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CAN VITAMIN D DEFICIENCY PREDICT CORONARY ARTERY DISEASE?

Vitamin D Eksikliği Koroner Arter Hastalığı İçin Öngördürücü müdür?

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Abstract

Aim: On the basis of emerging data about the association of vitamin D and coronary artery disease (CAD), we investigated whether a relationship exists among vitamin D, inflammation represented by C-reactive protein (CRP), and serum lipid profile in CAD.

Materials and Methods: Patients with newly diagnosed CAD (n = 115) and 62 healthy subjects were enrolled in the study. Blood lipids, CRP, and vitamin D levels were measured, and the patient and control groups' values were compared.

Results: The low-density lipoprotein cholesterol (LDL-C), triglyceride, and CRP levels were higher, and vitamin D and high-density lipoprotein cholesterol (HDL-C) levels were lower in the patient group. A positive correlation was found between the vitamin D and HDL-C levels (r=0.328; p<0.001) and a negative correlation was seen between vitamin D and CRP (r= -0.484; p<0.001). In the multivariate logistic regression analysis, smoking (p=0.001, OR = 5.301; 95% CI = 2.215 – 12.687), the presence of hypertension (p=0.040, OR = 2.355; 95% CI=1.039 – 5.336), LDL-C level (p=0.048, OR =1.021, 95% CI=1.000 – 1.042) and vitamin D level (p=0.001, OR = 0.937, 95% CI = 0.902 – 0.973) were found to be predictors of CAD.

Conclusion: Decreased level of vitamin D is associated with presence and CAD. Decreased vitamin D levels are associated with low HDL-C and high CRP levels in CAD. Smoking, hypertension, LDL-C and vitamin D are predictors of CAD.

Key Words: 25-hydroxyvitamin D, coronary artery disease, high-density lipoprotein cholesterol, C-reactive protein, coronary angiography.

Öz

Amaç: D vitamininin ve koroner arter hastalığının (KAH) ilişkisiyle ilgili ortaya çıkan verilere dayanarak, KAH'da D vitamini ile C-reaktif protein (CRP) ile temsil edilen inflamasyon ve serum lipid profili arasında ilişki bulunup bulunmadığını araştırdık.

Materyal ve Metot: Yeni KAH tanısı konmuş 115 hasta ve 62 sağlıklı birey çalışmaya alındı. Kan lipidleri, CRP ve D vitamini düzeyleri ölçüldü ve hasta ve kontrol gruplarının değerleri karşılaştırıldı.

Bulgular: Hasta grubunda düşük dansiteli lipoprotein kolesterol (DDL-K), CRP ve trigliserit düzeyleri yüksek, vitamin D ve yüksek dansiteli lipoprotein kolesterol (YDL-K) düşüktü. Vitamin D ile YDL-K arasında pozitif korelasyon (r=0.328; p<0.001), vitamin D ile CRP arasında negatif korelasyon (r=-0.484; p<0.001) vardı. Multivariate lojistik regresyon analizinde, sigara (p=0.001, OR = 5.301; 95% CI = 2.215 – 12.687), hipertansiyon varlığı (p=0.040, OR = 2.355; 95% CI=1.039 – 5.336), DDL-K düzeyi (p=0.048, OR =1.021, 95% CI=1.000 – 1.042) ve vitamin D düzeyi (p=0.001, OR = 0.937, 95% CI = 0.902 – 0.973) KAH belirleyicisi olarak bulundular.

Sonuç: Azalmış D vitamini seviyeleri, KAH'da düşük YDL-K ve yüksek CRP seviyeleri ile ilişkilidir. Sigara, hipertansiyon, DDL-K ve D vitamin KAH'ın belirleyicisidirler.

Anahtar Kelimeler: 25-hidroksi vitamin D, koroner arter hastalığı, yüksek dansiteli lipoprotein kolesterol, C-reaktif protein, koroner anjiografi.

