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ORIGINAL ARTICLE

The Effect of 25-OH Vitamin D on Biochemical and IL-12 Parameters in Patients with Metabolic Syndrome

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Abstract

Introduction: The present study investigates the effect of 25-OH vitamin D replacement on blood pressure, as well as biochemical and IL-12 parameters in patients with metabolic syndrome (MetS), and whether a threshold for vitamin D exists in such effect.

Methods: This prospective study included 44 metabolic syndrome patients who presented to the Internal Medicine Clinic of Haydarpaşa Numune Training and Research Hospital. The patients had a mean age of 44.68±11.49 years; 65.9% (n=29) were female and 34.1% (n=15) were male. Biochemical tests were made for 25-OH vitamin D, glucose, HbA1c, triglycerides, HDL-K, LDL-K, BUN, creatinine, uric acid, calcium, albumin, leukocytes, neutrophils, lymphocytes, hemoglobin, C-reactive protein, and spot urine albumin/creatinine ratio, and blood pressure measurements were made before and after vitamin D replacement. In addition, IL-12 levels were measured twice using the ELISA method. A statistical analysis of the data was made using IBM the SPSS Statistics 22 (IBM SPSS, Türkiye) software package.

Results: A statistically significant decrease was noted in systolic and diastolic blood pressure and IL-12 levels after vitamin D replacement when compared to the pre-replacement levels ($p<0.001$, $p=0.008$, $p<0.001$). When the patients were divided into two groups based on 25-OH vitamin D levels (Group-1, 25-OH vitamin D ≥32 ng/mL; Group-2, 25-OH vitamin D <32 ng/mL) after vitamin D replacement, the mean IL-12 level was found to be significantly lower in the Group-1 patients than in the Group-2 patients ($p<0.033$). In addition, a positive correlation was identified between vitamin D replacement and serum levels of magnesium.

Discussion and Conclusion: These findings suggested that vitamin D replacement had blood pressure-lowering and anti-inflammatory effects in MetS patients. The threshold for the anti-inflammatory effect was found to be ≥32 ng/mL.

Keywords: Inflammation; metabolic syndrome; Vitamin D.

According to the guidelines of the Society of Endocrinology and Metabolism of Türkiye, Metabolic Syndrome (MetS) is an endocrinologic disorder accompanied with insulin resistance, abdominal obesity, glucose intolerance, or diabetes mellitus[1,2]. The prevalence of MetS in our country is 28%, and 40% in women[3]. 25-OH vitamin D plays an effective role in the immune system, besides the calcium metabolism, musculoskeletal system, cardiovascular system and glucose metabolism, and deficiencies may cause medium- and long-term health problems in such

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systems[4]. Insulin resistance has been demonstrated to be high in 25-OH vitamin D deficiency[5,6]. Several studies have been conducted into the effects of vitamin D on inflammation. Vitamin D suppresses the proliferative and inflammatory effects of monocytes and T-cells[7]. Abdominal obesity – one of the metabolic syndrome criteria – has been associated with chronic, systemic, and low-grade continuous inflammation. Leukocytes, C-reactive protein (CRP), TNF-α, and IL-6, among the inflammatory markers, have been found to increase with obesity. Adipose tissue releases and increases cytokines such as TNF-α, IL-6, and IL-8, which are related to cardiovascular disease in case insulin resistance and type 2 DM[8]. It has been suggested that cytokines play a role in the etiopathogenesis of metabolic syndrome, and that inflammatory cytokines are responsible for increased insulin resistance and plasma free fatty acids. Interleukin 12 is a cytokine with an important role in immunity and increases the cytotoxic activity of NK cells and CD8 cytotoxic T lymphocytes[9]. It has been determined that plasma concentration of IL-12 is increased in diabetes and diabetic nephropathy patients[10,11]. Furthermore, increased serum IL-12 levels have been reported in type 2 diabetes patients when compared to healthy controls in relation to body mass index (BMI), insulin, proinsulin, and HDL-K[12]. Hyperglycemia has been suggested to increase IL-12 gene expression in murine macrophages[13].

The present study investigates the effect of 25-OH vitamin D replacement on blood pressure, biochemical parameters and the IL-12 cytokine selected as an inflammatory marker in patients with MetS, and whether there was a threshold for vitamin D in such an effect.

