Association Between Elevated Serum Uric Acid and Vitamin D Insufficiency Among the Middle-Aged and Elderly Population

Orta ve İleri Yaş Hastalarda Artmış Serum Ürik Asit Düzeyi ile D Vitamini Eksikliği Arasındaki İlişki

ABSTRACT

OBJECTIVE: Vitamin D insufficiency might have a role in numerous diseases including autoimmune disease, cancer, diabetes mellitus, hypertension and heart diseases. The relationship between vitamin D insufficiency and hyperuricemia has been shown previously but there are conflicting results in studies.

MATERIAL and METHODS: A total of 1562 patients who had serum uric acid and vitamin D levels measured at the same time were enrolled. Patients who were on vitamin D replacement therapy, receiving calcium and/or allopurinol, or had gout and chronic kidney disease were excluded.

RESULTS: Hyperuricemic patients had significantly lower levels of serum vitamin D level compared with normouricemic patients ($p<0.001$) whereas there was no difference between the groups in terms of serum calcium, phosphorus, parathormone and alkaline phosphatase. Severe deficiency (25(OH) vitamin D <10) was significantly more common among patients with hyperuricemia ($p<0.001$). When vitamin D levels were analyzed according to age, a significant inverse correlation between vitamin D and serum uric acid level was found in decades 7 and 8. Age, eGFR and vitamin D level below 20 appeared as independent associates of serum uric acid levels.

CONCLUSION: These data suggest that hyperuricemia associates with vitamin D deficiency. Further studies are needed to understand the mechanism underlying this association and its potential clinical implications.

KEY WORDS: Vitamin D, Uric acid, Inflammation, Kidney function

ÖZ

AMAÇ: D vitamini eksikliği başta otoimmünite, kanser, diyabetes mellitus, hipertansiyon ve kalp hastalıkları olmak üzere birçok hastalıkla ilişkili olabilir. D vitamini eksikliği ile hiperürisemi arasında çelişkili sonuçlar daha önceki çalışmalarda gösterilmiştir.

GEREÇ ve YÖNTEMLER: Serum D vitamini ve ürik asit değerleri eş zamanlı bakılan hastalar çalışmaya dahil edildi. D vitamini replasman tedavisi alanlar, kalsiyum ve/veya allopurinol kullananlar, gut ve kronik böbrek yetmezliği (glomeruler filtrasyon hızı <60 ml/min) olan hastalar çalışmaya dahil edilmedi.

BULGULAR: Hiperürisemik hastaların serum vitamin D düzeyleri normoürisemik hastalara göre daha düşük olduğu görülmesine ($p<0.001$) karşın, gruplar serum kalsiyum, fosfor, parathormon ve alkalen fosfataz düzeyleri bakımından benzerdi. D vitamini düzeylerine göre değerlendirildiğinde ağır (vitamin D <10) düzeyde eksikliği olan hastaların daha çok hiperürisemik ($p<0.001$) grupta olduğu görüldü. Yaşa göre serum D vitamini ve ürik asit düzeyleri arasında anlamlı derecede negatif korelasyonun 7. ve 8. dekatlarda olduğu görüldü. Yaş, serum D vitamini düzeyinin <20 olması ve eGFR düzeyleri, serum ürik asit düzeyi ile anlamlı korelasyon gösterdiği görüldü.

SONUÇ: Çalışmamızda, hiperüriseminin D vitamini eksikliği ile ilişkili olduğu saptanmıştır. Bu ilişkiyi açıklayabilecek mekanizma ve bunun klinik açıdan etkilerine yönelik daha ileri çalışmalara ihtiyaç vardır.

ANAHTAR SÖZCÜKLER: D vitamini, Ürik asit, İnflamasyon, Böbrek fonksiyonu

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INTRODUCTION

Vitamin D plays a pivotal role in bone health and the regulation of serum calcium and phosphate levels. Accruing evidence in recent years showed that vitamin D might modify immune function, cell proliferation, differentiation and apoptosis. As such, vitamin D deficiency has been associated with numerous health outcomes, including rickets and osteomalacia, increased risk of fractures, cancer, autoimmune disease, infectious disease, type 1 and 2 diabetes, hypertension and heart disease (1). Naturally occurring vitamin Ds, cholecalciferol and ergocalciferol, are mainly obtained from sun exposure and to some extent from the diet. These prohormones undergo hydroxylation first in the liver to produce 25(OH) vitamin D and then in the kidney to produce the active form of the hormone, 1,25(OH)2 Vitamin D. 25(OH) D level reflects the general vitamin D reserves of the body and is closely related to sun exposure and/or proper dietary intake (2).

