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The Relationship Between the Level of Parathormone and the Existence and the Degree of Coronary Atherosclerosis

Koroner Ateroskleroz Varlığı ve Derecesi ile Serum Parathormon Düzeyi Arasındaki İlişki

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Abstract

Objective: An elevated level of parathormone, which is the major regulator of bone and mineral metabolism, has detrimental effects on the heart and vascular system. In this study, we investigated the relationship between the risk and degree of coronary atherosclerosis and parathormone levels.

Material and Methods: A total number of 77 patients were included in the study. Serum levels of parathormone, calcium, albumin, phosphorus, and 25-OH vitamin D were analyzed in the samples collected pre-operatively from the patients who underwent elective coronary angiography. The severity and diffusiveness of coronary atherosclerosis were calculated from the angiographic images using Gensini score. Pearson's correlation test and logistic regression were used to analyze the correlation between parathormone levels and the Gensini scores.

Results: No significant relationship was observed between PTH values and Gensini scores. When the patients' Gensini scores were grouped as smaller and greater than 20 and then compared with the other variables individually, a positive correlation with the corrected calcium levels and 25-OH vitamin D levels was observed. In multivariate analysis, none of the compared variables showed a relationship with Gensini score. Lastly, when the patients were divided by the parathormone levels into three tertiles and compared with Gensini scores, no significant relationship was observed.

Conclusion: No relationship was observed between the parathormone levels and coronary atherosclerosis variables indicating that parathormone may not affect coronary atherosclerosis.

Keywords: Parathormone; coronary atherosclerosis; gensini score; coronary artery disease

Özet

Amaç: Kemik ve mineral metabolizmasının majör düzenleyicisi olan parathormon düzeylerinin artmasının, kalp ve damar sistemi üzerine de etkileri olduğu bilinmektedir. Bu çalışmada, kesitsel olarak koroner ateroskleroz varlığı ve yaygınlığı ile serum parathormon düzeyleri arasında ilişki olup olmadığının araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamıza toplam 77 hasta alındı. Koroner arter hastalığı şüphesiyle elektif anjiyografi kararı verilen hastanın işlem öncesi alınan kan örneklerinden parathormon, kalsiyum, albumin, fosfor ve 25-OH D3 düzeyleri çalışıldı. Anjiyografi görüntülerinden Gensini skorları hesaplanarak koroner ateroskleroz yaygınlığı ve şiddeti hesaplandı. Pearson korelasyon ve lojistik regresyon analizleri kullanılarak parathormon ve Gensini skorları arasındaki ilişki değerlendirildi.

Bulgular: Çalışmamızda, Gensini skoru ile parathormon düzeyleri arasında ilişki saptanmadı. Gensini skoru 20'nin altında ve üzerinde olarak iki gruba ayrılan hastalarda, lojistik regresyon analizi ile değişkenler tek tek incelendiğinde Gensini skorları ile 25-OH D3 düzeyi ve düzeltilmiş kalsiyum düzeyleri ile pozitif korelasyon bulundu. Lojistik regresyon analizi ile Gensini skoru açısından tüm bileşenler birlikte değerlendirildiğinde parathormon, 25-OH D3 vitamini, kalsiyum ve fosfor düzeyleri ile istatistiksel anlamlı bir ilişki saptanmadı. Ayrıca, Gensini skoru ve parathormon düzeyleri üç tertile bölünerek bu gruplar birbirleriyle karşılaştırıldı. Parathormon tertillerinin Gensini skorları arasında anlamlı bir fark saptanmadı.

Sonuç: Yapılan analizlerde parathormon düzeyi ve koroner ateroskleroz arasında ilişki saptanmadı. Sonuç olarak, koroner arter hastalığı gelişimi ve ciddiyeti üzerine parathormon düzeyinin etkisi olmayabilmektedir.

Anahtar kelimeler: Parathormon; koroner ateroskleroz; gensini skoru; koroner arter hastalığı

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Introduction

Parathormone (PTH) is the major regulator of bone and mineral metabolism (1); however, elevated levels of PTH have harmful effects on the heart and vascular system in primary hyperparathyroidism (pHPT) patients (2). The relationship between PTH levels and carotid intima-media thickness is well-known (3), and patients with high levels of PTH show left ventricular hypertrophy, lower arterial reactivity, and increased valve calcification (4-8). In addition, patients with secondary hyperparathyroidism (sHPT) and primary hyperparathyroidism due to parathyroid adenoma show a higher risk of atherosclerosis (9,10). PTH likely exerts these effects via endothelial nitric oxide synthase (eNOS), the receptor of advanced glycation end-products (RAGE) and IL-6 upregulation (11). The elevated levels of IL-6 and eNOS have a possible role in vascular calcification and endothelial injury (11), and PTH also induces fibroblasts resulting in increased fibrosis in the myocardial tissue (12,13). Some patients with pHPT show increased cardiovascular mortality in the absence of kidney disease, hypertension and metabolic abnormalities, which indicate a direct effect of PTH on the cardiac environment (14). Some studies have also observed a relationship between PTH levels and mortality in patients without kidney disease (15,16). Nevertheless, the exact role of PTH in atherosclerosis has not been elucidated. The aim of this study was to determine the relationship between PTH levels and the risk and degree of coronary atherosclerosis.

