included. Patients were divided into three groups as low, intermediate, and high based on the risk of coronary events determined by the evaluation of CAC scores according to age and gender.

Results: In our study, a statistically significant result was found between high serum phosphorus and GGT levels and CAC and coronary event high risk groups classified according to this score ($p<0.05$). No significant result was found with high calcium level ($p>0.05$).

Conclusion: The correlation of phosphorus and GGT levels, which are considered independent risk factors for CAD, with CAC, which is an indicator of atherosclerosis in coronary arteries, was significant.

Keywords: Coronary artery calcium score, calcium, phosphor, gamma-glutamyl transferase

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. CAD risk factors were first identified in the Framingham Heart Study in 1948 and later were confirmed by numerous studies. Non-modifiable risk factors are; gender, family history of premature CAD (CAD in a primary male relative before the age of 55 years and CAD in a primary female relative before the age of 65 years), age, racial background, and history of vascular disease. Modifiable risk factors are; diabetes mellitus, hypertension, hypercholesterolemia, smoking, central obesity, sedentary lifestyle, and hyperhomocysteinemia (1). Calcification of the coronary artery is a definite indicator of coronary atherosclerosis (2). Calcium scores in coronary arteries (CAC) can detect ischemic heart disease before the development of any cardiac event. CAC shows the current cardiac status of the patient and possible future pathologies (valvular heart disease, CAD) and provides the physician with the necessary information in this respect. In many studies, the coronary calcium score has been found to be a prognostic parameter with a high predictive value for severe cardiac events within 3-5 years in asymptomatic patients (3). Using multidetector computed tomography (MDCT), we can visualize coronary artery calcification non-invasively, sensitively, and safely (4-6).

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Serum gamma-glutamyl transferase (GGT) levels provide information about hepatobiliary diseases and alcohol consumption (7,8). Studies in the literature have demonstrated the pathway of GGT activity in the pathogenesis of atherosclerosis and its involvement in oxidative events related to atheroma plaque formation (9). GGT activity has been detected in pathological studies performed in coronary artery plaques (10,11). Studies have supported the idea that serum GGT levels have prognostic and predictive value for CAD formation.

Phosphorus is a mineral with many functions in our body. Regulation of body phosphorus content is an important homeostatic requirement due to its important functions such as cellular signal transduction, energy production and transfer, membrane transport, participation in the catalytic activity of many enzymes, and bone mineral formation (12). Experimental and clinical data from recent studies have identified a role for elevated serum phosphorus levels in the pathogenesis of vascular damage. Recent studies have shown that higher blood phosphorus and phosphorus-calcium combination levels in patients with a history of chronic kidney disease (CKD) are related to increased cardiovascular disease mortality by causing coronary atherosclerosis and coronary calcification (13-15).

Many studies in the medical literature are attempting to produce diagnostic or prognostic tools that provide the highest benefit and lowest cost. In our study, we assessed the correlation between MDCT, which is an excellent non-invasive radiological examination method to detect CAD, the CAC calculated by this imaging method, and the risk of coronary events predicted by evaluating this score according to age and gender, and serum GGT, calcium, and phosphorus levels, which have been accepted as independent risk factors for ischemic heart disease in recent studies.

Methods

Patients admitted to University of Health Sciences Turkey, İstanbul Training and Research Hospital with a prediagnosis of CAD and who underwent coronary artery imaging with MDCT were retrospectively analyzed. Age, gender, hemogram, and biochemistry parameters were obtained from the file information (Table 1). CAC score, plaque volume, and parameters related to the risk of coronary events obtained from radiological reports based on the table formed by the assessment of this information according to sex and age were obtained. CAC score below 100 was considered low risk, and above 400 was considered high risk. CAC score between 100 and 400 was considered moderate risk. Patients aged between 3570 years with renal failure and known CAD were excluded from the study.