Similarly, interest in uric acid as a cardiometabolic risk factor has surged. Uric acid has been shown to be a propagator of oxidative stress and inflammation. Both clinical and experimental studies link hyperuricemia with the development of heart disease, diabetes mellitus, hypertension and renal disease (3-7). Uric acid has been shown to reduce conversion of 25(OH) D to 1,25(OH)2D. Hsu et al. (8) showed that in rats sodium urate infusion suppressed calcitriol synthesis and inhibited receptor binding affinity for DNA. More recent data suggest this may be mediated by the activation of pro-inflammatory pathways (9). Consistent with these findings, elevated uric acid levels have been associated with lower 1,25(OH)2D levels in individuals with gout and in kidney disease (10,11). Whether elevated serum uric acid levels are associated with low 25(OH)D levels remains controversial. Whereas some published data indicate that elevated uric acid levels are inversely related to 25(OH)D levels (12), other studies have shown no such association (13). Thus, we aimed to investigate the potential association of serum uric acid and 25(OH)D levels.

MATERIAL and METHODS

This was a cross-sectional study that was conducted in Istanbul Medeniyet University, Goztepe Research and Training Hospital. The local ethics committee approved the study protocol. We screened the hospital electronic database and extracted patients who had had serum uric acid, 25(OH)D and creatinine levels measured simultaneously between November 2013 and February 2014. Patients who were on vitamin D replacement therapy, receiving calcium and/or allopurinol, had gout and chronic kidney disease (glomerular filtration rate <60 ml/min) were excluded. Remaining eligible patients were included in the study. Demographic features, serum creatinine, calcium, phosphate, parathormone, 25(OH)D, alkaline phosphatase (ALP) and serum uric acid levels were recorded for each study participant. To avoid the seasonal changes in serum 25(OH) D levels, we arbitrarily selected the winter months for patient inclusion. Correlation of 25(OH)D levels and serum uric acid levels was studied in different age groups and sexes to determine the effects of hormonal status and age related changes in both parameters. Estimated glomerular filtration rate (eGFR) values were determined via Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

25(OH)D levels were measured using High Performance Liquid Chromatography (HPLC). Uric acid was analysed by an enzymatic (uricase, peroxidase) colorimetric test on a Roche Cobas otoanalyzer. Serum uric acid levels above 6.8 mg/dL and 6.0 mg/dL in men and women were accepted as "elevated serum uric acid level", respectively. 25(OH)D levels were stratified into the following groups; ≥30 ng/ml -normal, 20-29 ng/ml-mild deficiency, 10-19 ng/ml -moderate deficiency, and <10 ng/ml-severe deficiency-(insufficiency).

Statistical Analysis

Statistical analyses were performed using the SPSS software version 16. The variables were investigated using Kolmogorov-Smirnov test to determine whether or not they are normally distributed. Descriptive analyses were presented as median (25th-75th percentile) for the non-normally distributed and ordinal variables. The univariate analyses to identify variables associated with elevated serum uric acid levels were investigated using Chi-square, Student's t and Mann-Whitney U tests, where appropriate. For the multivariate analysis, the possible factors identified with univarite analyses further entered into the logistic regression analysis to determine independent predictors of elevated serum uric acid levels. Hosmer- Lemeshow goodness of fit and Nagelkerke R Square were used to assess model fit. A 5% type-I error level was used to infer statistical significance.