Material and Methods

Patient Selection

The patients admitted to the outpatient cardiology clinic of Akdeniz University Hospital with chest pain and indicated for elective angiography were randomly recruited to the study. Eighty patients were initially enrolled but since the blood of three patients was unsuitable for evaluation due to hemolysis, 77 patients (42 males and 35 females) were finally selected. The laboratory tests of the patients conducted 30 days prior to the selection were screened, and those with pHPT and other thyroid anomalies, chronic kidney disease, liver abnormalities, calcium metabolism targeting diseases (e.g., Cushing syndrome, pheochromocytoma, hyperthyroidism, etc.) or drug intake affecting calcium metabolism (e.g., calcium supplements, 25-OH vitamin D supplements, diuretics, etc.) were excluded from the study. The levels of creatine, LDL-Ch, triglyceride, HDL-Ch, and HbA1c were also recorded at the time of application. Prior to the angiography, serum levels of PTH, calcium, phosphorus, 25-OH vitamin D, and albumin were analyzed.

Ethics and Financial Support

Our study was approved by the local ethics committee. (Akdeniz University Ethics Committee, 06.03.2012 dated, 88 numbered decision). The patients who provided informed consent were enrolled in the study. Akdeniz University Scientific Investigation Fund supported our study. (Project Approval Number: 2012.04.0103.006)

Evaluation of Coronary Atherosclerosis

The angiography images were evaluated by the same cardiologist who was blinded to the clinical status of the patients. The degree of coronary atherosclerosis was calculated by Gensini score (17). Scores ≤20 indicated the lack of coronary artery disease (CAD) while >20 was indicative of CAD. The severity of CAD was scored as 1 for 1-25% narrowing, 2 for 26-50%, 4 for 51-75%, 8 for 76-90%, 16 for 91-99% with the antegrade flow, and 32 for a completely occluded artery. The total score was restricted to 32 when there was more than one lesion in the same artery. The score was then multiplied by a previously described factor indicating the importance of the coronary artery. Half of this calculated score was from the collateral vessels with >2 mm diameter. Gensini scoring system is shown in Table 1.

Blood Sampling and analysis

Blood samples were taken one hour before the angiography after at least 8 hours of fasting. To avoid hemolysis, blood was collected without a tourniquet. The samples were centrifuged to separate the serum, which was then divided into aliquots and stored at -80°C. Intact PTH, 25-OH vitamin D, calcium, phosphorus and albumin levels were then analyzed by electrochemilumi-

Table 1. Gensini scoring system.

	Score	Multiplier Factor
Percentage of Narrowing		
0-25%	0	
26-50%	2	
51-75%	4	
76-90%	8	
91-99%	16	
100%	32	
Left main coronary artery		5
Left anterior descending artery		
Proximal segment		**2.5**
Mid-segment		**1.5**
Apical segment		**1**
1. diagonal		**1**
2. diagonal		**0.5**
Circumflex artery		
Proximal segment		**2.5 (3.5)***
Mid-segment		**1 (2)***
Distal segment		**1 (2)***
Obtuse marginal branch		**1**
Posterolateral branch		**0.5**
Right coronary artery		
Proximal segment		**1**
Mid-segment		**1**
Distal segment		**1**
Posterior descending artery		**1**

*If the circumflex artery is dominant, the multiplier factor in the parenthesis must be used.

nescence immunoassay (ECLIA; Roche Diagnostics GmbH, Mannheim, Germany), o-cresolphthalein endpoint colorimetry, phosphomolybdate colorimetry (both using Cobas 8000 auto-analyzer, Roche Diagnostics GmbH), and bromcresol green (BCG) method (Roche Diagnostics GmbH), respectively.

Statistical Analysis

This study was a non-randomized prospective cross-sectional trial. The sample size was determined via a sample power program considering the medium size effect as 85% power and an α value of 0.05 and was found to be 75. The statistical analysis was performed with SPSS 13.0. The Kolmogorov-Smirnov test was used to determine whether data conformed to a normal distribution. Pearson's correlation and logistic regression analysis were used to determine the association between the variables. Mann Whitney U test and independent sample T-test were used to compare abnormally distributed and normally distributed variables, respectively. P values less than 0.05 were considered statistically significant.

