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Vitamin D in Patients with Cardiac Syndrome X and its Relationship with Inflamatuar and Oxidative Stress Markers: A Case Control Study

Kardiyak Sendrom X Hastalarında D Vitamini ve Bunun İnflamatuar ve Oksidatif Stres Belirteçleri ile İlişkisi: Vaka-Kontrol Çalışması

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ABSTRACT Objective: Cardiac syndrome X (CSX) is used to define patients with ischemic chest pain and normal coronary arteries, as revealed by angiography. The etiology of CSX may be associated with extensive coronary microvascular endothelial dysfunction, inflammation, and oxidative stress. We aimed to simultaneously investigate the relationships of serum vitamin D levels with oxidative stress, atherogenic index of plasma (AIP) and systemic inflammation marker C-reactive protein (CRP) to albumin ratio in CSX patients. **Material and Methods:** The present study group included 52 consecutive symptomatic patients diagnosed with CSX and 42 healthy controls. Serum total cholesterol, high-density lipoprotein (HDL), triglyceride, vitamin D, CRP, serum advanced oxidation protein product, and Ferric reducing ability of plasma levels were measured. The CRP/albumin ratio was determined. The AIP was calculated as log (triglyceride/HDL-C). **Results:** Patients with CSX had decreased vitamin D levels [11.2 (IQR: 6.3) ng/mL vs. 14.8 (IQR: 6.4) ng/mL; p=0.05] and higher CRP/albumin ratios [1.42 (0.84) vs. 1.01 (0.36); p=0.01] and similar AIP (0.11±0.30 vs. 0.14±0.29; p=0.76) compared to the control group. There was a weak negative correlation between vitamin D and CRP/albumin ratio (r=-0.23, p=0.03) levels. **Conclusion:** The reduction of vitamin D levels and systemic inflammation may play a role in the development of CSX.

Keywords: Cardiovascular disease; inflammation; microvascular angina; oxidative stress; Vitamin D

ÖZET Amaç: Kardiyak sendrom X (KSX), anjiyografi ile ortaya konulan normal koroner arterleri olan ve iskemik göğüs ağrısı yaşayan hastaları tanımlamak için kullanılmaktadır. KSX'in etiyolojisi, yaygın koroner mikrovasküler endotel disfonksiyonu, inflamasyon ve oksidatif stres ile ilişkili olabilir. Bu çalışmada, KSX hastalarında serum D vitamini düzeylerinin oksidatif stres, plazmanın aterojenik indeksi [atherogenic index of plasma (AIP)] ve sistemik inflamasyon belirteci olan C-reaktif protein (CRP) ile albumin oranı arasındaki ilişkileri aynı anda araştırmayı amaçladık. **Gereç ve Yöntemler:** Bu çalışma grubunda, ardışık olarak KSX teşhisi konulan 52 semptomatik hasta ve 42 sağlıklı kontrol bulunmaktadır. Serum total kolesterol, yüksek yoğunluklu lipoprotein [high-density lipoprotein (HDL-K)], trigliserid, D vitamini, CRP, serum ileri oksidasyon protein ürünü ve plazmanın ferrik indirgeme gücü düzeyleri ölçüldü. CRP/albumin oranı belirlendi. Plazma AIP değeri log (trigliserid/HDL-K) ile hesaplandı. **Bulgular:** KSX hastalarında kontrol grubuna kıyasla düşük D vitamini düzeyleri [11,2 (IQR: 6,3) ng/mL vs. 14,8 (IQR: 6,4) ng/mL; p=0,05] ve daha yüksek CRP/albumin oranları [1,42 (0,84) vs. 1,01 (0,36); p=0,01] ve benzer AIP (0,11±0,30 vs. 0,14±0,29; p=0,76) tespit edildi. D vitamini ile CRP/albumin oranı arasında zayıf bir negatif korelasyon bulundu (r=-0,23, p=0,03). **Sonuç:** D vitamini düzeylerindeki azalma ve sistemik inflamasyonun, KSX gelişiminde rol oynayabileceği düşünülmektedir.