RESULTS

A total of 1562 patients (296 men (18.9%) and 1266 women (81.1%)) were included. Based on the above definition, 234 patients (14.9%) were found to be hyperuricemic. Patients with serum uric acid levels above upper limit of the reference values were older, and had lower eGFR values compared with patients with normal serum uric acid level. Hyperuricemic patients had significantly lower level of serum 25(OH)D level compared with normouricemic patients whereas there was no difference between the groups in terms of serum calcium, phosphorus, parathormone and alkaline phosphatase levels (Table I). When vitamin D levels were stratified into the abovementioned groups of vitamin D levels, severe deficiency (vitamin D < 10 ng/ml) was significantly more common among patients with elevated serum uric acid levels (Table II). Mean serum uric acid levels according to vitamin D groups are shown in Figure 1.

There was an inverse and significant correlation between serum uric acid and vitamin D level (r=-0.060, p=0.018). We also analyzed vitamin D levels according to age and gender, hence stratified whole patient population into decades and male

Table I: Comparison of 25 (OH) vitamin D, serum uric acid (SUA), Glomerular filtration rate (eGFR), parathyroid hormone (PTH), alkaline phosphatase (ALP), calcium and phosphate metabolism parameters between groups with normal and elevated serum uric acid.

	Elevated SUA (n=234)	Normal SUA (n=1328)	p
Age, years	63 (55-71)	54 (42-64)	**<0.001**
Male, n (%)	55 (3.5)	241 (15.4)	0.054
25-OH vitamin D	11 (7-18)	15 (8.5-25)	**<0.001**
Creatine (mg/dL)	0.92 (0.75-1)	0.75 (0.65-0.92)	**<0.001**
eGFR (mL/min/1.73m^2)	74.5 (59.9-90.2)	91.2 (75.5-105.6)	**<0.001**
Calcium (mEq/dL)	9.5 (9.2-9.7)	9.4 (9.1-9.7)	0.44
Phosphate (mEq/dL)*	3.52±0.53	3.50±0.55	0.68
PTH (pg/dl)	48.1 (34.8-66.3)	47.8 (36.1-63.3)	0.42
ALP (U/L)	73.5 (56-87.5)	68 (56-83)	0.14

* Comparison between groups was made by the Student - t test. Data are shown as median (25th-75th percentile). Comparison between groups was made by the Mann-Whitney U and Chi-square test. P value less than 0.05 was considered to show a statistically significant result (p< 0.05).

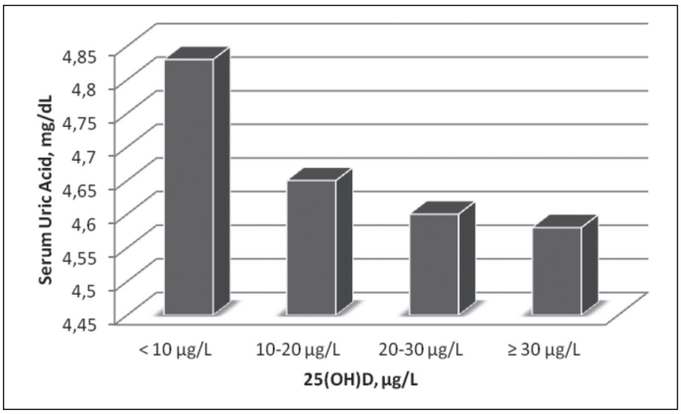

Figure 1: *Mean serum uric acid levels according to vitamin D groups.*

and female sexes. Vitamin D levels showed significant inverse correlation with serum uric acid level only in decades 7 and 8 (Table III, Figure 2). This inverse correlation was mainly driven by the inverse association between vitamin D and uric acid in female subjects in the 7th and 8th decades (Table III). There was no such correlation in male patients in the same decades. We also performed a linear regression analysis to determine the independent associates of serum uric acid. Age, eGFR and 25 (OH) vitamin D level below 20 ng/ml appeared as independent associates of serum uric acid levels (Table IV).

DISCUSSION

The salient finding of this current study is that patients with serum uric acid levels above the upper limit of laboratory reference had lower 25(OH) vitamin D levels compared with those of patients with normal serum uric acid levels. In addition,

Table II: Comparison of Vitamin D groups in patients with normal and elevated serum uric acid.