Technique

Sixteen-detector MDCT was used to obtain non-contrast volumetric axial slices with 0.1 cm slice diameter, 0.5 mm reconstruction, 0.75 mm collimation, and interval synchronized with ECG. Calcium scoring was evaluated in the left anterior descending artery, left main coronary artery, right main coronary artery, and circumflex artery according to the Agatston score using the "Siemens Calcium Scoring Software" (Figure 1).

Statistical Analysis

The correlation between the CAC score and the risk of coronary events and GGT, calcium, and phosphorus values was evaluated. SPSS 15.0 for Windows software was used for statistical analysis. Descriptive statistics are given as numbers and percentages for categorical variables and mean, standard deviation, minimum, and maximum for numerical variables. The correlations between the numerical variables were analyzed by Spearman's correlation analysis because parametric test conditions could not be met. Because the numerical variables compared in the two independent groups did not fulfill the normal distribution condition, they were compared using the Mann-Whitney U test. Numerical variables in more than two independent groups were analyzed by ANOVA when a normal distribution condition was provided and by the Kruskal-Wallis test when a normal distribution condition was not provided. Subgroup analyses were performed with

Figure 1. Calcified plaques in the left main coronary artery were detected in a 61-year-old male patient. The calculated Agatston score was 201, and the patient was considered to be at moderate risk for ischemic heart disease

Table 1. Patient characteristics

Number of patients (n)		190
Age mean ± SD (min.-max.)		53.6±9.0 (35-70)
Gender n (%)	Male	104 (54.7)
	Female	86 (45.3)
Plaque volume mean ± SD (min.-max.)		126.1±296.2 (0-2780)
CAC score mean ± SD (min.-max.)		139.5±358.2 (0-3569)
Coronary event risk n (%)	Low	105 (55.3)
	Intermediate	44 (23.2)
	High	41 (21.6)
GGT mean ± SD (min.-max.)		42.8±53.6 (6-559)
Calcium mean ± SD (min.-max.)		9.4±0.7 (4.6-10.7)
Phosphorus mean ± SD (min.-max.)		3.6±0.7 (2.1-5.2)
Calcium X phosphorus mean ± SD (min.-max.)		34.8±6.5 (20-50.5)

SD: Standard deviation, min.: Minimum, max.: Maximum, CAC: Calcium scores in coronary arteries, GGT: Gamma-glutamyl transferase

Tukey's test in the parametric test and the Mann-Whitney U test in the non-parametric test and were interpreted with Bonferroni correction. The ratios of categorical variables in the independent groups were tested by chi-square analysis. The factors determining the numerical variables were analyzed using linear regression analysis with the backward elimination method. P<0.05 was accepted as the statistically significant level.

Results

A total of 190 patients (104 males and 86 females) who underwent coronary artery imaging with MDCT and with a prediagnosis of CAD were included in the study. Demographic data of the patients are presented in Table 1. The mean age of the patients included in the study was 53.6±9.0 years. The mean plaque volume and CAC score were 126.1±296.2 and 139.5±358.2, respectively. According to the evaluation results, 55.3% of the patients had low coronary risk, 23.2% had intermediate risk, and 21.6% had high coronary risk. The mean GGT, calcium, phosphorus and CaxP values were 42.8±53.6, 9.5±0.6, 3.7±0.6 and 34.8±6.5, respectively.

A significant difference was found in the mean age, GGT, P, and CaxP in the coronary event risk groups (p<0.001, p=0.008, p<0.001, p<0.001, p<0.001) (Table 2). In the group with a high-risk of coronary events, mean age, P, and CaxP were significantly higher than in the low and intermediate groups (Table 3). The differences between the groups with low and intermediate risk of coronary events were not significant (Figure 1-4, Table 3). Mean GGT was significantly higher only in the high group compared to the low group. No significant difference was found in the gender ratios and Ca averages of the groups (Table 2).

In the model created to analyze the determinants of coronary artery calcium score, CaxP, age, and gender were found to be the most significant factors by multivariate linear regression analysis with the backward elimination method (p<0.001 p=0.002 p=0.024) (Table 4).