Materials and Methods

Approval for the study was obtained from the Health Sciences University Haydarpaşa Numune Training and Research Hospital (Date: 10.06 2019, No: HNEAH-KAEK 2019/60-876), and signed consent forms were obtained from the patients. The study included patients aged 18–70 with a 25-OH vitamin D level of <30 ng/ml, who were not using vitamin D, but were diagnosed with MetS according to the IDF Criteria[14] and did not have overt diabetes or any other systemic or infectious disease that might cause acute or chronic inflammation, among those admitted to the Internal Medicine clinic of the above-mentioned hospital as inpatients or outpatients. Table 1 presents demographic data of the MetS patients, while Table 2 shows the distribution of the diagnostic criteria components of the MetS patients (Tables 1 and 2).

Table 1. Demographic characteristics of metabolic syndrome patients

	Metabolic syndrome patients (n=44)
Age (years)	44.68±11.49 (22–64)
Gender n,%	
Female	29 (65.9%)
Male	15 (34.1%)
Height (m)	1.70±0.85 (1.55–1.92)
Weight (kg)	89.04±14.84 (62–144)
Body mass index (kg/m^2)	30.60±4.59 (25.80–52.73)
Waist circumference (cm)	97.84±14.99 (82–140)
Systolic blood pressure (mmHg)	134.72±3.48 (125–140)
Diastolic blood pressure (mmHg)	85.68±4.51 (68–94)

Table 2. Distribution of diagnostic criteria components of metabolic syndrome patients

	n (%)
Abdominal obesity	44 (100)
High blood pressure	42 (95.5)
Low HDL-K	35 (79.5)
High triglycerides	30 (68.2)
High blood glucose	22 (50)

Biochemical tests were requested for 25-OH vitamin D, glucose, HbA1c, triglycerides, HDL-K, LDL-K, BUN, creatinine, uric acid, calcium, albumin, leukocytes, neutrophils, lymphocytes, hemoglobin, CRP, and spot urine albumin/creatinine ratio. The recorded physical examination findings included mean blood pressure in mmHg, waist circumference in centimeters, height in meters, body weight in kilograms, and body mass index in kilogram/height in meters squared. All measurements, records, information, and vitamin D measurements, as well as IL-12 measurements, were made twice, before and after 6 weeks of vitamin D replacement. Forty-four patients with a 25-OH vitamin D level of <30 ng/mL provided extra blood into one gel tube for IL-12 cytokine measurement in addition to the predetermined biochemical markers between 08:00 and 10:00 A.M. after a 12-h fasting period. The blood samples were delivered to the hospital's Immunology Laboratory within 2 h, centrifuged and stored at −20°C, and recorded in a digital environment. The same patients were administered 50,000 IUs of oral vitamin D replacement once a week for 6 weeks, after which the same procedure was repeated.

Glucose Hexokinase/G-6-PDH, BUN urease, creatinine alkaline picrate, and 25-OH vitD3 were studied with a Chemiluminescent Microparticle Immunoassay (CMIA), urine albumin (microalbumin) through the turbidimetric method,

and urine creatinine alkaline picrate and urine protein through the biuret method, using an Abbott Architect device. HbA1c was studied using the immunoturbidimetric method on an ARCHITECT c16000 device. Hemogram tests were made using a Mindray BC-6800 device. Blood levels of calcium, albumin, uric acid, HDL-K, LDL-K, and triglycerides were studied using the Abbott Architect device. Human IL-12 (p70) was studied with a PicoKine ELISA 96 wells/kit (Boster Biological Technology, CA; Catalog number: EK0421) on an MCL-2100C ELISA device. The data analysis and statistical analyses were performed using IBM SPSS Statistics 22 (IBM SPSS, Türkiye) software.

Statistical Data Analysis

The data analysis and statistical analyses were performed using IBM SPSS Statistics 22 (IBM SPSS, Türkiye) software. The normality of the parameter distribution was evaluated based on kurtosis and skewness values during the study data assessment. The study data were assessed using descriptive statistical methods (mean, standard deviation, and frequency) and with an independent samples t-test to identify any difference in the means between the two groups. The other tests used in the study included a Student's t-test, a Wilcoxon signed-rank test and continuity correction. $p<0.05$ was considered statistically significant.

