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# The Effect of Vitamin D Deficiency on the Risk and Time of Stent Restenosis After Percutaneous Coronary Angioplasty: Case-Control Study

## Vitamin D Eksikliğinin Perkütan Transluminal Koroner Anjiyoplasti Sonrası Stent Restenoz Riski ve Zamanı Üzerine Etkisi: Olgu-Kontrol Çalışması

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**ABSTRACT Objective:** Many studies have emphasized the role of inflammation in the development of stent restenosis after percutaneous transluminal coronary angioplasty (PTCA). Vitamin D plays an important role in the modulation of the inflammatory system. Recent studies suggest that vitamin D deficiency is associated with an increased risk of cardiovascular disease. The aim of this study was to investigate the association between vitamin D levels and the development of stent restenosis and the time course of stent restenosis after PTCA. **Material and Methods:** Fifty-eight patients (Group 1) were consecutively selected among patients admitted to Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital with angina pectoris who developed stent restenosis following PTCA. The control group patients (Group 2) had no stent restenosis following PTCA. **Results:** The 25(OH) D values were lower in patients with stent restenosis. The difference was significant (11.2 ng/mL vs. 13.8 ng/mL, p=0.02). The risk of restenosis increased 3.4 times when vitamin D level was below 11.3 ng/mL (area under the curve=0.651, 95% confidence interval 0.529-0.773, p=0.02). Also, as time elapsed after PTCA, there was a statistically insignificant weak negative correlation between vitamin D and risk and the time course of stent restenosis (r=-0.181, p=0.219). **Conclusion:** These findings indicate that lower serum vitamin D levels increase the risk of stent restenosis following coronary interventions. Vitamin D may be a marker for predicting stent restenosis. The already increased risk of restenosis may augment over time as patients' vitamin D levels remain low.

**Keywords:** Vitamin D; stent restenosis

**ÖZET Amaç:** Birçok çalışma, perkütan transluminal koroner anjiyoplasti (PTKA) sonrası restenoz gelişiminde inflamasyonun rolünü vurgulamıştır. Vitamin D'nin, inflamatuar sistemin düzenlenmesinde önemli bir role sahip olduğu bilinmektedir. Son çalışmalar, vitamin D eksikliğinin kardiyovasküler riske sebep olduğunu göstermiştir. Bu çalışmanın amacı, vitamin D'nin PTKA sonrası restenoz gelişimi ve restenoz gelişim süresine etkisini araştırmaktır. **Gereç ve Yöntemler:** Dr. Siyami Ersek Göğüs Kalp ve Damar Cerrahisi Eğitim Ve Araştırma Hastanesine anjina pektoris ile başvuran, PTKA sonrası stent restenozu gelişen hastalardan ardışık 58 hasta seçilmiştir (Grup 1). Kontrol grubu (Grup 2), PTKA sonrası stent restenozu gelişmeyen hastalardır. **Bulgular:** 25 OH D düzeyleri, stent restenozlu hastalarda düşük bulunmuştur. Fark anlamlıydı (11,2 ng/mL vs. 13,8 ng/mL, p=0,02). D vitamini düzeyi, 11,3 ng/mL'nin altına indiğinde restenoz riski 3,4 kat artmıştır (eğrinin altındaki alan=0,651; %95 güven aralığı 0,529-0,773; p=0,02). Ayrıca PTKA sonrası zaman ilerledikçe, D vitamini ile restenoz risk ve gelişme zamanı arasında istatistiksel olarak anlamsız zayıf bir negatif korelasyon izlendi (r=-0,181; p=0,219). **Sonuç:** Bu bulgular, düşük D vitamini düzeylerinin PTKA sonrası stent restenoz riskini artırdığını göstermektedir. Vitamin D, stent restenozunu tahmin etmede bir gösterge olabilir. Hastaların D vitamini düzeyi düşük kaldığında, zaten artmış olan restenoz riski zamanla artabilir.