INTRODUCTION

Atherosclerosis is a multifactorial disease that initiates with deterioration of endothelial function and results in formation of fibroatheromas[1]. Further progression and complication of these plaques have clinical consequences such as myocardial infarction or

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stroke. Smoking, hypertension, diabetes mellitus together with inflammation and activated immune responses are known to play important role in the proccess of atherosclerosis[2-4]. Elevated C-reactive protein (CRP) levels, one of the markers of inflammation, is demonstrated to increase cardiovascular events in JUPITER study[5,6]. Decreased levels of high-density lipoprotein cholesterol (HDL-C) and increased levels of low-density lipoprotein cholesterol (LDL-C) are known to be risk factors for the development of atherosclerosis[7-10]. Although presence of atherosclerotic vascular disease can be explained by classical cardiovascular risk factors in most patients, a considerable amount of patients without specified risk factors also suffer from atherosclerosis. Therefore, the role of emerging risk factors, like vitamin D, is being evaluated in some studies.

Vitamin D is a lipid-soluble vitamin necessary for calcium absorption from intestines and bone mineralization[11,12]. Vitamin D deficiency has been linked to diabetes, hypertension, hyperlipidemia, peripheral vascular disease, CAD, myocardial infarction (MI), heart failure (HF), stroke, and death[13,14]. Furthermore, the magnitude of vitamin D deficiency is shown to correlate to severity of CAD and mortality[15-17]. Nevertheless, the exact mechanism of this association is elusive and needs clarification. The casual relationship between CAD, and vitamin D deficiency is still unclear. Only few studies addressed the association of vitamin D and CRP or HDL-C[19-22]. If vitamin D deficiency was a novel cardiovascular risk factor for CAD, there might be a relationship between serum vitamin D levels and CRP or serum lipids in CAD patients. Therefore, this study investigated whether any association exists between vitamin D and CRP or proatherogenic lipid profile in CAD patients and whether vitamin D is a predictor of CAD.

MATERIAL AND METHODS

Patients

Between January 2013 and February 2013, patients who were admitted to the cardiology clinic for the purpose of coronary angiography and who gave informed consent were involved into this study. The study group consisted of 177 individuals. Of 177 patients, 115 patients (75 men and 40 women, mean age 55.6 ± 9.1 years) with significant coronary artery stenosis on CAG constituted the CAD group and 62 patients (40 men and 22 women, mean age 56.9 ± 6.9 years) with normal coronary angiogram constituted the control group. Patients older than 75 years, patients with acute coronary syndromes, previous history of CAD, history of significant valvular disease, heart failure, liver or renal insufficiency, diseases related to bone mineralization, primary or secondary hyperparathyroidism, cancer or osteoporosis were excluded from the study. Patients with insulin dependent diabetes, or those who were being treated with insulin were not involved. Detailed medical histories were obtained and physical examination was performed. The presence of diabetes mellitus, hypertension, hyperlipidemia, smoking status, family history of CAD, systolic and diastolic blood pressures, and body mass index (BMI) values were recorded. BMI was calculated by dividing the patient's weight by the square of the height. Ethical approval for this study was granted by the Namık Kemal University Medical Faculty

Local Ethical Committee (2012/44/08/02). The study was conducted in accordance with the Helsinki Declaration principles.

Blood Sampling

Since vitamin D levels show seasonal variability, all subjects were tested in January and February. Blood samples were collected for biochemical analysis at the same intervals (7:00 to 11:00) after an overnight 12 hours fast.

Biochemical Analysis

A standard enzymatic method with an AU6B0 autoanalyser (Beckman Coulter, Brea, CA) was used for the measurement of fasting glucose, total cholesterol (TC), HDL-C, LDL-C, and triglyceride (TG) levels.

Measurement of CRP level

A standard nephelometry method was used for the measurement of CRP levels (Cobas c311; Roche Diagnostics, Mannheim, Germany) with a sensitivity of 0.1 mg/L.