Results

The study findings related to the effect of 25-OH vitamin D replacement on blood pressure, biochemical parameters, and the IL-12 cytokine selected as an inflammatory marker, in patients with MetS are provided in Tables 3 and 4. Table 3 shows the correlation between vitamin D levels before vitamin D replacement and demographic and biochemical parameters of MetS patients. Accordingly, the 29% positive correlation between vitamin D and magnesium levels was found to be statistically significant ($r=0.297$; $p=0.030$; $p<0.05$) (Table 3).

Table 4 shows the 25-OH vitamin D, glucose, HbA1c, triglycerides, HDL-K, LDL-K, BUN, creatinine, uric acid, calcium, albumin, leukocytes, neutrophils, lymphocytes, hemoglobin, CRP, spot urine albumin/creatinine ratio, and IL-12 values of the MetS-diagnosed patients included in the study from before and after the 6-week vitamin D replacement.

First, there was a statistically significant increase in the mean 25-OH vitamin D levels of the MetS-diagnosed patients after vitamin D replacement when compared to the pre-replacement levels ($p<0.05$). There was a statistically significant decrease in the mean systolic blood pressure levels of the MetS-diagnosed patients between the pre- and post-vitamin D replacement measurements ($p<0.05$). There was a statistically significant decrease in the mean diastolic blood pressure levels of the MetS-diagnosed patients between the pre- and post-vitamin D replacement measurements ($p<0.05$). There was a statistically significant increase in the mean albumin levels of the MetS-diagnosed patients between the pre- and post-vitamin D replacement measurements ($p<0.05$). There was a statistically significant decrease in the mean calcium levels of the MetS-diagnosed patients between the pre- and post-vitamin D replacement measurements ($p<0.05$). There was a statistically significant decrease in the mean IL-12 levels of the MetS-diagnosed patients between the pre- and post-vitamin D replacement measurements ($p<0.05$).

Table 3. Correlation between vitamin D levels before vitamin D replacement and demographic and biochemical parameters of metabolic syndrome patients

	r	p
Vitamin D – Age	–0.091	0.563
Vitamin D – Height	0.082	0.601
Vitamin D – Weight	–0.125	0.425
Vitamin D - Body mass index	–0.137	0.381
Vitamin D - Waist circumference	–0.030	0.849
Vitamin D - Systolic blood pressure	–0.066	0.676
Vitamin D - Diastolic blood pressure	–0.196	0.208
Vitamin D – Glucose	0.150	0.337
Vitamin D - HbA1c	–0.166	0.646
Vitamin D – ALT	0.198	0.214
Vitamin D - HDL-K	0.038	0.809
Vitamin D - LDL-K	0.028	0.860
Vitamin D – Triglycerides	0.198	0.203
Vitamin D – ALP	–0.444	0.199
Vitamin D – GGT	0.321	0.285
Vitamin D – Uric Acid	0.007	0.482
Vitamin D – BUN	–0.024	0.877
Vitamin D – Creatinine	0.213	0.170
Vitamin D – Albumin	0.030	0.852
Vitamin D – Calcium	–0.008	0.958
Vitamin D – Magnesium	0.297	0.030
Vitamin D – Leukocytes	–0.246	0.058
Vitamin D – Neutrophils	–0.234	0.068
Vitamin D – Lymphocytes	–0.132	0.203
Vitamin D – NLO	0.002	0.495
Vitamin D – Hemoglobin	0.212	0.089
Vitamin D – Platelets	–0.001	0.498
Vitamin D – AAO	0.043	0.409
Vitamin D – CRP	0.064	0.343
Vitamin D – IL-12	–0.014	0.465

Table 4. Comparison of demographic characteristics and biochemical parameters of MetS patients before and after vitamin D replacement