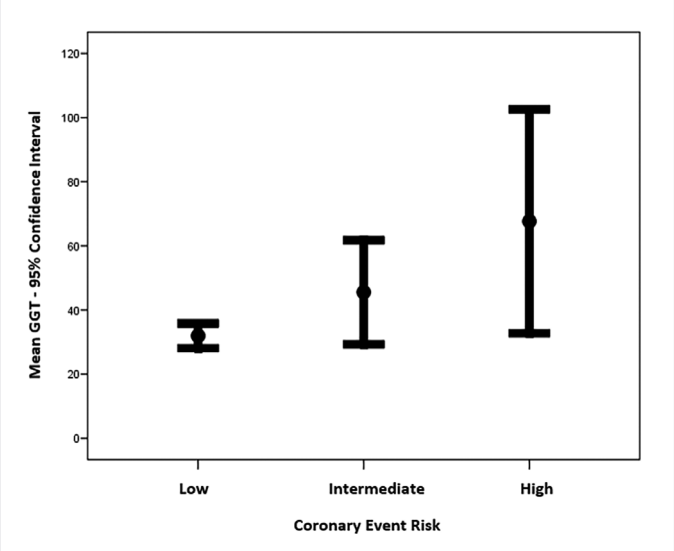

Figure 2. Risk of coronary events according to GGT levels
GGT: Gamma-glutamyl transferase

Discussion

We found that; the correlation of phosphorus and GGT levels, which are considered independent risk factors in predicting ischemic heart disease, with CAC, which is an indicator of atherosclerosis, was significant. This result will be helpful in our clinical practice in the early diagnosis and treatment of ischemic heart disease.

To date, many studies, including long-term follow-up investigations of the correlation of serum GGT activity with long-term metabolic syndrome development, cardiovascular disease development, and mortality, have been conducted (16). Studies have shown that GGT is an important marker of the probability of coronary heart disease independent of cardiovascular disease risk factors in the long term, and moderate increases in the reference range reflect a significant increase in the probability.

In 1993, Block et al. (17) unexpectedly described the correlation of increased serum GGT levels with cardiac mortality while conducting

