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Original Article

The relationship between serum vitamin d and bare-metal in-stent restenosis in patients with stable coronary artery disease

Stabil koroner arter hastalığı olan hastalarda serum d vitamini ve çıplak metal stent restenozu arasındaki ilişki

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Abstract

Aim: It has been shown that low levels of vitamin D are associated with increased cardiovascular risk factors and adverse events. The relationship between serum vitamin D level and bare-metal stent in-stent restenosis was investigated in our study.

Material and Methods: A total of 181 patients with stable coronary artery disease and previously implanted (>3 months) bare-metal stent were included in the study. Two groups were formed according to angiographic results as Group 1 (≥50% in-stent stenosis) and Group 2 (<50% in-stent stenosis). Serum vitamin D measurements were performed by reverse-phase HPLC.

Results: The mean serum vitamin D levels were found to be significantly lower in Group 1 compared to Group 2 (17.7 ± 5.3 ng/ml and 20.9 ± 6.7 ng/ml, p<0.01, respectively) and length of stent was longer in Group 1 compared to Group 2 (18.7 ± 5.3 mm and 17.1 ± 11.2 mm, p<0.01, respectively). In multivariate logistic regression analysis, only low level of serum vitamin D and stent length were independent risk factors for bare-metal in-stent stenosis.

Conclusion: Low level of vitamin D might be related to fibrosis and inflammation resulting in in-stent stenosis. Further studies are warranted to determine whether vitamin D supplementation could prevent progression of stent re-stenosis.

Keywords: coronary artery disease; in-stent stenosis; serum 25(OH)D3

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Öz

Amaç: Düşük D vitamini düzeylerinin artmış kardiyovasküler risk faktörleri ve yan etkiler ile ilişkili olduğu gösterilmiştir. Çalışmamızda serum D vitamini düzeyi ile çıplak metal stent restenozu arasındaki ilişki araştırıldı.

Gereç ve Yöntemler: Çalışmaya stabil koroner arter hastalığı olan ve daha önce çıplak metal sten implante edilmiş (> 3 ay) olan toplam 181 hasta dahil edildi. Anjiyografik sonuçlara göre Grup 1 (≥% 50 stent darlığı) ve Grup 2 (<% 50 stent darlığı) olarak iki grup oluşturuldu. Serum D vitamini ölçümleri ters faz HPLC ile yapıldı.

Bulgular: Ortalama serum D vitamini düzeyleri Grup 1'de Grup 2'ye göre anlamlı derecede düşük bulundu (sırasıyla 17.7 ± 5.3 ng / ml ve 20.9 ± 6.7 ng / ml, p <0.001) ve stent uzunluğu Grup 1'de Grup 2'ye göre daha uzun bulundu (sırasıyla 18.7 ± 5.3 mm ve 17.1 ± 11.2 mm, p <0.001). Çok değişkenli lojistik regresyon analizinde, sadece düşük serum D vitamini düzeyi ve stent uzunluğu, çıplak metal stent restenozu için bağımsız risk faktörleriydi.

Sonuç: Düşük D vitamini düzeyi stent stentenozuna neden olan fibrozis ve inflamasyonla ilişkili olabilir. D vitamini takviyesinin stent restenozunu önleyip önleyemeyeceğini belirlemek için ileri çalışmalar yapılması önerilir.

Anahtar kelimeler: koroner arter hastalığı; stent restenozu; serum 25(OH)D3

Introduction

Serum 25-hydroxyvitamin D [25(OH)D3] is the main circulating form of vitamin D (Vit D). In cross-sectional and observational studies, it has been shown that low levels of 25(OH) D3 are associated with increased prevalence of cardiovascular disease (CVD) and risk factors.[1-5] Vitamin D deficiency is recently recognized as an independent risk predictor for CVD. [1-5] The pathobiologic mechanisms related these effects are unclear, however a possible mechanism may be linked to vitamin D regulation of related fibrotic pathways.[6]

Although drug-eluting stents (DES) are increasingly used for their much lower in-stent stenosis rate compared to balloon angioplasty, widespread use of bare metal stents (BMS) are currently going on, especially in developing countries. Bare metal stent successfully prevents abrupt closure of the artery and reduces the restenosis rate. The efficacy of BMS implantation was hugely hampered by vascular smooth muscle cell proliferation and the resultant neointimal hyperplasia, which is the main mechanism responsible for restenosis.[7]

The aim of the current study was to determine the relationship between serum vitamin D level and coronary bare-metal in-stent restenosis in patients with stable coronary artery disease (SCAD).

