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ARAŞTIRMA / RESEARCH

Relationship between metabolic syndrome and vitamin D level in patients with ankylosing spondylitis

Ankilozan spondilit hastalarında metabolik sendrom ile vitamin D düzeyi arasındaki ilişki

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Abstract

Purpose: The purpose of this study is to reveal the relationship between the level of Vitamin D and the development of Metabolic Syndrome (MetS) in patients with Ankylosing Spondylitis (AS).

Materials and Methods: 67 AS patients were included in this cross-sectional descriptive study. Socio-demographic data, waist circumference and systolic blood pressure were evaluated. Fasting blood glucose, HDL cholesterol, Triglyceride and Vitamin D values were recorded. Diagnosis of MetS was made according to National Cholesterol Education Program's Adult Treatment Panel (NCEP/ATP III). Disease activity and quality of life were assessed.

Results: In the present study, a significantly negative correlation was detected between Vitamin D levels and MetS in AS patients. HDL levels and Vitamin D levels were significantly lower in patients with MetS. Multiregression analysis showed that MetS was positively associated with BMI, Triglyceride level, fasting glucose and negatively associated with HDL cholesterol and Vitamin D.

Conclusion: This study shows that vitamin D may have a role in the development of MetS in patients with AS. However, more studies are needed to explain the relationship between vitamin D and metabolic syndrome in patients with ankylosing spondylitis.

Keywords: Ankylosing spondylitis, anti-tumor necrosis factor-alpha, cardiovascular risk, metabolic syndrome, vitamin D

Öz

Amaç: Bu çalışmanın amacı, Ankilozan Spondilit (AS) hastalarında D vitamin seviyesi ile Metabolik Sendrom (MetS) gelişimi arasındaki ilişkiyi ortaya koymaktır.

Gereç ve Yöntem: Kesitsel tanımlayıcı tipteki bu çalışmaya 67 AS hastası dahil edildi. Sosyo-demografik veriler, bel çevresi ve sistolik kan basıncı değerlendirildi. Açlık kan şekeri, HDL kolesterol, Trigliserid ve Vitamin D değerleri kaydedildi. MetS teşhisi, Ulusal Kolesterol Eğitim Programının Yetişkin Tedavi Paneli'ne (NCEP / ATP III) gore yapılmıştır. Hastalık aktivitesi ve yaşam kalitesi değerlendirildi.

Bulgular: Bu çalışmada AS hastalarında Vitamin D seviyeleri ile MetS arasında anlamlı negatif bir ilişki tespi tedildi. HDL seviyeleri ve Vitamin D seviyeleri MetS'li hastalarda anlamlı olarak daha düşüktü. Çoklu regresyon analizi, MetS'nin BMI, Trigliserit seviyesi, açlık glikozu ile pozitif olarak ilişkili olduğunu ve HDL kolesterol ve Vitamin D ile negatif olarak ilişkili olduğunu gösterdi.

Sonuç: Bu çalışma, AS'li hastalarda MetS gelişiminde D vitamininin rolü olabileceğini göstermektedir. Bununla birlikte, ankilozan spondilitli hastalarda D vitamin ve metabolik sendrom arasındaki ilişkiyi açıklamak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: Ankilozan spondilit; anti-tümör nekroz faktör-alfa; kardiyovasküler risk; metabolic sendrom; vitamin D

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INTRODUCTION

Ankylosing spondylitis (AS) is a chronic and progressive inflammatory disease characterized by axial skeletal and sacroiliac joint involvement[1]. AS might also cause anterior uveitic, cardiac, renal, pulmonary and gastrointestinal involvement in addition to typical musculoskeletal system findings such as peripheral arthritis, and enthesitis[2]. The risk of atherosclerosis and cardiovascular disease is increased in patients with AS due to the presence of both systemic inflammation and other cardiac risk factors[3,4]. AS is associated with several cardiovascular manifestations. The inflammatory processes in AS may affect various structures of the heart. The most characteristic conditions are conduction defects and aortic insufficiency, and less commonly pericarditis, cardiomyopathy, and mitral valve disease. Genetic predisposition and decreased physical activity in AS also cause cardiovascular disease[5].