**Anahtar Kelimeler:** Vitamin D; stent restenozu

Although the angiographic restenosis rates have been reduced with the use of drug-eluting stents (DES), restenosis remains a problem following percutaneous transluminal coronary angioplasty. It was reported as approximately 30% after bare metal stents (BMS), 12% after newer generation DES implantation. Prolapse of disrupted plaque, elastic recoil of the vessel wall, constrictive vascular remodeling, neointimal hyperplasia, and neoatherosclerosis are all mechanically contributing components to the devel-

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opment of restenosis. When compared with BMS, neoatherosclerotic change inside the stent is seen at a higher rate after DES implantation. Early neoatherosclerosis begins with macrophage infiltration after 4 months in DES patients and 2 years after coronary angioplasty in BMS patients.[1] The involvement of inflammation in the development of restenosis following percutaneous transluminal coronary angioplasty (PTCA) has been highlighted in numerous research.[2] Vitamin D insufficiency and deficiency are major public health concerns around the world. Serum 25(OH) D levels below 20 ng/mL indicate vitamin D deficiency in most clinical studies.[3] Modern life in cities, conservative clothing and the increased use of sunscreen creams are associated with low levels of vitamin D. Uçar et al. reported that the prevalence of vitamin D deficiency was 51.8% in Turkey.[4]

Vitamin D is well known for its role in the modulation of the inflammatory system. Vitamin D suppresses inflammation in a variety of ways, including inhibition of prostaglandin and cyclooxygenase pathways, upregulation of anti-inflammatory cytokines, reduction of cytokine-induced expression of adhesion molecules, reduction of matrix metalloproteinase 9, and downregulation of the renin-angiotensin aldosterone system (RAAS). The detrimental effects of the RAAS on the cardiovascular system are well-known and it has been shown to play an important role in the development of atherosclerosis. Vitamin D deficiency is associated with increased activity of the RAAS. This may explain the direct myocardial and vascular effects of vitamin D. There are observational studies supporting the relationship between vitamin D levels and cardiovascular diseases.[2,3] However, in some studies, no significant relationship between vitamin D levels and cardiovascular disease has been documented.[4,5]

Vitamin D deficiency may be prognostic for major post infarction adverse events such as heart failure, acute myocardial infarction, or restenosis after PTCA. Vitamin D levels can be considered a cardiovascular risk marker. 25(OH) D is used as a marker of vitamin D status.[2,3,6,7] The aim of this study was to investigate the association between vitamin D levels and the development of restenosis and the time course of restenosis following PTCA.

## MATERIAL AND METHODS

### STUDY POPULATION

This study is a single-center, case-control study conducted at our hospital between March 2012 and December 2015. A total of 100 patients were included in this study. The Group 1 and Group 2 patients (n=58 vs. n=42, respectively) were selected consecutively among the patients who had a history of stent implantation and were admitted to the outpatient polyclinic of our hospital with angina pectoris leading to angiography. All coronary angiography procedures were performed via the femoral route by an experienced cardiologist (Siemens Axiom Artis Zee, Germany). Patients in Group 1 had stent restenosis in angiography. The control group (Group 2, n=42) had no stent restenosis. Angiographic stent restenosis was defined as greater than or equal to 50% stenosis in-stent or within 10 mm proximal or distal to the stent.[8]

The exclusion criteria were liver or kidney disease, hyperparathyroidism, use of drugs including vitamin D and calcium (Ca), history of malignancy, acute coronary syndrome.

The Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (committee no: 2020/242-2993, date: 23.11.2020). This study was carried out following the Declaration of Helsinki Principles. Informed consent was obtained from all patients.

Laboratory measurements: The blood samples were obtained at the time of angiographic procedures (Coulter LH780, Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). All patients were prescribed acetylsalicylic acid, beta-blockers, and statins, according to their electronic prescriptions.

### STATISTICAL TESTS

The Number Cruncher Statistical System NCSS 2007 (Kaysville Utah-USA) for Windows program was used for data input and statistical analysis. Mean, median and standard deviation were used to report results. The Shapiro-Wilk test was used to test data

normality. Variables with normal distribution were compared using Student's t-test. If the normality test failed, the Mann-Whitney U test was used. Categorical variables were compared using the chi-square ($\chi^2$) and the Fisher-Freeman-Halton exact test. Receiver operating characteristics (ROC) curve analysis was used to identify the optimal cut-off values of vitamin D. Logistic regression analysis was used to determine the risk factors for restenosis. P values <0.05 were considered to be statistically significant.

## RESULTS

The demographic and clinical data of the study groups are shown in Table 1. Group 1 and Group 2 were alike in terms of sex distribution (male n=44, 76% vs. male n=34, 81%, respectively). The mean age was similar between the groups (60±9 vs. 59±9). Hypertension was more frequent in the stent restenosis group (n=37, 64% vs. n=17, 41%, p=0.021). There were more diabetic patients in Group 1. However it was insignificant (45% vs. 26%, p=0.06). Only one patient in the stent restenosis group had a high body mass index (>30 kg/m$^2$).