Material and Methods

A total of 243 consecutive patients with previously stented were reviewed for possible contribution to the study. Diagnostic coronary angiography was performed to all patients due to anginal complaints and/or abnormal exercise/pharmacological stress tests. However after performing below mentioned exclusion criteria, we enrolled a total of 181 patients with BMS. Two groups were performed according to angiographic results that 106 patients having in-stent stenosis of at least 50% formed Group 1 and the remaining 75 patients without stenosis or with <50% stenosis as Group 2. Exclusion criteria included patients having control coronary angiography within 3 months of the first procedure (n=7), creatinine level exceeding 1.5 mg/dl or calculated GFR <60 ml/min (n=25), any contraindication to coronary angiography (n=1), and patients under vitamin D supplements for various indications such as osteoporosis (n=29). This study was approved by our Institutional Review Board. Informed consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

Coronary angiography

Selective coronary angiography was performed via the femoral or radial route by the Judkins technique. Two experienced interventional cardiologists blinded to the study protocol evaluated the coronary angiography results. With the contrast-filled injection catheter as the calibration source, stenosis % was measured by quantitative angiography on digital angiograms by use of a validated automated edge detection algorithm. An unforeshortened angiographic projection with minimal degree of vessel overlap displaying the restenosis in its sharpest and tightest view was used for analysis in acquired images. Binary restenosis was defined as a stenosis diameter of ≥50% in stented segment of the vessel.

Laboratory measurements

Just after selective coronary angiography, venous blood samples were drawn from the patients for analyses of the serum 25(OH)D3 levels. Fasting plasma glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and creatinine were determined by using standardized methods. Serum 25(OH)D3 was determined by reverse-phase HPLC. The intraassay percent coefficient of variation for this assay ranges from 1.9% at a 25(OH)D3 concentration of 61.5 ng/ml to 6.3% at a 25(OH)D3 concentration of 14.3 ng/ml. The interassay percent CV is 3.2% at a 25(OH)D3 concentration of 59.8 ng/ml and 3.9% at a 25(OH)D3 concentration of 14.3 ng/ml. Normal reference values of our laboratory were 20.0-120.0 ng/ml.

Statistical analysis

Data were analyzed using SPSS 15.0 for Windows. Continuous variables were expressed as mean ± SD and categorical variables as percentages. Kolmogorov-Smirnov test was used for testing distribution of the data. Student's t test was used for normally distributing variables and Mann-Whitney U test for variables without normal distribution. Multivariate logistic regression analysis was used whether serum 25(OH)D3 is an independent risk factor for in-stent stenosis. A two-tailed p value < 0.05 was regarded as significant.

Results

Baseline clinical, demographic and laboratory characteristics of both groups were outlined in Table 1. Deficiency (<20 ng/mL) and insufficiency (<30 ng/mL) of 25(OH)D3 were common among our study population (107 patients 59% and 170 patients 93%, respectively). In Group 1, levels of 25(OH)D3 were lower (17.7 ± 5.3 ng/ml and 20.9 ± 6.7 ng/ml, p<0.001, respectively) and length of stent was longer than in Group 2 (18.7 ± 5.3 mm and 17.1 ± 11.2 mm, p<0.001, respectively). Other parameters were comparable in Group 1 and 2. Variables found to be statistically significant in univariate analysis between Group 1 and 2 were entered into multivariate logistic regression analysis. After multivariate analysis, level of vitamin D and stent length were independent predictors of BMS in-stent stenosis (Table 2). Considering to the ROC curve analysis, the best cutoff value of vitamin D for estimating in-stent restenosis was <16.9 ng/dl (AUC 0.618, p=0.006, Figure 1).

Table 1. Baseline clinical, demographic and laboratory characteristics of study groups.