Metabolic syndrome (MetS), one of the factors associated with the risk of cardiovascular disease, is a common public health issue[6]. According to the US National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATP III), MetS is characterized by the presence of three or more of the following risk factors: (1) abdominal obesity (waist circumference >102 cm in men and >88 cm in women); (2) serum triglycerides ≥150 mg/dL; (3) HDL cholesterol <40 mg/dL in men and <50 mg/dL in women; (4) blood pressure ≥130/85 mmHg; and (5) fasting blood glucose >110 mg/dL[7]. Patients with MetS carry the risk of cardiovascular disease and diabetes mellitus. Also, there is an increased level of risk for conditions such as chronic kidney disease, gout and sleep apnea[8-10]. Previous studies have shown that MetS incidence increases in AS patients although it varies depending on the diagnostic criteria used; however, there is insufficient data regarding the associated factors.

The main role of Vitamin D is to maintain the balance of bone metabolism as well as many other functions in the body. Vitamin D receptors are found in more than 30 different cells including in the skeletal muscles, cardiac muscle and fatty tissue[11]. In recent years, the level of Vitamin D has been shown to be associated with several conditions such as atherosclerosis and insulin levels[11-13]. Vitamin D plays an important role in carbohydrate and lipid metabolism as reflected by its association with diabetes mellitus, MetS, insulin secretion, insulin resistance and obesity. Vitamin D regulates calcium homeostasis and calcium flux through cell membranes, and activation of a cascade of key enzymes and cofactors associated with metabolic pathways. Cross-sectional and observational studies reported inverse correlations between vitamin D status with hyperglycemia and glycemic control in patients with diabetes mellitus, decrease the rate of conversion of prediabetes to diabetes, and obesity[13]. There are few studies in the literature regarding the role of Vitamin D in the development of MetS in patients with AS. The purpose of this study is to propose an association between the level of Vitamin D and the development of MetS in patients with AS.

MATERIALS AND METHODS

Sample

67 patients who presented at Gaziantep University Faculty of Medicine Physical Medicine and Rehabilitation Department/Rheumatology outpatient clinic between January-December 2018 and were diagnosed with AS were enrolled in this cross-sectional descriptive study. Patients with ankylosing spondylitis were selected according to the Modified New York criteria. The Modified New York criteria include clinical and radiological criteria. The presence of one of the clinical and radiological criteria is sufficient for diagnosis.

Clinical criteria:

1. Low back pain and stiffness for more than 3 months which improves with exercise but is not relieved by rest.
2. Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
3. Limitation of chest expansion relative to normal values corrected for age and sex

Radiologic criteria:

1. Sacroiliitis grade 2 bilaterally or sacroiliitis grade 3-4 unilaterally[14].

Patients with ankylosing spondylitis were consecutively selected according to their admission to the outpatient clinic. 103 patients were evaluated for the study. 36 patients were excluded because they did not meet the inclusion criteria. Patients who had a history of inflammatory disease other than AS, Myocardial Infarction, Stroke and Angina and those who did not provide consent were excluded. Patients

were informed about the study and written informed consent was obtained from patients who accepted to participate in the study. The approval of the Ethics Committee of Gaziantep University was obtained for the study (2019/128) and the study was conducted in accordance with the principles set out in the Declaration of Helsinki.

Procedure

Parameters of all enrolled patients such as age, gender, height, weight, waist circumference and systolic blood pressure in the patient files were assessed and noted. Venous blood samples were taken in the laboratory after 12 hours of fasting and studied on the same day. Fasting blood glucose, HDL cholesterol, triglyceride, erythrocyte sedimentation rate (ESR), C-Reactive Protein and Vitamin D values were recorded. Serum levels of 25-hydroxyvitamin D [25(OH) D] were measured with a commercial radioimmunoassay kit (immune diagnostic systems, Boldon, UK). The serum levels of 30 ng/mL were considered as normal, < 20 ng/mL as deficiency, and 20.1 to 29 ng/mL as vitamin D insufficiency.

Clinical evaluation

A diagnosis of metabolic syndrome was made in patients who met at least three of the five criteria of the National Cholesterol Education Program's Adult Treatment Panel (NCEP/ATP III)[6]. All clinical evaluations were made by the same physician for the diagnosis of metabolic syndrome. Waist circumference (WC) was measured with an inelastic tape that was placed perpendicular to the long axis of the body directly on the skin with the body standing balanced on both feet and arms hanging at the side. The measurement was recorded in centimeters (cm) at the end of expiration, at the midpoint between the lowest rib and the highest point of the iliac crest on the mid-axillary line.