Anahtar Kelimeler: Kardiyovasküler hastalık; inflamasyon; mikrovasküler anjina; oksidatif stres; Vitamin D

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Cardiac syndrome X (CSX), is used to define patients with ischemic chest pain, positive exercise stress tests, and normal coronary arteries at angiography. The diagnosis of CSX also requires the exclusion of any other cardiac disease (e.g., hypertrophic or dilated cardiomyopathy).[1]

Although the etiology of CSX has not yet been fully elucidated, extensive coronary microvascular endothelial dysfunction, inflammation, and oxidative stress have been implicated.[1-4]

Reactive oxygen species are formed as by-products of normal metabolism in organisms, and antioxidant protection systems provide protection to organisms by neutralizing reactive oxygen radicals.[5] Oxidative stress occurs when this balance is disrupted in favour of free radicals. Total antioxidant capacity of plasma is the main indicator of oxidative stress, which has been observed in several diseases, including CSX.[3] Various methods have been developed to measure total antioxidant capacity of the plasma. Among these methods, ferric reducing ability of plasma (FRAP) is a simple test, and can actually provide more relevant information than the information obtained by measuring individual antioxidant concentrations; and define the dynamic balance that has occurred.[6]

Vitamin D is a prohormone; in addition to many biological effects, it exerts antioxidative activities on the cellular membrane.[7] It has been implicated that there is a relationship between vitamin D deficiency and cardiovascular diseases.[8] Vitamin D levels have also been found to be low in CSX patients and are thought to be involved in the development of microvascular angina in these patients.[9] Animal studies have suggested to improvements in cardiac oxidative stress and inflammatory markers with vitamin D therapy.[10,11]

We hypothesized that vitamin D, which is also correlated with oxidative stress and inflammation, may make a contribution to the pathogenesis of the CSX.

Therefore, we aimed to investigate the relationships of serum vitamin D levels with the FRAP test which measures the total antioxidant system, atherogenic index of plasma (AIP) and systemic inflammation marker C-reactive protein (CRP)/albumin ratio in CSX patients.

MATERIAL AND METHODS

The study was approved by University of Health Sciences Bursa Yüksek İhtisas Education and Research Hospital's Clinical Research Ethics Committee on June 06, 2018 (no: 2011-KAEK-25 2018/06-39). It was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. All participants provided informed consent in the format required by the ethics board.

The present prospective study was conducted in the department of cardiology. Fifty-two consecutive symptomatic patients diagnosed with CSX and forty-two healthy controls without any previous histories of chest pain or acute/chronic disease were considered for inclusion in the present study. Criteria for the inclusion of patients with CSX included history of typical exercise angina, positive exercise treadmill electrocardiogram stress test response, and angiographically normal epicardial coronary arteries. Criteria for the exclusion of patients with CSX included refusal to participate in the study, left ventricular dysfunction or hypertrophy, valvular heart disease, congenital heart disease, kidney or liver failure, history of diabetes, chronic systemic inflammatory diseases and malignancy.

The age, gender, height, body weight, the presence of diabetes mellitus, and smoking were recorded. The body mass index (BMI) of each participant was calculated (kg/m^2). Heart rate and blood pressure were obtained with the volunteer seated after ten minutes of rest. Left ventricular ejection fraction (EF) was calculated with the Modified Simpson method.[12]

Fasting blood samples were collected via venipuncture from the control and patient groups. Samples were centrifuged at 3,000xg for 10 minutes to separate serum. The serum was stored at -80°C until analysis. gamma-glutamyltransferase, albumin, creatinine, total cholesterol, high-density lipoprotein (HDL-C), and triglyceride levels were analyzed using commercial kits from Olympus Diagnostics in an Olympus AU 2700 autoanalyzer (Beckman Coulter Inc., USA). Vitamin D levels were analyzed with an Advia Centaur XP hormone device (Siemens Medical Solutions Diagnostics, USA). CRP levels were

analyzed with a BN II System nephelometer (Siemens Healthcare Diagnostics, USA). The CRP/albumin ratio was determined by dividing the CRP level by the albumin level.

The AIP was calculated as log (TG/HDL-C), with units for TG and HDL-C in mmol/L.[13]

Advanced oxidation protein products (AOPP) were determined using the spectrophotometric method on a Shimadzu UV 1201V spectrophotometer (Shimadzu, Kyoto, Japan).[14] The AOPP levels of the samples were determined to be µmol/L in chloramine-T equivalents. The FRAP levels were studied as markers of total antioxidant capacity, which could determine the cumulative action among different individual antioxidants.[6] FRAP levels were measured with an in-house colorimetric assay in microplates with a Readwell Touch Elisa plate analyzer (Robonik PVT Ltd. Mumbai, India).[6]