Characteristics	Group 1 (n = 106)	Group 2 (n = 75)	P value
Age, years	60.5 ± 9.8	63.5 ± 9.8	0.06
Male sex, n (%)	70 (66%)	52 (69%)	0.62
Diabetes mellitus, n (%)	50 (47%)	30 (40%)	0.35
Hypertension, n (%)	57 (53%)	45 (60%)	0.44
Hyperlipidemia, n (%)	53 (50%)	47 (63%)	0.17
Family history of CAD, n (%)	36 (34%)	24 (32%)	0.87
Smoking, n (%)	38 (35%)	19 (25%)	0.14
Vessel for intervention			0.34
LMCA, n (%)	0 (0%)	1 (1%)	
LAD, n (%)	45 (43%)	37 (50%)	
Cx, n (%)	31 (30%)	19 (26%)	
RCA, n (%)	28 (26%)	16 (21%)	
Stenosis location			0.60
Proximal, n (%)	57 (54%)	36 (49%)	
Mid-segment, n (%)	36 (34%)	30 (41%)	
Distal, n (%)	11 (10%)	7 (9%)	
Body mass index, kg/m2	29.2 ± 11.8	28.3 ± 5.5	0.62
Fasting plasma glucose, mg/dl	127 ± 52	133 ± 66	0.69
Creatinine, mg/dl	0.94 ± 0.22	0.93 ± 0.25	0.85
Total cholesterol, mg/dl	168 ± 41	176 ± 41	0.11
LDL cholesterol, mg/dl	96 ± 35	104 ± 39	0.07
HDL cholesterol, mg/dl	38 ± 9	38 ± 9	0.74
Triglycerides, mg/dl	157 ± 65	168 ± 93	0.97
Follow-up period, days	580	795	0.35
Stent diameter, mm	2.90 ± 0.36	2.93 ± 0.37	0.76
Stent length, mm	18.7 ± 5.3	17.1 ± 11.2	<0.001
Vitamin D level, ng/dl	17.7 ± 5.3	20.9 ± 6.7	<0.001

Abbreviations: CAD, coronary artery disease; LMCA, left main coronary artery; LAD, left anterior descending; Cx, circumflex; RCA, right coronary artery; LDL, low density lipoprotein ; HDL, high density lipoprotein

Table 2. Multivariate analysis of determinants of in-stent stenosis in study patients.

Variable	Mulivariate analysis	
	Odds ratio, 95% CI	p Value
Age	0.975 (0.945-1.006)	0.111
Low density lipoprotein	0.993 (0.985-1.002)	0.107
Stent length	1.038 (1.007-1.078)	0.026
Vitamin D level	0.924 (0.874-0.976)	0.005

Volume 11 Number 4 p: 237-242

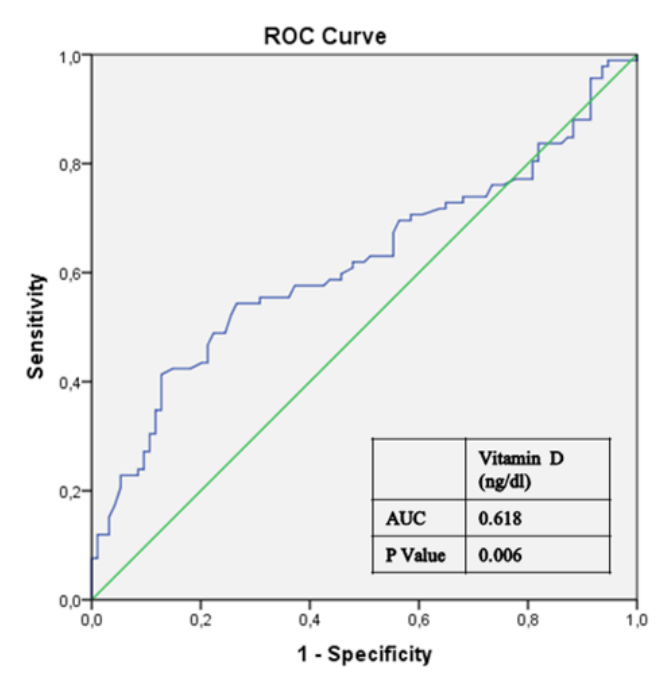

Figure 1: Receiver operator characteristic (ROC) curve of Vitamin D level for the development of bare-metal is-stent restenosis.

Discussion

To our knowledge, this is the first study to evaluate the relationship between levels of 25(OH)D3 and in-stent stenosis in patients with SCAD. Our observations suggest that low levels of 25(OH)D3 are associated with an increased risk of in-stent stenosis.