25-OH vitamin D	Elevated SUA (n=234)	Normal SUA (n=1328)
< 10 µg/L	107 (45.7)	439 (33.1)
10-19 µg/L	81 (34.6)	448 (33.7)
20-29 µg/L	22 (9.4)	231 (17.4)
≥ 30 µg/L	24 (10.3)	210 (15.8)

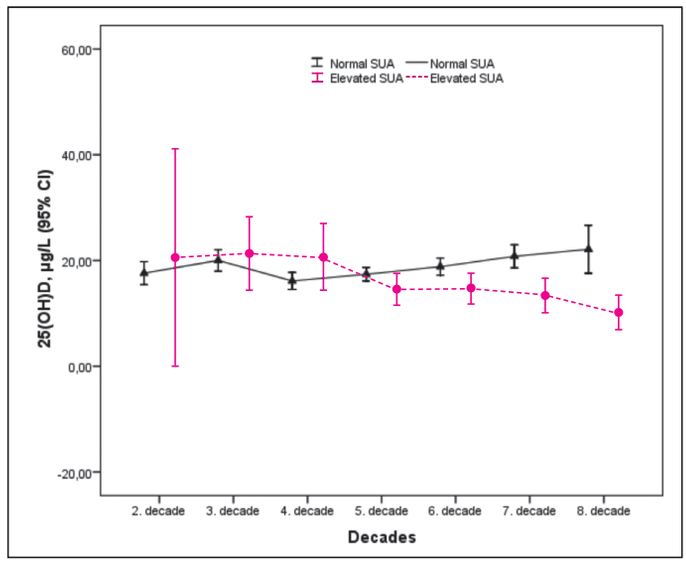

Figure 2: *Correlation of 25(OH) vitamin D level with serum uric acid level according to decade.*

Table III: Correlation between serum uric acid/creatine ratio and 25 (OH) vitamin D levels in subjects.

25(OH)vitamin D, μg/L	All	Male	Female
2nd decade			
r coefficient	0.082	0.095	0.086
p value	0.362	0.610	0.404
n count	127	31	96
3rd decade			
r coefficient	-0.097	-0.247	-0.063
p value	0.217	0.090	0.502
n count	164	48	116
4th decade			
r coefficient	0.076	0.207	0.055
p value	0.216	0.199	0.408
n count	269	40	229
5th decade			
r coefficient	-0.047	-0.003	-0.051
p value	0.346	0.983	0.343
n count	411	60	351
6th decade			
r coefficient	-0.078	-0.015	-0.091
p value	0.160	0.901	0.143
n count	329	67	262
7th decade			
r coefficient	-0.287	-0.096	-0.326
p value	<0.001	0.573	0.001
n count	194	37	157
8th decade			
r coefficient	-0.492	0.209	-0.596
p value	<0.001	0.492	<0.001
n count	68	13	55

Table IV: Linear regression analysis to determine independent associates of serum uric acid.

	OR	p-value	95% CI for OR	
			Lower	Upper
Age, years	1.03	**<0.001**	1.02	1.04
eGFR (mL/min/1.73m²)	0.97	**<0.001**	0.96	0.98
25(OH)vitamin D, μg/L				
< 10 μg/L	2.23	**0.002**	1.36	3.67
10-19 μg/L	1.57	0.08	0.95	2.62
20-29 μg/L	0.69	0.26	0.37	1.30

Nagelkerke R square=0.169, Hosmer and Lemeshow test=0.32

A backward elimination approach was used for the logistic regression, with entry at p value of <0.05 and removal at p<0.1. Performance of the model was assessed with classification plots, Hosmer and Lemeshow test and Nagelkerke R Square.

serum uric acid levels were inversely and significantly associated with serum vitamin D levels. Notably, this association was somehow modulated by age and most remarkable in the seventh and eighth decade of life. In fact, the correlation was driven by female patients in the 7th and 8th decade. Vitamin D remained an independent associate of serum uric acid levels even when controlled for kidney function (eGFR) and age.

The possibility of a direct causal relationship between uric acid levels and 25(OH) vitamin D levels is twofold. Both disorders are related directly or indirectly to a number of cardiometabolic risk factors. Thus, presence of hyperuricemia may lead to untoward clinical outcomes directly per se as well as indirectly by means of reducing serum 25(OH) vitamin D levels. Secondly, if a true causal association exists, treatment of one condition may indirectly alleviate the other disorder.