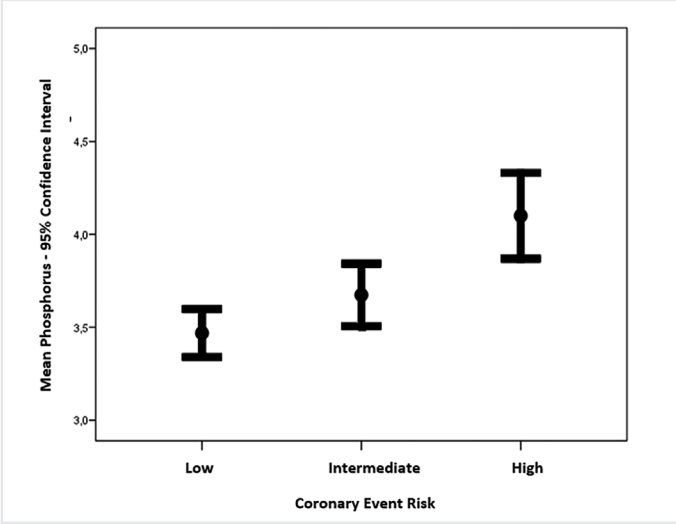

Figure 3. Risk of coronary events according to phosphorus levels

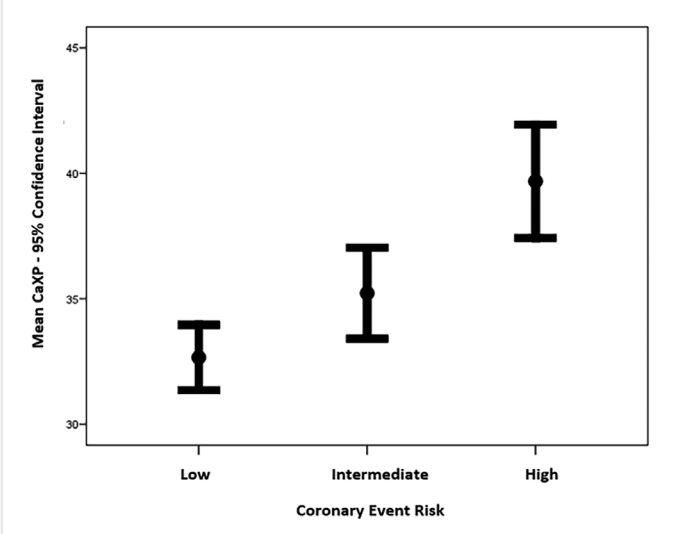

Figure 4. Risk of coronary events according to CaxP levels
CaxP: Calcium X phosphorus

Table 2. Coronary artery disease risk 1

Low		Coronary artery disease risk			
		Intermediate	High	p-value	
Age mean ± SD (min.-max.)		51.2±9.0 (35-68)	54.7±7.8 (36-69)	58.8±8.1 (41-70)	<0.001
Gender n (%)	Male	53 (50.5)	27 (61.4)	24 (58.5)	0.409
	Female	52 (49.5)	17 (38.6)	17 (41.5)	
GGT mean ± SD (min.-max.)		32.0±17.7 (6-124)	45.6±49.4 (9-279)	67.7±96.8 (13-559)	0.008
CA mean ± SD (min.-max.)		9.4±0.7 (4.7-10.6)	9.6±0.3 (9-10.4)	9.7±0.4 (9.1-10.6)	0.069
P mean ± SD (min.-max.)		3.5±0.6 (2-5.3)	3.7±0.5 (2.8-4.9)	4.1±0.6 (2.8-5.2)	<0.001
CaxP mean ± SD (min.-max.)		32.7±6.0 (20-48.8)	35.2±5.5 (26.9-47.0)	39.7±6.3 (28.5-50.5)	<0.001

SD: Standard deviation, min.: Minimum, max.: Maximum, CA: Calcium, CaxP: Calcium X phosphorus, GGT: Gamma-glutamyl transferase, P: Phosphoru

Table 3. Coronary artery disease risk -2

	Coronary artery disease risk		
	Low vs. intermediate	Low vs. high	Intermediate vs. high
Age	0.020	<0.001	0.011
GGT	0.166	0.002	0.114
P	0.045	<0.001	0.004
CaxP	0.073	<0.001	0.006

CA: Calcium, CaxP: Calcium X phosphorus, GGT: Gamma-glutamyl transferase, P: Phosphorus

Table 4. Predictors of the coronary artery calcium score

	B	Beta	p-value
Constant	-695,031		
CaxP	17,479	0.316	<0.001
Age	10,164	0.253	0.002
Gender	-129,200	-0.180	0.024

CaxP: Calcium X phosphorus

studies on the damage caused by alcohol use in the organism using laboratory test results.

Reynolds et al. (18) investigated the correlation between serum GGT levels and new cardiovascular events and mortality, new metabolic syndrome, and cardiovascular risk factors in a prospective study of 3451 Framingham Offspring Study participants with an average follow-up time of 19 years. A correlation was found between high GGT activity and the risk of cardiovascular events and cardiovascular mortality. The results of this study support the notion that GGT activity is an important marker in predicting cardiovascular risk (18).

GGT has emerged as a new risk factor in addition to traditional cardiovascular risk factors. It has been observed in epidemiological studies that high values of GGT activity in the normal reference range are a strong independent marker for metabolic syndrome and cardiovascular events in the long term, a prognostic value in coronary heart disease, and an independent correlation with all causes of mortality. Further studies are needed to determine whether drugs used for treating atherosclerosis affect serum GGT activity, which contributes to the formation of atherosclerosis. Further research should be conducted to determine the most risky combination by examining the correlation of biochemical activation of GGT in atheroma plaque with global serum activity, inflammation markers, and plasma lipoproteins, develop aggressive treatment approaches, help prognostically classify patients, and prevent future adverse cardiac events and mortality.