	Before vitamin Dreplacement	After vitamin D replacement	p
Weight (kg)	89.04±14.84	89.02±14.67	0.655
Body mass index (kg/m^2)	30.60±4.59	30.60±4.58	0.655
Waist circumference (cm)	97.84±14.99	97.70±14.87	0.083
Systolic blood pressure (mmHg)	134.72±3.48	131.72±8.13	<0.001
Diastolic blood pressure (mmHg)	85.68±4.51	84.56±4.01	0.008
25-OH vitamin D (ng/ml)	15.39±7.36	34.79±12.03	<0.001
Glucose (mg/dl)	97.34±9.70	97.40±12.02	0.861
HbA1c (%)	5.55±0.40	-	-
ALT (IU/L)	31.42±25.73	25.90±18.92	0.061
HDL-K (mg/dL)	41.95±7.27	42.77±8.99	0.454
LDL-K (mg/dL)	139.34±39.09	136.20±34.14	0.684
Triglycerides (mg/dL)	168.25±49.77	152.02±54.82	0.096
ALP (IU/L)	80.90±16.07	69.16±18.54	0.133
GGT (IU/L)	34.07±23.41	23.17±9.60	0.765
Uric Acid (mg/dL)	5.63±1.38	5.73±1.34	0.468
BUN (mg/dL)	12.54±3.11	13.38±3.08	0.179
Creatinine (mg/dL)	0.80±0.10	0.83±0.10	0.129
Albumin (g/dL)	4.41±0.28	4.48±0.23	0.049
Calcium (mg/dL)	9.45±.033	9.08±0.36	<0.001
Magnesium (mg/dL)	1.95±0.17	1.97±0.26	0.416
Leukocytes (10^3/mm^3)	7.76±1.72	7.73±1.83	0.687
Neutrophils (10^3/mm^3)	4.51±1.34	4.48±1.33	0.861
Lymphocytes (10^3/mm^3)	2.51±0.68	2.43±0.61	0.140
NLO	2.22±2.88	1.89±0.51	0.279
Hemoglobin (g/dL)	14.08±1.68	14.18±1.58	0.450
Platelets (10^3/mm^3)	269.93±76.38	271.54±64.32	0.811
AAO (mg/g creatinine)	29.79±58.89	48.54±113.92	0.310
CRP (mg/dL)	0.40±0.36	0.47±0.56	0.531
IL-12 (pg/mL)	1.64±4.93	0.58±2.17	<0.001

Discussion

A review of the biochemical and immunological effects of 25-OH vitamin D replacement in MetS patients reveals that vitamin D inhibits the release of inflammatory cytokines and suppresses the proliferative and stimulative abilities of monocytes and T-cells. Wieder-Huszla et al.[15] reported lower 25-OH vitamin D levels in Type 2 diabetic patients than in non-diabetic people. A study by Suárez-Álvarez et al.[16] in Mexico investigated the relationship between obesity-related parameters and the inflammatory marker IL-12 and reported that IL-12 levels were increased in the overweight and obese, thereby establishing a relationship of IL-12 with inflammation and obesity markers. Nikołajuk et al.[17] examined the association between IL-12 levels and lipid parameters in overweight and obese women, and established a statistically significant positive correlation between IL-12 levels and total cholesterol levels among such patients (r=0.32, p=0.042).

The study by Guillot et al.[18] demonstrated that Vitamin D suppressed the proliferative and stimulative abilities of monocytes and T cells. Vitamin D also decreases pro-inflammatory cytokines such as CRP (C-reactive protein), TNFa (tumor necrosis factor-a), interleukin-6, interleukin-1, and interleukin-8 during the regulation of anti-inflammatory cytokines such as IL-10. The study by Deluca et al.[7] reported that vitamin D reduced concentrations of inflammatory cytokines such as TNF-a and IL-6 and may also increase the release of such anti-inflammatory cytokines as IL-10. Laird et al.[19] conducted a study with 957 individuals to examine the association between vitamin D and immune markers of inflammation. Yalçın et al.[20] established a significant decrease in CRP and IL-6 levels, and in CRP/IL-10 and IL-6/IL-10 ratios with increasing vitamin D levels. The authors found the mean CRP level to be 4.20 mg/L, the