The coronary stent characteristics of the subjects are presented in Table 2. The percentage of DES use was similar between the groups. The stent diameters and lengths were similar. The time passed from stent placement to angiography was similar in both groups (28 months vs. 24 months, p>0.05).

The mean 25(OH) D values were statistically significantly lower in patients with in-stent restenosis (Table 3) (11.2 ng/mL vs. 13.8 ng/mL, p=0.02). The optimal threshold point of vitamin D for restenosis using ROC curve analysis was found as 11.3 (Figure 1). The area under the ROC curve (AUC) was 0,651 (AUC=0.651, 95% confidence interval 0.529-0.773, p=0.02). When the vitamin D level was below 11.3, the risk of restenosis increased 3.4 fold (Table 4). However, as time elapsed

**TABLE 1:** Participants' characteristics in both Group 1 (restenosis) and 2 (control).

| | | | Groups | | |
|---|---|---|---|---|---|
| | | Total | Restenosis (n=58) | Control (n=42) | p value |
| Age (years) | Mean±SD | 59.8±8.9 | 60.1±8.9 | 59.4±8.8 | [a]0.676 |
| Gender, n (%) | Male | 78 (78.0) | 44 (75.9) | 34 (81.0) | [b]0.544 |
| Hypertension, n (%) | | 54 (54.0) | 37 (63.8) | 17 (40.5) | [b]0.021* |
| Diabetes, n (%) | | 37 (37.0) | 26 (44.8) | 11 (26.2) | [b]0.057 |
| Hyperlipidemia, n (%) | | 46 (46.0) | 29 (50.0) | 17 (40.5) | [b]0.346 |
| Current smokers, n (%) | | 26 (26.0) | 16 (27.6) | 10 (23.8) | [b]0.671 |

[a]Student t-test; bPearson chi-square test; *p<0.05; SD: Standard deviation.

**TABLE 2:** Participants' characteristics in Group 1 (restenosis) and 2 (control).

| | | | Groups | | |
|---|---|---|---|---|---|
| | | Total | Restenosis | Control | p value |
| Clinical stent indication, n (%) | SAP | 36 (36.7) | 21 (36.8) | 15 (36.6) | |
| | USAP | 3 (3.1) | 1 (1.8) | 2 (4.9) | *[c]0.873* |
| | NSTEMI | 25 (25.5) | 15 (26.3) | 10 (24.4) | |
| | STEMI | 34 (34.7) | 20 (35.1) | 14 (34.1) | |
| Stent length (mm) | Mean±SD | 19.8±6.2 | 20.2±6.1 | 19.2±6.4 | *[a]0.481* |
| Stent diameter (mm) | Median (minimum-maximum) | 3 (2.25-4) | 3 (2.5-3.5) | 3 (2.25-4) | *[d]0.908* |
| Stent, n (%) | BMS | 69 (72.6) | 44 (78.6) | 25 (64.1) | |
| | DES | 26 (27.4) | 12 (21.4) | 14 (35.9) | *[b]0.120* |
| Angiography following stent (month) | Median (minimum-maximum) | 25 (1-120) | 28 (1-118) | 24 (2-120) | *[d]0.910* |

[a]Student t-test; [b]Pearson chi-square test; [c]Fisher-Freeman-Halton test; [d]Mann-Whitney U test; SAP: Stable angina pectoris; USAP: Unstable angina pectoris; NSTEMI: Non-ST myocardial infarction; STEMI: ST-elevation myocardial infarction; SD: Standard deviation; BMS: Bare metal stent; DES: Drug eluting stent.