In our study, blood GGT levels were significantly higher in patients with a high-risk of ischemic heart disease detected by coronary CT angiography. This finding will be beneficial in the early diagnosis and treatment of ischemic heart disease, but it should be supported by controlled studies involving more patients.

The dose-dependent correlation between cardiovascular disease and phosphorus levels in the abnormal range that can be seen in late renal disease is known. In this process, which ends with widespread vascular calcification, observational studies in dialyzed patient populations have shown that high serum phosphorus levels are correlated with cardiovascular events and mortality (19,20). This correlation has led investigators to associate elevated serum phosphorus levels in the reference range with ischemic heart disease in patients with normal renal function. Studies in the literature have shown that serum phosphorus levels are an independent risk factor for the development of cardiovascular events and cardiovascular mortality in patients with or without CAD with normal renal function.

In a study conducted by Dhingra et al. (21) with a mean follow-up of 16.1 years in 3,368 adult Framingham study participants without a history of cardiovascular disease and with normal kidney function, high serum phosphorus values and calcium-phosphorus composite values at the reference range were correlated with an increased risk of cardiovascular disease. It has been mainly reported that subjects with serum phosphorus values higher than 3.5 mg/dL within the reference range have a 1.55-fold higher risk of cardiovascular events than subjects with ≤2.8 mg/dL. In addition, in this study, it was shown that serum phosphorus levels were directly proportional to total/high-density lipoprotein cholesterol ratio and age and proportional to body mass index and systolic blood pressure, which are risk factors for cardiovascular disease. Blood calcium levels were not correlated with the risk of cardiovascular disease. This study is important in terms of being the first study to explain the independent correlation of high serum phosphorus levels with cardiovascular disease risk in a population-based sample of males and females without cardiovascular disease or CKD (21).

According to studies in the literature, the association between high P and cardiovascular events was independent of other traditional risks and the amount of P in the diet. We did not investigate dietary calcium

and phosphorus intake in our patient population. Additionally, since vitamin D was not measured in every patient, we could not examine its relationship with CAD. Park et al. (22) showed that lower serum P concentrations within the previously claimed normal range were associated with lower Agatston score; this suggests that people with normal kidney function have less coronary artery calcification.

In the prospective study by Foley et al. in 3015 healthy young adults as part of the Risk of CAD development in young adults study, the relationship between serum phosphorus levels and the degree of coronary artery calcification determined by CT imaging at 15 years was investigated. A significant correlation was found between high serum phosphorus levels and coronary artery calcification. In this study, high serum phosphorus levels were shown to be a risk factor for the development of coronary atherosclerosis in healthy young adults (23).

Treatment methods continue to support the hypothesis that correcting the calcium-phosphorus balance in end-stage CKD improves cardiovascular outcomes. Further studies involving more patients are needed to evaluate whether high serum phosphorus levels lead to the risk of cardiovascular events and mortality in patients with normal kidney function, and to elucidate the underlying mechanism and provide preventive or therapeutic interventions in the future.

Study Limitations

Our study has certain limitations, such as being a retrospective design, being a single-center study, and having a limited number of patients. Therefore, prospective studies with a larger number of patients are required. However, it should be considered an effective study in terms of demonstrating the effectiveness of non-invasive and low-cost screening in the early detection of CAD, which is the most common cause of death worldwide.

Conclusion

The results showed a significant correlation between the coronary artery calcium score and serum GGT and phosphorus levels. In our clinical practice, we can use these two laboratory data as useful predictive markers in patients with suspected ICH. Further studies on this subject are needed.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee (approval number: 594, date: 23.01.2015).

Informed Consent: Retrospective study.