Blood pressure (BP) was measured by using the same sphygmomanometer in a sitting position after resting for five minutes. Systolic blood pressure above 135 mmHg, diastolic blood pressure above 85 mmHg or receiving antihypertensive treatment were considered hypertensive.

Functional Assesment

Functional evaluation was made by the same physician in the outpatient clinic during the patient examination. Disease activity and quality of life were assessed with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Quality of Life (AS-QoL) scale, respectively.

BASDAI

This scale conssits of an evaluation on a visual analogue scale (0–10) of fatigue, axial pain, peripheral pain, stiffness and enthesopathy. The Turkish validity and reliability study of the scale was conducted by Akkoc et al[15].

AS-QoL scale

The AS-QoL scale is an 18-item dichotomous patient-reported outcome measure allowing calculation of a total score ranging from 0 to 18, and was developed to assess the impact of interventions for AS on quality of life. The Turkish validity and reliability study of the scale was conducted by Duruöz et al[16] .

Statistical analysis

The data were represented using means ± standard deviation. Normal distribution of numerical variables was analyzed by using the Shapiro-Wilk test. The Student's t-test was used in the comparison of normally distributed numerical variables between the two groups, and the Mann-Whitney U test was used to compare variables that were not distributed normally between the two groups. The correlation between categorical variables and the correlation between digital variables were tested with the Chi-Square test and Spearman's correlation coefficient, respectively. Multiple logistic regression analysis was performed to investigate the effect of variables on metabolic syndrome. Age, Vitamin D, BMI, Trygliceride, HDL, Glucose was examined in multi regression analysis. The parameters to be examined in the multiregression analysis were determined by looking at the literature[17]. SPSS version 22.0 (Armonk, New York: United States of America IBM Corp.) was used in the analyses. $P<0.05$ was considered significant.

RESULTS

Of 67 patients included in the study, 55 (82.1%) were male and 12 (17.9%) were female. The mean age was 36.79±9.47 years and the mean duration of disease was 7.14±5.50 years. Of 67 patients included in the study, 23 (34.3%) were on conventional synthetic

Disease-Modifying Antirheumatic Drugs (csDMARD) and 44 (65.7%) were receiving biologic Disease-Modifying Antirheumatic Drugs (Anti-Tumor Necrosis Factor-Alpha [anti-TNF] therapy). 42 (62.7%) patients were HLA-B 27 positive while 25 (37.3%) patients were HLA-B 27 negative. The clinical and demographic data of the patients is provided in Table 1.

Table 1. Sociodemographic and clinical features of the patients

Variable	Mean ± SD
Age (year)	36.79 ± 9.47
Body Mass Index	28.15 ± 4.72
Time of diagnosis (year)	7.1 ± 5.5
Erythrocyte Sedimentation Rate (mm/h)	15.55±14.49
C-Reactive Protein (mg/L)	7.34 ± 9.46
BASDAI†	4.33 ± 1.95
AS-Qol ‡	8.49 ± 4.63
Tryglicerides (mg/dL)	149.83 ± 71.49
HDL (mg/dL)	44.56 ± 11.16
Waist circumference (cm)	99.76 ± 12.25
Glucose (mg/dL)	96.64 ± 18.52
Systolic blood pressure (mmHg)	113.13 ± 15.83
Diastolic blood pressure (mmHg)	72.01 ± 9.84
Vitamin D (ng/mL)	18.27 ± 8.44

†: Bath Ankylosing Spondylitis Disease Activity Index, ‡: Ankylosing Spondylitis Quality of Life; SD: Standard deviation

Twentythree (34.3%) of 67 AS patients included in the study had metabolic syndrome. MetS was not found to be significantly correlated with gender, drug use or HLA-B 27 positivity. There was a significant correlation between the presence of MetS and Vitamin D groups (p=0.027) (Table 2), and interestingly, Vitamin D levels of all patients who had MetS were below 30. This result shows the importance of vitamin d deficiency in the development of metabolic syndrome.

