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.

ABSTRACT

ÖZAM: D vitamini eksikliği başta otoimmünite, kanser, diyabetes mellitus, hipertansiyon ve kalp hastalıkları olmak üzere birçok hastalıka iliskili olabilir. D vitamini eksikliği ile hipertürisemi arasında çelişkili sonuçlar daha önceki çalışmalarla gösterilmiştir.

GENEÇ 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, gout ve kronik böbrek yetmezliği (glomeruler filtresi hızı <60 ml/min) olan hastalar çalışmaya dahil edildi.

Bulgular: Hipertürisemi hastaların serum vitamin D düzeyleri normoürisemi hastalara göre daha düşük olduğu görülmesine (p<0.001) karşın, gruplar serum kalsiyum, fosfor, parathormon ve alkalin fosfat düzeyleri bakımından benzerdi. D vitamini düzeylerine göre değerlendirildiğinde ağır (vitamin D <10) düzeyde eksikliği olan hastalar daha çok hipertürisemi (p<0.001) grupta olduğu görüldü. Yaşça göre serum D vitamini ve ürik asit düzeyleri arasında anlamlı derecede negatif korelasyonun 7. ve 8. dekadlarda olduğu görülü. Yaş, serum D vitamini düzeyinin <20 olması ve eGFR düzeyleri, serum ürik asit düzeyi ile anlamlı korelasyon gösterdiği görüldü.

Sonuç: Çalışmamızda, hipertüriseminin D vitamini eksikliği ile ilişkili olduğu saptanmıştır. Bu iliskiyi açıklayabilecek mekanizma ve bunun klinik açıdan etkilerine yönelik daha ileri çalışmalarla ihtiyaç vardır.

ANAHTAR SÖZCÜKLER: D vitamini, Ürik asit, İnflamasyon, Böbrek fonksiyonu
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 eligible patients based on the given inclusion criteria. 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 univariate 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
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,
A few earlier clinical studies, both in women, have shown serum uric acid and 25(OH) vitamin D to be inversely correlated.

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.
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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