Measurement of Vitamin D and Parathormon

The 25-hydroxyvitamin D concentration was measured by automatic direct electro-chemiluminescence immunoassay (Elecsys; Roche Diagnostics). The lower limit was 3.0 ng/ml; according to the manufacturer's instructions, a measured vitamin D level of less than 30 ng/ml was accepted as vitamin D deficiency. The intra-assay coefficient of variation (CV) was 3.4% and the interassay CV was 4.5%.

The normal parathormon (PTH) reference level was assessed as 15–65 pg/ml by the electro-chemiluminescence microparticle immunoassay with a Cobase 601 kit (Roche Diagnostics). The intra-assay CV was 2.5% and the interassay CV was 4.2%.

Echocardiography

The echocardiographic examination was performed with a 2.5–3.5MHz probe and a Vivid-5 machine (GE Vingmed Sound, Horten, Norway), with the patient lying in the left lateral decubitus position. The left ventricular ejection fraction (LVEF) was measured with Simpson's method as suggested by the recommendations of the American Society of Echocard iography. An LVEF greater than 50% was accepted as normal systolic function[23].

Coronary Angiography

The selective coronary angiography was performed with a monoplane angiography machine (Axiom Artis; Siemens, Erlangen, Germany) and Judkins catheters via the femoral artery. The left anterior descending, circumflex, and right coronary arteries were evaluated with cine films taken at right and left anterior oblique, cranial, and caudal angles. Coronary reference segments were chosen from the proximal and distal parts of the coronary lesions. The luminal narrowing of the coronary arteries were measured quantitatively by two cardiologists. Patients with significant narrowing in at least one epicardial coronary artery (≥70% stenosis) were enrolled into patient group, and patients with normal coronary arteries were enrolled into the control group.

Statistical Analysis

Variables were evaluated with PASW Statistics for Windows, version 18, software (SPSS Inc., Chicago, IL). The distribution of the variables was evaluated with the Kolmogorov-Smirnov test. Continuous variable results were given as

mean and standard deviation, and categorical variable results were given as numbers and percentages. The chi-square test (χ2) was used to compare the categorical variables and the independent- samples t-test was used to compare the continuous variables.The Pearson and Spearman rank test was used to detect whether acorrelation exists between vitamin D, CRP, LDL-C, HDL-C, CRP, presence of diabetes, hypertension, family history of CAD, smoking and the number of vessel with significant stenosis. After conducting univariate logistic regression analysis, a backward logistic multivariate regression analysis was conducted for significant variables to determine the CAD predictors. A p value of less than 0.05 was accepted as significant.

RESULTS

Demographic findings of the patient and control groups are presented in Table 1. No differences in terms of age, gender, BMI, heart rate, LVEF and systolic or diastolic blood pressures were seen between the two groups (p> 0.05). Family history of CAD, smoking, hypertension, diabetes, and hyperlipidemia were more common in the CAD patients than those in the control group (p<0.05). No differences were found in terms of medication (statins, beta blockers, acetylsalicylic acid, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers) between the two groups. Of the 115 subjects in the patient group, 51 had one-vessel disease, 36 had two-vessel disease, and 28 had three-vessel disease (Table 1).