BMI, Triglyceride levels, waist circumference and fasting glucose values of patients who were diagnosed with MetS were significantly higher than those without MetS (p=0.001, p=0.001, p=0.001, p=0.003 respectively). The HDL and Vitamin D levels of the patients who were diagnosed with MetS were significantly lower than those without MetS (p=0.017, p=0.026 respectively). No significant difference was found in age, diagnosis time, ESR, CRP, BASDAI, ASQOL, and Systolic and Diastolic BP between the two groups (p>0.05) (Table 3).

There was a negative correlation between Vitamin D levels and BASDAI score (p<0.05). Vitamin D level was positively correlated with HDL levels (p<0.05). Vitamin D level was not found to be correlated with other clinical and demographic data (p>0.05).

Multiregression analysis showed that MetS was positively associated with BMI, Triglyceride level, fasting glucose (p=0.031, p=0.006, p=0.028 respectively) and negatively associated with HDL cholesterol and Vitamin D (p=0.03, p=0.033 respectively) (Table 4).

Table 2. Assessment of factors associated with metabolic syndrome

Variable		MetS				
		Negative		Positive		
		N	%	N	%	P
Sex	Male	39	88.6%	16	69.6%	0.059
	Female	5	11.4%	7	30.4%	
Treatment	csDMARD†	16	36.4%	7	30.4%	0.627
	Anti-TNF‡	28	63.6%	16	69.6%	
HLA-B27	HLA-B 27+	31	70.5%	11	47.8%	0.069
	HLA-B 27-	13	29.5%	12	52.2%	
Level of Vitamin D (ng/mL)	<10	4	9.1%	6	26.1%	0.027
	10-19.9	22	50.0%	13	56.5%	
	20-29.9	11	25.0%	4	17.4%	
	>30	7	15.9%	0	0.0%	

†: Disease-Modifying Antirheumatic Drugs, ‡: Anti-Tumor Necrosis Factor-Alpha

Table 3. Comparison of the groups with and without metabolic syndrome

	MetS	N	Mean ± Std. Deviation	P
Age (year)	Negative	44	35.45 ± 9.72	0.111
	Positive	23	39.35 ± 8.60	
Body Mass Index	Negative	44	26.85 ± 3.69	0.001
	Positive	23	30.63 ± 5.51	
Time of diagnosis (year)	Negative	44	7.52 ± 6.11	0.874
	Positive	23	6.41 ± 4.12	
Erythrocyte Sedimentation Rate (mm/h)	Negative	44	14.77 ± 15.96	0.065
	Positive	23	17.04 ± 11.32	
C- Reactive Protein (mg/L)	Negative	44	7.05 ± 10.54	0.164
	Positive	23	7.90 ± 7.16	
BASDAI†	Negative	44	4.50 ± 2.01	0.323
	Positive	23	4.00 ± 1.85	
ASQOL‡	Negative	44	9.25 ± 4.52	0.064
	Positive	23	7.04 ± 4.60	
Trygliceride (mg/dL)	Negative	44	123.52 ± 56.76	0.001
	Positive	23	200.17 ± 70.74	
HDL (mg/dL)	Negative	44	46.86 ± 11.65	0.017
	Positive	23	40.17 ± 8.81	
Waist circumference(cm)	Negative	44	95.15 ± 10.09	0.001
	Positive	23	108.56 ± 11.30	
Glucose (mg/dL)	Negative	44	91.45 ± 10.05	0.003
	Positive	23	106.56 ± 25.97	
Systolic BP (mmHg)	Negative	44	110.34 ± 12.54	0.260
	Positive	23	118.47 ± 19.96	
Diastolic BP (mmHg)	Negative	44	70.79 ± 10.22	0.163
	Positive	23	74.34 ± 8.82	
Vitamin D (ng/mL)	Negative	44	19.92 ± 9.01	0.026
	Positive	23	15.11 ± 6.24	

†: Bath Ankylosing Spondylitis Disease Activity Index, ‡: Ankylosing Spondylitis Quality of Life

Table 4. Multiple regression analysis between metabolic syndrome and possible variables

Variables	**Metabolic Syndrome**			
	p value	OR†	CI‡	
Age	0.337	1.071	0.931	1.234
Vitamin D (ng/mL)	0.033	0.846	0.725	0.986
Body Mass Index	0.031	1.274	1.022	1.590
Trygliceride (mg/dL)	0.006	1.031	1.009	1.054
HDL (mg/dL)	0.030	0.853	0.738	0.984
Glucose (mg/dL)	0.028	1.122	1.013	1.243

†: Odds ratio, ‡: Confidental Interval

DISCUSSION

In this study, in which we aimed to reveal the relationship between vitamin D and MetS in AS patients, a significantly negative correlation was detected between Vitamin D levels and MetS. HDL levels and Vitamin D levels were significantly lower in patients with MetS. There was a significant correlation between the presence of MetS and Vitamin D groups, and Vitamin D levels of all patients who had MetS were below 30.