Results

The age of the patients ranged from 35 and 78 years (mean 58). The study population included 40.9% patients with diabetes mellitus, 45.5% with hypertension, and 40.3% with hyperlipidemia. While 37.2% of the patients had a smoking history, only 2.6% were consuming alcohol. Sixty percent of the female patients were post-menopausal. The demographic characteristics of the patients stratified by genders are shown in Table 2.

Sixty-two percent (48) of the patients had a Gensini score below 20, while 38% (29) had a score ≥ 20. The mean Gensini score in the low scoring group was 5.08, and that of the high score group was 39.2. Furthermore, patients with high Gensini score tended to be older males and had significantly higher creatine levels and incidence of hypertension compared to those in the low score group (Table 3).

The correlation between the PTH values and Gensini scores was analyzed by Pearson's test, and no significant relationship was observed. Univariate regression analysis showed a positive correlation between the corrected calcium levels and 25-OH vitamin D levels after the patients were stratified into the low and high Gensini score groups. However, a multivariate analysis showed no association between either of the variables and the Gensini score group (Table 4). Furthermore, no significant relationship was observed between coronary atherosclerosis

Table 2. The demographic characteristics of the patients.

Patient Characteristics	Male (n:42)	Female (n:35)
Age	58.5 (35–78)	57.7 (38–77)
DM	38% (16)	42.9% (15)
HT	42% (18)	51.4% (18)
HPL	42% (18)	40% (14)
Smoking	52% (22)	20% (7)
Alcohol Consumption	4.7% (2)	0% (0)
Menopausal Status	N/A	60% (21)

DM: Diabetes Mellitus, HT: Hypertension, HPL: Hyperlipidemia.

Table 3. Comparison of patient characteristic according to Gensini Score.

Variables	Gensini Score <20 (62%) (Min-Max)		Gensini Score ≥20 (38%) (Min-Max)		p-value
Age (Years)	(37-78)	57*	(35-77)	61*	**0.04**
Sex (Male/Female)		19/29		24/6	**0.001**
Diabetes Mellitus (%)		37		43	0.6
Hypertension (%)		37		60	**0.05**
Hyperlipidemia (%)		47		30	0.1
Smoking (%)		31		46	0.1
Alcohol (%)		0		7	0.07
Creatinine (mg/dL)	(0.4-1.2)	0.8[t]	(0.6-1.1)	0.9[t]	**0.012**
HbA1c (%)	(4.3-8.7)	5.6*	(5.1-8.2)	6.1*	0.31
LDL-Cholesterol (mg/dL)	(56-295)	126*	(60-191)	114*	0.9
Triglyceride (mg/dL)	(37-397)	132*	(65-385)	110*	0.52
PTH (pg/mL)	(19.6-130)	49*	(24-161.2)	41*	0.16
Corrected Calcium (mg/dL)	(7.2-10.8)	9.6*	(8.5-10.9)	9.5*	0.39
Phosphorus (mg/dL)	(2.3-4.8)	3.5t	(2.7-4.4)	3.3[t]	0.61
25 OH vitamin D (ng/mL)	(3-48.1)	16.2*	(4.5-50.9)	23*	0.08
Albumin (g/dL)	(3.4-5.7)	5.06*	(4.4-5.5)	5.07*	0.6

*Median values, [t]Mean values

and either calcium, phosphorus, PTH or 25-OH vitamin D levels using the Mann Whitney U and independent sample t-test.
Finally, no significant relationship was found after dividing PTH levels divided into three tertiles and comparing with the Gensini score (p=0,51).

Discussion

We found no significant relationship between coronary atherosclerosis and pre-angiography PTH levels. Although low 25-OH vitamin D levels were significantly correlated with coronary atherosclerosis, which was not an independent predictor as per the multivariate analysis. Although we and others have used the Gensini score to determine the presence of CAD, the optimal cut-off value for this algorithm may be controversial. Therefore, even the patients who had a Gensini score ≤ 20 in our study may have coronary atherosclerosis.
Studies investigating the relationship between CAD and PTH have reported conflicting results. Xxx Although the mechanisms of any potential role of PTH in coronary atherosclerosis are still unknown, some hypotheses have been proposed. One hypothesis suggests that PTH induces vascular calcification and remodeling either directly via receptor binding or indirectly by inducing inflammation and vascular dysfunction (18-21). Another study states that PTH may be related to left ventricular hypertrophy, congestive heart failure, myocardial calcification, and fibrosis (22-26). The final hypothesis considers PTH responsible for risk factors for coronary atherosclerosis such as inflammation, kidney disease, and cardiac pathology (15,27).
An atherosclerotic effect of PTH has been shown on the peripheral and large blood

Table 4. Univariate and multivariate analyses using the logistic regression model.