Authorship Contributions: Surgical and Medical Practices - İ.G.; Concept - İ.G., H.P.; Design - İ.G., H.P.; Data Collection or Processing - İ.G., G.B.S., S.A.; Analysis or Interpretation - İ.G.; Literature Search - İ.G.; Writing - İ.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Fruchart JC, Nierman MC, Stroes ES, Kastelein JJ, Duriez P. New risk factors for atherosclerosis and patient risk assessment. Circulation 2004; 109 (23 Suppl 1): III15-9.
2. Chambless L, Keil U, Dobson A, Mähönen M, Kuulasmaa K, Rajakangas AM, et al. Population versus clinical view of case fatality from acute coronary heart disease: results from the Who Monica Project 1985-1990. Multinational MONItoring of Trends and Determinants in CArdiovascular Disease. Circulation 1997; 96: 3849-59.
3. Blankenhorn DH, Stern D. Calcification of the coronary arteries. Am J Roentgenol Radium Ther Nucl Med 1959; 81: 772-7.
4. Stanford W, Thompson BH. Imaging of coronary artery calcification. Its importance in assessing atherosclerotic disease. Radiol Clin North Am 1999; 37: 257-72.
5. Nieman K, van der Lugt A, Pattynama PM, de Feyter PJ. Noninvasive visualization of atherosclerotic plaque with electron beam and multislice spiral computed tomography. J Interv Cardiol 2003; 16: 123-8.
6. Jakobs TF, Wintersperger BJ, Herzog P, Flohr T, Suess C, Knez A, et al. Ultra-low-dose coronary artery calcium screening using multislice CT with retrospective ECG gating. Eur Radiol 2003; 13: 1923-30.
7. Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci 2001; 38: 263-355.
8. Rollason JG, Pincherle G, Robinson D. Serum gamma glutamyl transpeptidase in relation to alcohol consumption. Clin Chim Acta 1972; 39: 75-80.
9. Paolicchi A, Tongiani R, Tonarelli P, Comporti M, Pompella A. gamma-Glutamyl transpeptidase-dependent lipid peroxidation in isolated hepatocytes and HepG2 hepatoma cells. Free Radic Biol Med 1997; 22: 853-60.
10. Paolicchi A, Minotti G, Tonarelli P, Tongiani R, De Cesare D, Mezzetti A, et al. Gamma-glutamyl transpeptidase-dependent iron reduction and LDL oxidation--a potential mechanism in atherosclerosis. J Investig Med 1999; 47: 151-60.
11. Paolicchi A, Emdin M, Ghliozeni E, Ciancia E, Passino C, Popoff G, et al. Images in cardiovascular medicine. Human atherosclerotic plaques contain gamma-glutamyl transpeptidase enzyme activity. Circulation 2004; 109: 1440.
12. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. Lancet 1998; 352: 391-6.
13. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31: 607-17.
14. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12: 2131-8.
15. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005; 16: 520-8.
16. Emdin M, Passino C, Pompella A, Paolicchi A. Gamma-glutamyltransferase as a cardiovascular risk factor. Eur Heart J 2006; 27: 2145-6.
17. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004; 15: 2208-18.
18. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, et al. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. J Am Soc Nephrol 2004; 15: 2857-67.
19. Eroğlu Kayacık Ö, Kalaycı AG. Karaciğer İşlev Testleri. Journal of Experimental and Clinical Medicine 2009; 25: 35-44.
20. Ratanasavanh D, Tazi A, Gaspart E. Hepatic-glutamyl transferase release: effect of bile salt and membrane structure modification. Adv Biochem Pharamacol 1982; 3: 93-103.
21. Dhingra R, Sullivan LM, Fox CS, Wang TJ, D'Agostino RB Sr, Gaziano JM, Vasan RS. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. Arch Intern Med. 2007 May 14;167(9):879-85.
22. Park KS, Chang JW, Kim TY, Kim HW, Lee EK, Kim HS, et al. Lower concentrations of serum phosphorus within the normal range could be associated with less calcification of the coronary artery in Koreans with normal renal function. Am J Clin Nutr 2011; 94: 1465-70.
23. Emdin M, Pompella A, Paolicchi A. Gamma glutamyl transferase, Atherosclerosis, And Cardiovascular Disease. Circ 2005; 112: 2078-80.