mean IL-6 level to be 2.29 pg/mL, the mean CRP/IL10 ratio to be 2.10, and the IL-6/IL-10 ratio to be 1.45 in a group with a 25(OH) vitamin D level of <25 nmol/L, while the mean CRP level was 2.00 mg/L, the mean IL-6 level was 1.45 pg/ml, the mean CRP/IL10 ratio was 1.11, and the IL-6/IL-10 ratio was 0.88 in the group with a 25(OH) vitamin D level of >75 nmol/l, which was a statistically significant difference ($p<0.05$)[20]. The study by Yarım et al.[21] established a positive association between 25-OH vitamin D levels and insulin sensitivity in normal-weight people with normal glucose tolerance and concluded that a low level of 25-OH vitamin D was an independent risk factor for MetS in large populations. Ahangar-Parvin et al.[22] demonstrated that IL-12 was closely associated with inflammation in MetS. Increased serum levels of IL-12 have been reported in type 2 DM patients when compared to healthy individuals in relation to BMI, insulin, proinsulin, and HDL-K, although the authors did not test whether a change in IL-12 levels occurred after administering vitamin D to the patients.

In the present study, all patients had abdominal obesity, while 30 (68.2%) had high triglycerides, 35 (79.5%) had low HDL, 42 (95.5%) had high blood pressure, and 22 (50%) had high fasting plasma glucose levels. Furthermore, we could find no statistically significant correlation between IL-12 levels, and demographic characteristics and biochemical parameters. When analyzing the MetS patients after dividing them into two groups based on IL-12 levels beofore vitamin D replacement (Group-1, IL-12 <0.75; and Group-2, IL-12 >0.75), the mean triglyceride level was 154.84±47.29 mg/dL in Group-1 compared to 187.61±47.77 mg/dl in Group-2, which was statistically significantly higher ($p=0.030$). In other words, elevated IL-12 level–as the inflammation marker–increases the level of triglycerides, and inflammation and triglycerides are in parallel with each other.

The mean vitamin D level and the mean IL-12 level of MetS-diagnosed patients before vitamin D replacement were 15.39±7.6 ng/mL and 1.62±4.87, respectively. After vitamin D replacement was administered to the patients, the mean vitamin D level was 34.79±12.03 ng/mL and the mean IL-12 level was 1.48±6.32. Accordingly, the vitamin D level was statistically significantly increased after vitamin D replacement, while the IL-12 level statistically significantly decreased. Accordingly, vitamin D and Il-12 followed a negative course as a result of replacement therapy. We determined IL-12 as the inflammation marker in our study and interpreted its decrease as a process to anti-inflammation, that is, improvement in MetS.

On establishing a significant decrease ($p<0.001$) in IL-12 levels after the 6-week vitamin D replacement in MetS patients, we carried out a detailed analysis to ascertain the critical vitamin D level affecting IL-12. For this purpose, we divided the study patients into two groups based on 25-OH vitamin D levels (Group-1, 25-OH vitamin D ≥32 ng/ml; Group-2, 25-OH vitamin D <32 ng/mL) after vitamin D replacement and found the mean IL-12 level to be significantly lower in the Group-1 patients than in the Group-2 patients ($p<0.033$). In other words, vitamin D had a greater effect on IL-12 when it was above 32 ng/mL, indicating a threshold value of 32 ng/mL.

On the other hand, our statistical analysis revealed a statistically significantly positive correlation between vitamin D and magnesium ($r=0.297$; $p=0.030$; $p<0.05$), although there was no correlation between vitamin D and calcium ($r=-0.008$; $p=0.958$; $p>0.05$). There was a statistically significant decrease in the mean calcium levels of the MetS-diagnosed patients between the pre- and post-vitamin D replacement measurements ($p<0.05$). There was a statistically significant decrease in the mean systolic and diastolic blood pressure levels of the MetS-diagnosed patients between the pre- and post-vitamin D replacement measurements ($p<0.05$). The link between the decrease in calcium level and the decrease in blood pressure as a result of vitamin D supplementation may be due to the prevention of secondary hyperparathyroidism.

Conclusion

These findings suggest that vitamin D replacement has an anti-inflammatory effect in patients with metabolic syndrome. The anti-inflammatory effect of IL-12 becomes more obvious when the 25-OH vitamin D level is above 32 ng/mL in a detailed statistical analysis, and therefore, we can consider the threshold for vitamin D to be ≥32 ng/mL.

Ethics Committee Approval: Approval for the study was obtained from the Health Sciences University Haydarpaşa Numune Training and Research Hospital (Date: 10.06 2019, No: HNEAH-KAEK 2019/60-876), and signed consent forms were obtained from the patients.

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