	Gensini Score	
	Univariate analysis p-value	Multivariate analysis p-value
Hypertension	**.02**	**0.91**
Hyperlipidemia	**.02**	**0.93**
Diabetes Mellitus	.56	**0.86**
PTH	.51	**0.91**
25-OH D3	**.01**	**0.54**
Calcium	**.003**	**0.51**
Phosphorus	.31	**0.92**
LDL-cholesterol	.42	**0.91**
Triglyceride	**.65**	**0.99**

vessels, which is responsible for non-fatal cardiovascular events (28). In a recent study, Shakrar et al. showed a relationship between the diffusiveness of coronary atherosclerosis and PTH (29). Another study reported elevated PTH levels after acute myocardial infarction (AMI) in 26 patients (30). In contrast, Ljunghall et al. showed no changes in PTH levels in patients who were hospitalized in an intensive care unit after an AMI (31). The elevated PTH levels seen after AMI could be a systemic response to the same and was correlated to increased survival, myocardial cell repair and long-term heart failure in some animal models (32). Therefore, we only analyzed elective coronary angiographic performance in our study. Furthermore, one study found a relationship between proven coronary atherosclerosis and PTH levels (33), and another study in China found elevated PTH levels in patients with high coronary calcium scores (CCS), but no significant correlation between increasing levels of PTH and CCS (34). Although several studies have shown a relationship between PTH levels and coronary, valvular, aorta, and carotid calcifications (35-39), Watson et al. found no correlation between PTH levels and CCS (40). The difference between the studies could be related to other risk factors such as ethnicity, hypertension, and long-term calcium and 25-OH vitamin D intake. The Tromso study, a large epidemiological community-based trial, found that even normal PTH levels had a predictive value for CAD, and both male and female patients with PTH levels near the upper limit had a higher relative risk (1.78 and 1.67 fold, respectively) of coronary events (41). Consistent with these findings, two studies found elevated levels of PTH to be an independent risk factor for sudden cardiac death due to unknown CAD (42) and other cardiovascular events (43). In a community-based observational study, no relationship was seen between PTH and cardiovascular mortality, ischemic stroke, heart failure, atrial fibrillation and peripheral arterial disease (44). These ambiguous results could be due to the differences in PTH receptor levels across tissues, as well as different ethnicities and individual genetic make-up. In agreement with our findings, Öztürk et al. found no relationship between PTH levels and diffusiveness of coronary atherosclerosis (45), while another study conducted in Turkey by Alsancak et al. reported a weak but significant relationship between PTH and Gensini score, although it could not correlate PTH and diffusiveness of CAD (46).

Recent studies have implicated 25-OH vitamin D in atherosclerosis, but the results are ambiguous. Although the Tromso study could not establish a direct link between CAD and 25-OH vitamin D levels, the authors hypothesized that elevated PTH levels may arise as an epiphenomenon of low vitamin D levels (41). Consistent with this, Scrrag et al. showed that AMI was correlated to low levels of 25-OH vitamin D (47), while Arad et al. reported no relationship between these two variables (48). In our study, we did not find any association between CAD and 25-OH vitamin D levels. However, the low levels of this vitamin in the study population limited the accurate comparison between the groups. The inclusion of a control group with sufficient levels of 25-OH vitamin D may rectify this problem.

Taken together, we found no relationship between diffusiveness of coronary atherosclerosis and PTH levels before the elective angiography in patients with suspicion of CAD. The higher number of patients with low Gensini score indicated a false-positive diagnosis of CAD and unnecessary indications of angiography. Furthermore, the small population size and the incidental low Gensini scores restricted evaluation of the associated parameters. We only evaluated the elective coronary angiographic procedure of patients without other stress conditions. Also, exclusion of the calcium metabolism affecting drugs and diseases may have had a potential effect on our results. For example, anti-hypertensive drugs such as diuretics may lower the risk of atherosclerosis. However, it was necessary to exclude these drugs since they are known to alter the serum calcium and PTH levels, which would have compromised the correlation between coronary atherosclerosis and PTH. The same study design might have different results in a more atherosclerotic population. The cross-sectional evaluation of long-term pathologies such as atherosclerosis and its causative factors might have yielded incor-

rect results. Therefore, further studies have to be conducted to evaluate these parameters periodically over several years.

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Authorship Contributions

Idea/Concept: İsmail Beypınar, Hasan Altunbaş; Design: İsmail Beypınar, Hasan Altunbaş; Control/Supervision: Hasan Altunbaş, İsmail Beypınar; Data Collection and/or Processing: İsmail Beypınar; Analysis and/or Interpretation: Sebahat Özdem, Ramazan Can Öncel, Mustafa Kemal Balcı; Literature Review: İsmail Beypınar; Writing the Article: İsmail Beypınar; Critical Review: Ramazan Sarı, Hasan Altunbaş; Materials: İsmail Beypınar.

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