Table 1. Comparison of baseline characteristics of the patient and control group

Parameters	Patient (n=115)	Control (n=62)	p value
Age, years	55.6 ± 9.1	56.9 ± 6.9	0.341
Male gender, n (%)	75 (65.2)	40 (64.5)	0.845
BMI, kg/m²	28.9 ± 3.7	29.3 ± 4.6	0.583
Smoking, n (%)	80 (69.6)	15 (24.2)	0.001
Family history of CAD, n (%)	55 (47.8)	15 (24.2)	0.002
Hypertension, n (%)	68 (59.1)	25 (40.3)	0.013
Diabetes, n (%)	39 (33.9)	15 (24.2)	0.015
Hyperlipidemia, n (%)	54 (47)	23 (37.1)	0.012
Systolic BP, mm/Hg	134.4 ± 14.9	133.8 ± 14.8	0.784
Diastolic BP, mm/Hg	80.8 ± 8.6	79.8 ± 8.2	0.483
Heart rate, beat/min	71.6 ± 8.2	70.3 ± 7.3	0.091
LVEF, %	56.2± 6.9	57.7 ± 7	0.194
Statin use, n (%)	46 (40)	21 (33.9)	0.423
Beta blocker use, n (%)	55 (47.8)	23 (37.1)	0.170
Acetyl salicylic acid use, n (%)	48 (41.7)	22 (35.5)	0.417
ACEI use, n (%)	44 (38.2)	17(27.4)	0.148
ARB use, n (%)	17 (14.8)	5 (8.1)	0.196
1 vessel disease	51	0	
2 vessel disease	36	0	
3 vessel disease	28	0	

ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin reseptor blocker, BMI: body mass index, CAD: coronary artery disease, LVEF: left ventricular ejection fraction Data are n (%) for categorical variables, means±SD for continuous variables, or median (25% and 75% interquartiles) for non-normally distributed variables. The chi-square test was used to analyze the categorical variables and the Student's t-test was used to compare the continuous variables.

The biochemical findings of the patient and control groups are presented in table 2. No differences were seen in fasting glucose, TC, calcium, or PTH levels (p>0.05) between groups. Triglyceride, LDL-C, and CRP levels were higher in the patient group (179.2±55.2 vs. 159.2±61.2 mg/dl for TG; p=0.008, 132.8±23.6 vs. 120.4±23.1 mg/dl for LDL-C; p<0.001 and 4.6±3.3 vs. 3.0±2.1 mg/dl for CRP; p=0.007 respectively) than they were in the control group. On the other hand, vitamin D and HDL-C levels were significantly lower in the patient group than they were in the control group (21.8±11.8 vs. 34.7±14.3 ng/ml for vitamin D; p<0.001 and 37.6±7.6 vs. 45.3±10.4 mg/dl for HDL-C levels; p=0.001) (Table 2).

Table 2. Comparison of laboratory findings of the patient and the control group

Parameters	Patient (115)	Control (62)	p value
Glucose, mg/dL	88 ± 31.2	84.1 ± 19.9	0.270
Creatinin, mg/dL	0.6 ± 0.1	0.5 ± 0.1	0.703
Total Cholesterol, mg/dL	200.9 ± 25.7	194.9 ± 27.1	0.591
Triglyceride, mg/dL	179.2 ± 55.2	159.2 ± 61.2	0.008
HDL - C, mg/dL	37.6 ± 7.6	45.3 ± 10.4	0.001
LDL - C, mg/dL	132.8 ± 23.6	120.4 ± 23.1	0.001
CRP, mg/L	4.6 ± 3.3	3.0 ± 2.1	0.007
Vitamin D, ng/ml	21.8 ± 11.8	34.7 ± 14.3	<0.001
Calcium, mg/dL	8.7 ± 0.8	8.6 ± 0.8	0.663
Parathormon, pg/mL	52.1 ± 5.9	52.5 ± 7.8	0.486

CRP: C reactive protein, HDL–C: high density lipoprotein cholesterol, LDL– C: low density lipoprotein cholesterol, Data are means±SD for continuous variables and Student's t-test was used.

The correlation analysis of vitamin D, CRP, LDL-C, HDL-C, presence of diabetes, hypertension, family history, smoking and the number of vessel with significant stenosis are presented in Table 3. A positive correlation was found between vitamin D and HDL-C levels in the patient group (r=0.328, p<0.001). In addition, a negative correlation was seen between vitamin D and CRP levels (r=-0.484, p<0.001), number of diseased vessels (r=-0.358, p<0.001) and presence of diabetes (r=-0.266, p= 0.004) in the patient group.