Percutaneous coronary intervention (PCI) with stenting has become a standard treatment option for coronary artery disease (CAD). In-stent stenosis after PCI remains a challenging clinical problem. The main mechanism responsible for restenosis is neointimal proliferation, which is caused primarily by the effects of vascular smooth muscle cell proliferation.[8]

This cell proliferation after stent implantation occurs both early, as part of the acute injury response, and late, due to inflammatory response. Although some neointima formation is necessary for vessel healing after stenting to prevent exposure to the formed blood elements such as platelets, excessive neointima formation, neointimal hyperplasia, causes stenosis and narrows the luminal area of the stent.[9] The vascular endothelium plays a central role in maintaining vascular hemostasis via its anti-inflammatory and antithrombotic properties.[10]

Vitamin D induces the production of prostacyclin by vascular smooth muscle cells, which prevents thrombus formation, cell adhesion, and smooth muscle cell proliferation.[11] Vitamin D can directly affect the development of CAD with some possible mechanisms including reduction in inflammation, suppression of the renin-angiotensin-aldosteron system, and modulation of cardiovascular remodeling. Also vitamin D acts as a direct factor on cardiac tissues and the vasculature. In vitro and in vivo studies have evaluated its role acting directly on cardiac tissue, especially in response to injury. Vitamin D inhibits pro-fibrotic inflammatory markers, suggesting that vitamin D might also have a direct effect on the vascular tissue in response to injury.[12] In a double-blind, randomized, placebo-controlled trial of vitamin D supplementation (a daily supplement of 50 ng (2000 IU) cholecalciferol) in subjects with congestive heart failure demonstrated significant reductions in inflammatory cytokines.[13] Therefore, Vit D may reduce cardiovascular risk by inhibiting vascular smooth muscle proliferation via decreasing calcium cellular influx and increasing matrix Gla protein and reducing inflammation via inhibiting cyclooxygenase 2 pathway, matrix metalloproteinase 9 and several proinflammatory cytokines.[14] Vitamin D induces its nuclear receptor and modulates related transcription factors resulting in anti-fibrotic signaling pathways in smooth muscle cells characterized by inhibiting expression of pro-fibrotic markers and increasing expression of anti-fibrotic markers leading to an effective reduction in collagen synthesis, and supports the emerging clinical findings linking vitamin D deficiency to adverse cardiovascular events.[15]

Al Mheid et al. showed that vitamin D insufficiency was associated with increased arterial stiffness and endothelial dysfunction in healthy humans.[16] Investigators found that vitamin D supplementation improves endothelial function, in patients with diabetes and in healthy adults with vitamin D-insufficiency.[17,18] Motiwala et al have recently reviewed prospective cohort and randomized clinical trials that studied the association between serum vitamin D and CVD.[19] A low level of serum 25 (OH)D3 has been found as a risk factor for CAD and cardiovascular death. In addition, multiple recent epidemiologic and prospective studies have showed a strong association between vitamin D insufficiency and risk of CVD, diabetes mellitus, metabolic syndrome, obesity, hypertension, peripheral vascular disease, ischemic heart disease, sudden cardiac death, and heart failure.[20-24]

It was recently demonstrated that serum 25(OH)D3 levels are

inversely associated with coronary lesion severity established by coronary angiography.[25] This data suggests that vitamin D may play a role in the development and progression of atherosclerosis. These findings should be confirmed by larger trials and determined whether vitamin D supplementation prevent the development of CVD. Prospective, randomized and placebo-controlled studies evaluating the effect of vitamin D supplementation on in-stent stenosis are needed before the use of this therapy for patients who have received a stent.

Study limitations

One of the major limitations of our study was limited sample size. Second, only patients with anginal complaints or ischemia demonstrated with non-invasive tests were taken in the study. Moreover in-stent restenosis were not evaluated by vascular imaging such as IVUS or OCT. Our study was an observational cross-sectional study that a causative association between serum vitamin D and in-stent stenosis cannot be defined. Geography, seasonality, latitude, and altitude presumably as a result of sunlight exposure can influence levels of vitamin D. 25(OH)D3 has a relatively long circulating half-life (approximately 3 weeks) and is considered a good biomarker, but serum vitamin D levels may change throughout the day and season of the year. A single measurement of vitamin D may not reflect lifetime status, and coronary atherosclerosis progresses over many years. The reason for the lower range of serum vitamin D levels in our study was explained probably with the minimum effect of the sunlight exposure between the autumn and winter months. On the other hand, we did not evaluate uric acid, hs-CRP, monocytes, lymphosites and other inflammatory markers which contribute development of CAD.

Conclusion

Low level of Vitamin D might be related to fibrosis and inflammation resulting in in-stent stenosis. Further studies are warranted to determine whether vitamin D supplementation could prevent progression of stent restenosis.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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