**TABLE 3:** Laboratory characteristics of groups.

| | | Groups | | | |
|---|---|---|---|---|---|
| | | Total | Restenosis | Control | p value |
| Leukocyte (x10$^9$/L) | Mean±SD | 8.1±2.1 | 8.2±2.4 | 7.9±1.6 | [a]*0.409* |
| Hb (g/dL) | Mean±SD | 13.7±1.6 | 13.4±1.8 | 14.06±1.2 | [a]*0.034** |
| Hct (x10$^{12}$/L) | Mean±SD | 40.1±6 | 39.8±5.2 | 40.4±6.9 | [a]*0.593* |
| Platelets (x10$^9$/L) | Mean±SD | 226.2±62 | 220.7±56.4 | 233.5±69 | [a]*0.311* |
| Neutrophil (x10$^9$/L) | Mean±SD | 5±1.9 | 5.2±2.2 | 4,7±1.4 | [a]*0.127* |
| Lymphocyte (x10$^9$/L) | Mean±SD | 2.2±0.9 | 2.1±0.9 | 2.4±0.9 | [a]*0.149* |
| MPV (fL) | Mean±SD | 9.3±1.1 | 9.1±0.9 | 9.5±1.1 | [a]*0.100* |
| RDW (%) | Mean±SD | 13.8±1.1 | 13.6±1 | 14±1.3 | [a]*0.099* |
| FPG (mg/dL) | Median (minimum-maximum) | 104 (53-323) | 110 (53-323) | 98 (70-247) | [b]*0.085* |
| BUN (mmol/L) | Median (minimum-maximum) | 17 (6-108) | 16 (6-108) | 17 (11-23) | [b]*0.972* |
| Creatinine (mg/dL) | Median (minimum-maximum) | 0.9 (0.37-4.3) | 0.9 (0.37-4.3) | 0.93 (0.6-1.57) | [b]*0.445* |
| LDL (mg/dL) | Median (minimum-maximum) | 104 (38-822) | 104.5 (38-207) | 96.5 (58-822) | [b]*0.672* |
| HDL (mg/dL) | Mean±SD | 41.2±9.2 | 41.6±10 | 40.6±8.4 | [a]*0.576* |
| Triglycerides (mg/dL) | Mean±SD | 176.6±82.8 | 178.5±76.3 | 173.9±92.1 | [a]*0.788* |
| HbA1c (%) | Median (minimum-maximum) | 6 (4.9-12.8) | 6.15 (5-12.8) | 5.7 (4.9-9.7) | [b]*0.142* |
| LVEF (%) | Median (minimum-maximum) | 60 (25-65) | 60 (25-65) | 57.5 (30-65) | [b]*0.346* |
| Vitamin D (ng/dL) | Median (minimum-maximum) | 12.4 (6-34) | 11.2 (6-28.3) | 13.8 (6.2-34) | [b]*0.022** |
| hsCRP (mg/dL) | Median (minimum-maximum) | 0.3 (0-3.4) | 0.3 (0-3.4) | 0.2 (0-2.4) | [b]*0.210* |
| NLR | Median (minimum-maximum) | 2.2 (0.7-12.8) | 2.2 (0.7-12.8) | 2.2 (0.7-4.6 ) | [b]*0.396* |

[a]Student t-test; [b]Pearson chi-square test; *p<0.05; SD: Standard deviation; Hb: Hemoglobin; Hct: Hematocrit; MPV: Mean platelet volume; RDW: Red cell distribution width; FPG: Fasting plasma glucose; BUN: Blood urea nitrogen; HDL: High density lipoprotein; LDL: Low density lipoprotein; HbA1C: Hemoglobin A1 C; LVEF: Left ventricular ejection fraction; hsCRP: High sensitivity C-reactive protein; NLR: Neutrophil to lymphocyte ratio.

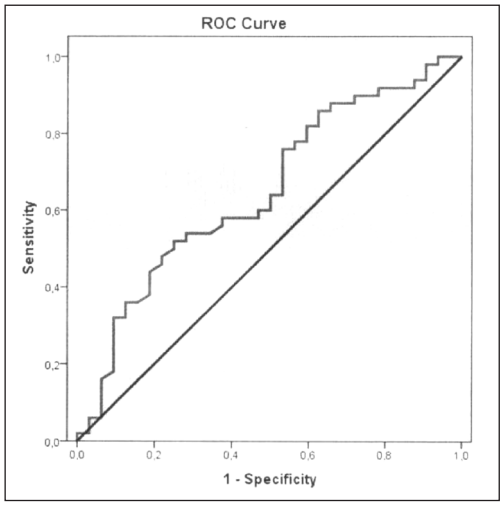


**FIGURE 1:** ROC curve analysis to identify the optimal threshold point of vitamin D in the detection of restenosis following percutaneous transluminal coronary angioplasty. ROC: Receiver operating characteristic.

after PTCA, there was a weak negative correlation between vitamin D, risk of stent restenosis and time (r=-0.181, p=0.219).