STATISTICAL METHOD

Mean, standard deviation, median, interquartile range were calculated. The distribution of variables was tested using a Kolmogorov-Smirnov test. An independent sample t-test and a Mann-Whitney U test were used for the analysis of quantitative data. Categorical variables are shown as absolute frequencies (%), and analyzed using the chi-square test. Logistic regression analysis was used for risk factor analysis. Correlation analysis was performed using the Pearson test. $p<0.05$ was considered to be statistically significant. The SPSS 21.0 program e (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A power analysis was conducted using the MedCalc statistical software (MedCalc, Belgium) to reach a power of 95%. An overall sample size of 87 subjects was calculated with an a level of 0.05 and an effect size derived from previously reported serum vitamin D levels of 6±5.2 ng/mL for CSX patients and 11.9±7 ng/mL for control group.[9]

RESULTS

The mean age, gender, smoking history and BMIs were similar between groups (Table 1). The patient group had higher CRP/albumin ratios [1.42 (0.84) vs. 1.01 (0.36); p=0.01] compared to the control group. Vitamin D levels were lower (p=0.05) and FRAP levels were higher in the patient group compared to control group, respectively. The mean AOPP levels were 74 µmol/L (IQR: 12) in the control group and 83 µmol/L (IQR: 12; p=0.07) in the patient group.

A logistic regression was performed to ascertain the effects of CRP, FRAP CRP/albumin ratio and vitamin D. Increasing CRP/albumin ratio was associated with an increased likelihood of exhibiting CSX (Table 2).

TABLE 1: Demographic and laboratory results of CSX patients and controls.

	Control	CSX patients	p value
n	42	52	
Age (years)	53.1±7.3	53.6±7.5	0.73
Male/Female	21/21	31/21	0.37
BMI (kg/m^2)	28.1±4.1	29.6±4.7	0.39
Heart rate (bpm)	80 (8)	80 (8)	0.46
EF (%)	60 (5)	60 (5)	0.21
Systolic pressure (mmHg)	130 (15)	130 (29)	0.08
Diastolic pressure (mmHg)	80 (11)	79 (10)	0.54
Smoking (Yes %)	17 (40%)	20 (38%)	0.77
Diabetes (Yes %)	22 (52%)	31 (59%)	0.25
CRP (mg/L)	3.7 (0.7)	4.0 (2.0)	<0.01**
Total cholesterol (mmol/L)	3.83±0.98	3.52±0.96	0.12
HDL (mmol/L)	1.4 (0.65)	1.27 (0.54)	0.65
Trigliserid (mmol/L)	1.39 (2.72)	1.76 (1.04)	0.63
Creatinine (mg/dL)	0.80 (0.23)	0.81 (0.29)	0.22
Albumin (g/L)	3.3±0.7	3.1±0.9	0.27
CRP/albumin ratio	1.01 (0.36)	1.42 (0.84)	0.01*
AIP	0.14±0.29	0.11±0.30	0.75
Vit D (ng/mL)	14.8 (6.4)	11.2 (6.3)	0.05
FRAP (µmol/L)	921 (287)	948 (422)	0.02*
AOPP (µmol/L chloramine-T equivalents)	74 (123)	83 (120)	0.07

*p<0.05; **p<0.01; CSX: Cardiac syndrome X; BMI: Body mass index; EF: Ejection fraction; CRP: C-reactive protein; HDL: High density lipoprotein; AIP: Atherogenic index of plasma; Vit D: 25-OH-D vitamin; FRAP: Ferric reducing ability of plasma; AOPP: Advanced oxidation protein products.

TABLE 2: Univariate logistic regression analysis of separate parameters potentially associated with CSX.

Independent variable	Odds ratio (95% CI)	p value
FRAP (µmol/L)	1.002 (1.000-1.004)	0.024*
CRP (mg/L)	1.631 (1.098-2.425)	0.015*
CRP/albumin ratio	2.479 (1.036-5.932)	0.041*
Vitamin D (ng/mL)	0.966 (0.911-1.024)	0.248

*p<0.05; CSX: Cardiac syndrome X; FRAP: Ferric reducing power plasma; CRP: C-reactive protein; CI: Confidence interval.

There was a negative correlation between vitamin D and serum CRP to albumin ratio (r=-0.23, p=0.03). There were no correlations between vitamin D levels and any of the other parameters analyzed.