Since the early experiments carried out by Hsu and coworkers (8), little has been suggested to account for the exact relationship between vitamin D metabolism and uric acid. We now have some experimental evidence that serum uric acid can suppress 1 alpha hydroxylase, the enzyme that is needed to convert 25 (OH) vitamin D to its active form, 1,25 (OH)2 vitamin D. Chen et al. (9) showed that in rats hyperuricemia suppressed 1-αHydroxylase leading to lower 1,25(OH)2 vitamin D and higher parathyroid hormone (PTH) levels. The underlying mechanism of this interaction seemed to be mediated by the NFκB pathway. In the same study, the authors evaluated NHANES data and found that increased serum uric acid level was independently associated with increased odds for elevated PTH level. Interestingly this association remained significant when glomerular filtration was controlled as a confounding factor. However in this study, 25(OH)D levels were lacking. A recent study conducted on children found that serum uric acid, 25(OH) vitamin D and phosphorus were independent predictors of fibroblast growth factor 23 (FGF 23) (14). The authors also suggested a direct relationship between serum uric acid and FGF 23 levels independent of the relation between uric acid and PTH, based on their results. Due to the cross-sectional design, which factor comes first and affects the other cannot be surely determined from this study. On the other hand, from the results of this latter study, additional mechanisms beyond mere suppression of 1-α Hydroxylase by uric acid seem to play a role here. The findings of the latter study were confirmed in another study by Gutierrez et al. (15). The authors evaluated the data of Health Professionals Follow-up Study and showed that serum uric acid and PTH but not 25(OH) vitamin D levels were significantly higher in patients in the highest quartile of FGF23 compared with patients in the lowest FGF23 quartile. We did not study FGF23 in our study; however, serum phosphate and PTH level did not show any significant difference between hyperuricemic and normouricemic patients in our study.

A few earlier clinical studies, both in women, have shown serum uric acid and 25(OH) vitamin D to be inversely correlated.

Peng and colleagues (12) studied the association of vitamin D insufficiency and serum uric acid levels in Chinese Han women. The study showed that vitamin D insufficiency was significantly associated with elevated uric acid among postmenopausal but not premenopausal Chinese Han Women. The authors constructed a linear regression model in which diabetes, hypertension, metabolic syndrome, and smoker status were taken into account. The results showed an independent inverse association of serum uric acid and 25(OH) vitamin D insufficiency in postmenopausal women. However, the study did not take into account the renal function of the participants, which is an important determinant of serum uric acid levels. Moreover, calcium, phosphorus and PTH levels of the patients were not studied.

In a nested case-control study, in which basal 25(OH) vitamin D and development of incident hypertension were investigated, Forman et al. (16) found that among women who developed hypertension, serum uric acid and PTH were higher and 25(OH) vitamin D levels were lower compared with those women who remained normotensive. The latter two studies only recruited women. Of note, our study recruited both men and women with a wider age range than the previous studies. Similarly, we also found an inverse correlation between high serum uric acid and 25 (OH) vitamin D levels in females especially in elder females whereas we did not find an association between serum uric acid and 25 (OH) vitamin D levels in males. All aforementioned factors and a large sample-size increase the strength of our findings.

Some limitations deserve mention; first, this was a retrospective study, thus, although we showed an association between serum uric acid and 25(OH) vitamin D, a causal association cannot be drawn from our data. Though we did our best to select patients who were in agreement with inclusion criteria, due to the retrospective database search design, we might have included some inappropriate patients. We did not have any data regarding components of metabolic syndrome that may have an impact on serum uric acid levels.

In conclusion, serum uric acid and 25(OH) vitamin D had an inverse and significant association. This association seemed to be modulated by age and female gender in our patients. Further studies are warranted to elucidate the potential mechanisms of this association and the effect of treatment of hyperuricemia and 25(OH) vitamin D with long-term follow up and composite outcomes.

The authors declare that they have no conflict of interest.

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