The laboratory data of the study groups are shown in Table 3. C-reactive protein (CRP) levels were similar between both groups. The neutrophil to lymphocyte ratio was higher in patients in Group 1 than in Group 2 (2.12 vs. 2.18, p>0.05). The neutrophil to lymphocyte ratio was higher in Group 1 patients (n=43) with insufficient vitamin D than Group 1 (n=6) patients who had sufficient vitamin D (2.3 vs. 1.4, p=0.03). The difference was statistically significant. There was a nega-

**TABLE 4:** Logistic regression analysis results for the risk of restenosis following percutaneous coronary angioplasty.

| | | 95% CI | | |
|---|---|---|---|---|
| | p value | Odds | Lower | Upper |
| Hypertension (+) | *0.122* | 2.537 | 0.780 | 8.257 |
| Diabetes (+) | *0.236* | 2.057 | 0.624 | 6.777 |
| Stent length | *0.447* | 1.032 | 0.952 | 1.118 |
| Stent diameter | *0.450* | 2.056 | 0.317 | 13.324 |
| Vitamin D (≤11.3) | *0.037** | 3.429 | 1.074 | 10.943 |

*p<0.05; CI: Confidence interval.

tive correlation between vitamin D levels and neutrophil to lymphocyte ratio in the stent restenosis group. In Group 2 patients there was no correlation between vitamin D levels and the neutrophil to lymphocyte ratio. The creatinine, albumin, glycated hemoglobin (HbA1C), Ca, triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein cholesterol levels were alike. The mean ejection fraction was 50.8% in Group 1, and 53.9% in Group 2 ($p>0.05$).

## DISCUSSION

The main finding of our study is that patients with restenosis have lower vitamin D levels than patients without restenosis. Especially vitamin D levels below 11.3 ng/mL increased the risk of restenosis 3.4 fold. Also, as time elapsed after PTCA, the effect of low levels of vitamin D upon the risk of restenosis increased.

Vitamin D deficiency stimulates systemic and vascular inflammation. Calcitriol 1, 25 dihydroxy vitamin D reduces the expression of angiotensin-1 receptors in endothelial cells, improves endothelial function and prevents overproduction of reactive oxygen species.[2,9,10] Experimental evidence supports the role of inflammatory reactions as a link between risk factors for atherosclerotic disorder and the pathophysiology of the disease.[11] The crucial role of inflammation on the development of in-stent restenosis following PTCA has been demonstrated in some studies.[12] Recent studies established that vitamin D levels played a significant role as an anti-proliferative factor in the magnitude of restenosis development following balloon angioplasty.[13,14] In Satish et al.'s study, low levels of vitamin D were found to be associated with increased in-stent restenosis and high mobility group box 1-mediated inflammation in swine coronary arteries after coronary stent implantation. Vitamin D levels of the swines were above 28 ng/mL. Increased neointimal hyperplasia was correlated with vitamin D levels in this animal study.[15] Our study was different than Satish et al.'s study. The vitamin D levels were less than 20 ng/mL in most of the patients in our groups. In Gunasekar et al's study, PTCA was performed in Yucatan microswine that were fed with a high cholesterol diet. After 1 year, the optical quantification showed higher rates of restenosis in the vitamin D deficient group (51±11%) compared to the vitamin D sufficient group (15±2%) and the vitamin D supplemental group (14±2%).[16] Gupta et al. supported this study. They showed 3,000 U vitamin D supplementation limited neointimal formation following coronary balloon angioplasty in atherosclerotic swine.[17] In another study, 6 hemodialysis patients with recurrent arteriovenous restenosis were performed successful percutaneous transluminal angioplasty. Calcitriol was administered directly via catheter into the vessel after angioplasty. Three months later, Sato et al. observed vascular smooth muscle proliferation was blocked by calcitriol.[18]

Van Ballegooijen et al. found that lower serum 25(OH) D concentrations were related to high CRP levels.[19] In Byrne et al.'s review, baseline CRP levels were not correlated with restenosis. The changes in CRP values between baseline and after the procedure were closely related to angiographic restenosis.[1] In our study, the mean baseline CRP levels were similar between the patients with and without restenosis and no significant correlation was found between serum vitamin D and CRP levels, neutrophil counts and neutrophil/lymphocyte ratio in both groups. The CRP and the other markers of inflammation were also similar between the groups. We also found that vitamin D levels below 20 ng/mL were associated with a higher neutrophil to lymphocyte ratio in patients with restenosis. In the control group, there was no correlation between vitamin D levels and the neutrophil to lymphocyte ratio. This result was not our main goal and the number of patients with sufficient vitamin D was low. In a previous study, it was demonstrated that diet-induced vitamin D deficiency in mice contributed to the development of hypertension through activation of the RAAS and accelerated atherosclerosis through activation of macrophage endoplasmic reticulum stress.[20] Siadat et al.'s study results demonstrated that vitamin D deficiency increased the risk of coronary artery disease even after adjustment for cardiovascular risk factors such as diabetes, smoking, obesity, physical activity, high blood cholesterol.[21] In our study, most patients with vitamin D deficiency were hypertensive individuals. Sachs et al. reported that impaired vitamin D metabolism did not contribute to the development of atherosclerosis among patients with Type 1 diabetes mellitus. Surprisingly, they observed lower concentrations of vitamin D metabolites were associated with reduced coronary artery Ca scores preva-