DISCUSSION

Vitamin D has anti-inflammatory and antioxidant properties, and its deficiency may pose a threat to the development of CSX.[9] We found that CRP and CRP to albumin levels were higher and vitamin D levels were lower in CSX patients than in the control group. CRP is a sensitive biomarker of chronic low-grade inflammation and a marker of vascular disease.[15] Accordingly, a number of studies showed higher CRP levels in patients with CSX than in healthy controls that highlighting the potentially important role that chronic inflammation plays in the pathophysiology of CSX.[16-21]

The relationship between vitamin D deficiency and cardiovascular disease has been investigated in many studies, which have yielded contradictory results.[22] We found lower serum vitamin D levels in CSX patients than in normal group. Similarly, a number of studies have shown decreased vitamin D levels in CSX patients compared to healthy controls.[9,23] Babür Güler et al. demonstrated that female patients with CSX have low levels of vit D and an abnormal blood pressure response to exercise.[23] Tarcin et al. not only demonstrated an association between vitamin D deficiency and endothelial dysfunction but also showed improvements in endothelial function after vitamin D replacement therapy.[24]

We found a weak inverse correlation between the CRP/albumin ratio, and vitamin D levels. To the best of our knowledge, there is no study that evaluates the relationship between the CRP/albumin ratio and vitamin D in patients with CSX. The CRP/albumin ratio is considered a more reliable indicator of systemic inflammation and has been found to be associated with disease severity in patients with acute coronary syndrome.[25-27] In the study of Sabanoglu and Inanc which included 355 patients, it was demonstrated that higher CRP/albumin levels were significantly associated with the severity of coronary artery disease and ischemia.[28] In addition, vitamin D replacement therapy in patients with CSX resulted in beneficial initial outcomes.[29]

Previous studies of CSX patients have examined FRAP, AOPP, lipid hydroperoxides, malondiadehyde and total antioxidant status, and have shown that oxidative stress is increased in CSX patients compared with healthy controls.[3,30-32]

We suggested that a number of events triggered by the interaction of inflammation and oxidative stress may make a contribution to in CSX. However, we found that AOPP levels (the biochemical parameter that reflects modification of albumin molecules by oxidative stress) were the same among the groups. CSX patients had significantly higher FRAP levels (an indicator of total antioxidant level). The FRAP method is based on the measurement of the ability of plasma to eliminate the effects caused by reactive oxygen species. A decrease in FRAP is observed at a later stage of oxidative stress, and is caused by the reduction of antioxidant defense mechanisms.[33] This finding advocates that compensatory mechanism involved in dealing with increased oxidant parameters in CSX patients. Similarly, Gawron-Skarbek et al., showed that men with coronary heart disease had higher FRAP values than healthy individuals; and suggested that in the early stages of these disorders, the antioxidant defense system responds to sustained oxidative stress by increasing its activity.[34]

In our study, patients with CSX had similar total cholesterol, HDL, triglyceride and AIP levels compared to the control group. Supporting our study, Aciksari et al. found no considerable variation in lipid ratios between CSX patients and healthy individuals.[35]

One constraint of this study was the limited number of patients. Additionally, we did not measure any other inflammatory proteins. Sources of variability in vitamin D status, such as patients' nutritional status, vitamin D supplementation, and seasonal differences were not included in the study. A single measurement of vitamin D may not reflect lifetime status. The present study was cross-sectional in nature. Therefore, a causal relationship between the vitamin D and inflammation in CSX patients can only be postulated It is particularly difficult to identify the

effects of confounding variables that might influence CRP and CRP/albumin ratio.

CONCLUSION

The reduction of vitamin D levels and systemic inflammation may make a contribution to the development of CSX.

Future studies are necessary to clarify whether vitamin D evaluation may represent a new approach for prevention of this important cardiological condition.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

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: *Yasemin Üstündağ;* ***Design:*** *Yasemin Üstündağ, Dursun Topal, Fahri Er, Kağan Huysal;* ***Control/Supervision:*** *Yasemin Üstündağ;* ***Data Collection and/or Processing:*** *Yasemin Üstündağ, Dursun Topal, Fahri Er, Kağan Huysal;* ***Analysis and/or Interpretation:*** *Yasemin Üstündağ, Dursun Topal, Fahri Er, Kağan Huysal;* ***Literature Review:*** *Yasemin Üstündağ, Dursun Topal, Fahri Er, Kağan Huysal;* ***Writing the Article:*** *Yasemin Üstündağ;* ***Critical Review:*** *Dursun Topal, Fahri Er, Kağan Huysal;* ***References and Fundings:*** *Yasemin Üstündağ, Dursun Topal, Fahri Er, Kağan Huysal;* ***Materials:*** *Yasemin Üstündağ, Dursun Topal, Fahri Er, Kağan Huysal.*

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