Table 3. Correlation between vitamin D and other parameters in the patient group

Variables	Correlation coefficient	p
HDL-C[a]	0.328	<0.001
CRP[a]	-0.484	<0.001
Number of the vessels[b]	-0.358	<0.001
Diabetes[b]	-0.266	0.004
Smoking[b]	-0.58	0.538
Triglyceride[a]	-0.089	0.342
LDL-C[a]	-0.166	0.076
Hypertension[b]	-0.046	0.622
Family history of CAD[b]	-0.017	0.855

CAD: Coronary artery disease, CRP: C reactive protein, HDL–C: high density lipoprotein cholesterol, LDL – C: low density lipoprotein cholesterol. [a] - The Pearson test [b] - The Sperman rank

In univariate logistic regression analysis, the family history of CAD, smoking, hypertension, triglyceride, HDL –C, LDL – C, vitamin D and CRP were found to be predictors for the presence of CAD (Table 4). In the multivariate logistic regression analysis, smoking (p=0.001, OR = 5.301; 95% CI = 2.215 – 12.687), the presence of hypertension (p=0.040, OR = 2.355; 95% CI=1.039 – 5.336), LDL-C level (p=0.048, OR =1.021, 95% CI=1.000 – 1.042) and the vitamin D level (p=0.001, OR = 0.937, 95% CI = 0.902 – 0.973) were found to be independent predictors of CAD (Table 5).

Table 4. Univariate logistic regression analysis to predict the presence of CAD

Variable	Odds ratio	95 % CI	p
Age	1.020	0.982 – 1.059	0.305
Gender	1.150	0.604– 2.190	0.671
Family history	2.983	1.502 – 5.926	0.002
Smoking	6.630	3.316 – 13.258	0.001
Hypertension	2.029	1086 – 3.790	0.027
Diabetes	1.469	0.738– 2.923	0.274
Hyperlipidemia	1.412	0.754 – 2.645	0.281
BMI	1.035	0.957 – 1. 119	0.387
Glucose	1.006	0.993 – 1.019	0.362
T C	1.009	0.997 – 1.021	0.149
Triglyceride	1.006	1.001 – 1.012	0.030
HDL –C	0.906	0.869 – 0.945	0.001
LDL – C	1.023	1.009 – 1.038	0.002
Vitamin D	0.929	0.902 – 0.957	0.001
CRP	1.222	1.080 – 1.382	0.001
Systolic BP	1.003	0.982 – 1.024	0.782
Diastolic BP	1.013	0.977 – 1.051	0.481
Creatinin	1.538	0.171 – 13.863	0.701

BMI: body mass index, BP: blood pressure, CRP: C reactive protein, HDL-C: high density cholesterol, LDL-C: low density cholesterol, TC: total cholesterol

Table 5. Multivariate logistic regression analysis to predict the presence of CAD

Variable	Odds ratio	95 % CI	p
Family history	1.447	0.586 – 3.572	0.423
Smoking	5.301	2.215 – 12.687	0.001
Hypertension	2.355	1.039 – 5.336	0.040
Triglyceride	1.001	0.993 – 1.009	0.794
HDL –C	0.960	0.898 – 1.027	0.235
LDL – C	1.021	1.000 – 1.042	0.048
Vitamin D	0.937	0.902 – 0.973	0.001
CRP	1.017	0.851 – 1.216	0.851

CRP: C reactive protein, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol

DISCUSSION

This study showed that serum vitamin D was significantly lower in patients with CAD and it was positively correlated with HDL and

negatively correlated with plasma CRP levels, the extensity of CAD and the presence of diabetes. Among various variables, smoking, hypertension, LDL-C level and vitamin D level were independent predictors of the presence of CAD.