The prevalence of cardiovascular disease and the risk of cardiovascular mortality increased in patients with AS[18, 19]. In recent years, it has been demonstrated that the MetS incidence in patients with AS was higher than the control group, which was revealed to be

associated with mortality. In their study, Maleci et al[20]. found MetS incidence to be 45.8% in patients with AS and 10.5% in the control group. Maia et al[21]. found MetS incidence to be 27% in their AS patients who were on anti-TNF therapy and 9.1% in the control group. Similarly, in the present study, MetS incidence was found to be highly positive in patients with AS.

The main function of Vitamin D is to maintain various metabolic functions by ensuring calcium and phosphorus balance in the body[22]. A Vitamin D deficiency is a serious problem worldwide and is associated with many diseases and with economic loss[23]. In their review, Zhao et al[24]. concluded that a Vitamin D deficiency was higher in AS patients than in healthy controls and Vitamin D levels were inversely associated with disease activity. In their study on the Turkish population, Erten et al[25]. found Vitamin D levels to be lower in AS patients than in the control group.

Kultur et al[26]. found that serum vitamin D receptor levels were higher in Turkish AS patients compared to healthy controls, and they found a significant relationship between serum vitamin D receptor level and BASDAI. Zhao et al[27]. demonstrated a negative correlation between Vitamin D levels and BASDAI scores in their patients with AS. Similarly, in the present study, Vitamin D levels were low and negatively correlated with disease activity. On the other hand, Cuzdan et al[28]. found that Vitamin D levels were low in both inflammatory conditions and non-inflammatory conditions. This might be attributed to the immunomodulatory effects of Vitamin D as well as decreased mobilization and reduced exposure to sunlight.

Song et al[29]. investigated the relationship between Vitamin D and MetS in 778 patients with postmenopausal osteoporosis. They found a negative correlation between Vitamin D levels and MetS, and that low Vitamin D levels were associated with approximately three times as much risk for the development of MetS. Similarly, Wang et al[30]. investigated the relationship between Vitamin D and MetS in 523 geriatric patients and found Vitamin D level statistically and significantly higher in those without MetS. Likewise, in the present study, a significantly negative correlation was detected between Vitamin D levels and MetS in AS patients. Although several studies investigated the correlation between Vitamin D and MetS, it is thought that there are multiple mechanisms that explain this correlation. Many studies show that Vitamin D increases insulin secretion and insulin sensitivity. Moreover, Vitamin D increases insulin sensitivity in fatty and skeletal tissues by also affecting calcium levels[31-33]. The impact of Vitamin D on blood pressure has also been demonstrated in many studies. Vitamin D deficiency is thought to be associated with high blood pressure due to the elimination of its suppressive effect on the renin-angiotensin system[34-36].

Another potential factor involved in the correlation between Vitamin D and MetS may be the anti-inflammatory action of Vitamin D. Vitamin D decreases IL-2 and IFN-ɣ levels and also inhibits the formation of atherosclerotic plaque by stimulating T helper cells[37]. Therefore, it is thought that a Vitamin D deficiency may play a role in the development of MetS, a cardiovascular risk factor. All these potential mechanisms appear to be possible mechanisms associating a Vitamin D deficiency with MetS.

This study had some limitations. First of all, it was cross-sectional. It did not include sufficient information about the factors that could affect Vitamin D levels. The sample consisted of patients who were taking medication and where the diagnosis time was belated. Another limitation of the study was the relatively low number of patients and absence of control group.

Consequently, present study shows that vitamin D may have a role in the development of MetS in patients with AS. Its results suggest that Vitamin D replacement may decrease the risk of cardiovascular disease in patients with AS.

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