lence and severity.[22] Medial artery calcification is more prominent in diabetic patients. After balloon injury, neointimal hyperplasia was increased by medial artery calcification in rats that had excessive vitamin D injection.[23] We had more diabetic patients in the restenosis group. Therefore, the beneficial effect of vitamin D on restenosis might have been reduced.

In some atherosclerosis studies, our hypothesis was supported. Carrelli et al.'s study has shown a negative correlation between vitamin D and carotid atherosclerosis. In this study, lower levels of 25(OH) D were associated with thicker plaque and higher intima media thickness among patients with carotid plaques. It was thought that this finding might be a subclinical marker of atherosclerosis and low level vitamin D was an independent risk factor for angiographically proven coronary artery disease.[24] Ma et al. showed a negative relationship between vitamin D and atherosclerosis in postmenopausal women who were normotensive and euglycemic.[25] Kazlauskaite et al. supported this hypothesis in their study and found a positive association between vitamin D and atheroprotective HDL particle subclasses in postmenopausal women.[26] Schnatz et al. showed that lower concentrations of activated vitamin D receptors were associated with greater atherosclerotic plaque size in female monkeys.[27] In the study of Satilmis et al., a negative correlation between vitamin D levels and the number of plaques in coronary arteries was demonstrated. Subjects with coronary atherosclerosis had lower vitamin D and HDL cholesterol levels.[28] There was no association between HDL and vitamin D levels in our study.

However, some studies investigating the relationship between vitamin D and atherosclerotic cardiovascular disease don't support our hypothesis. Gepner et al. showed that vitamin D levels were not associated with changes in arterial stiffness measures after nearly a decade of follow up.[29] Blondon et al. supported this study finding no relationships of 25(OH) D levels with carotid intima-media thickness or plaque. At baseline, the prevalence of statin use in participants who had 25(OH) D <20 ng/mL was low.[30]

## LIMITATIONS

The limitations of this study include the inherent weakness of observational studies. Seasonal differences in our data were not investigated. Mean vitamin D levels were less than 20 ng/dL in most of the patients in both groups. There were more diabetic and hypertensive patients in Group 1 than in Group 2. Our study shows angiographic restenosis, and the "clear stent" feature was not used, so procedural causes such as malposition and stent fracture could not be excluded.

## CONCLUSION

Vitamin D is known to play an important role in the modulation of the inflammatory system. Recent studies suggest that vitamin D deficiency is associated with an increased risk of cardiovascular disease. Our data suggest that lower vitamin D levels may affect stent restenosis following PTCA and vitamin D might be a biomarker for predicting restenosis. The higher rate of diabetic patients in the restenosis group may have masked the effect of vitamin D deficiency on restenosis**.** As elapsed time after PTCA increases, it may augment the effect of low levels of vitamin D on the risk of restenosis. Further and larger prospective studies using intravascular ultrasonography are required to confirm our findings.

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***Conflict of Interest***

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

***Authorship Contributions***

***Idea/Concept:*** *Aysun Erdem Yaman, Ufuk Sadık Ceylan;* ***Design:*** *Aysun Erdem Yaman;* ***Control/Supervision:*** *Aysun Erdem Yaman, Ufuk Sadık Ceylan;* ***Data Collection and/or Processing:*** *Aysun Erdem Yaman, Ufuk Sadık Ceylan;* ***Analysis and/or Interpretation:*** *Aysun Erdem Yaman, Ufuk Sadık Ceylan;* ***Literature Review:*** *Aysun Erdem Yaman, Ufuk Sadık Ceylan;* ***Writing the Article:*** *Aysun Erdem Yaman, Ufuk Sadık Ceylan;* ***Critical Review:*** *Aysun Erdem Yaman, Ufuk Sadık Ceylan.*

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