Although serum vitamin D levels were not found to be related to subclinical vascular disease and cardiovascular disease risk in a previous study[18]; recent studies set evidence of a clear association with vitamin D deficiency and CAD, multivessel disease, stroke, peripheral vascular disease,and death [13-15, 24, 25]. Seker et al. reported low vitamin D levels in patients with CAD and a significant correlation between vitamin D, Syntax score, hypertension, CRP, and BMI[16]. They indicated the predictors of CAD as hypertension, diabetes, serum creatinine, and vitamin D levels. Similarly, hypertension, vitamin D and LDL levels were predictors of CAD in our study. Vitamin D has established antiangiogenetic, antiproliferative, immunomodulatory, and prodifferentiative effects[12]. In the presence of vitamin D deficiency, the renin-angiotensin-aldosterone system is shown to be activated, PTH and the proinflammatory cytokines are increased, all of which have been implicated in the pathogenesis of atherosclerosis[26]. We consider that vitamin D deficiency play a role in development and progression of CAD.

Decreased HDL-C level is a known risk factor for CAD[8]; one mg increase in HDL-C level decreases the CAD risk by 2–3%[27]. Low HDL-C and high CRP levels have been associated with the presence of CAD. A correlation was seen between the severity of CAD and HDL-C[28].Higher vitamin D levels were associated with higher HDL-C levels and lower LDL-C and triglyceride levels[29]. In addition, a substantial correlation between HDL-C and vitamin D levels has been demonstrated[30].In a study, higher vitamin D levels were found to be related to larger HDL-C particles. That study proposed that vitamin D reverses the transport of cholesterol and promotes the formation of larger HDL-C particles; thus, a low vitamin D level is a negative cardiovascular risk factor[31]. The present study found a positive association between vitamin D and HDL-C levels. This suggests that vitamin D deficiency is related to lower HDL-C levels in CAD patients. Decreased levels of high-density lipoprotein cholesterol (HDL-C) and increased levels of low-density lipoprotein cholesterol (LDL-C) are risk factors for developing atherosclerosis [7-10].

Inflammatory response plays an important role in every stage of the atherosclerotic process; therefore, atherosclerosis is an inflammatory disease[5]. When smoking, hypertension, hyperlipidemia, and other risk factors, alone or in combination, initiate endothelial dysfunction, the inflammatory response becomes evident[4]. An increased CRP level is a marker for inflammation. The lower CRP levels were related to a decrease in cardiovascular events[5,6]. Several studies have been conducted on vitamin D and CRP levels in healthy adults[19], and decreased levels of vitamin D have been found to be a risk factor for inflammation and endothelial dysfunction[20]. Moreover, inverse relations between vitamin D level and the extent of CAD and CRP level have been documented in CAD patients[21].Vitamin D has an anti-inflammatory effect by decreasing the production of IL-2, lymphokines, and interferon gamma[32]. Vitamin

D deficiency is also related to the prevalence and severity of immuno-inflammatory diseases, and vitamin D has immunomodulatory and anti-inflammatory features[33]. In agreement with previous studies, this study showed an inverse relationship between vitamin D and CRP level in patients with CAD. Vitamin D deficiency increased inflammation and changed the immune response, potentially playing a substantial role in the pathogenesis of CAD. This suggests that vitamin D and HDL-C deficiency increases the inflammation by contributing to higher CRP levels.

Limitations

The first limitation was the relatively small sample size with the patient group being roughly twice the size of the control group. Second, including other inflammatory markers besides CRP, such as interleukin and TNF, the findings of the study would have been more valuable. Finally, the numbers of subjects with diabetes, hypertension, hyperlipidemia, a history of smoking, or a family history of CAD were greater in the patient group than they were in the control group. All these confounding factors can lead to vitamin D deficiency. However, these risk factors were taken into account as confounding variables. Therefore, our findings were more validated.

In conclusion, coronary artery disease is related to reduced vitamin D and HDL-C levels and increased CRP and LDL-C levels. Substantial relationships exist between vitamin D deficiency, lower HDL-C, and higher CRP levels in patients with CAD. Lower vitamin D, lower HDL-C and elevated CRP, together play role in the development and progression of CAD. Vitamin D deficiency is decisive for coronary artery disease. Larger clinical and molecular studies are needed to explain these relationships.

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