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Correlation between Vitamin D and Uric Acid in Menopausal Women

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Abstract

BACKGROUND: Vitamin D deficiency and hyperuricemia are global health problems in postmenopausal women in which parathyroid hormone increases hyperuricemia incidence.

AIM: This research purpose was to determine correlation between Vitamin D and uric acid levels in postmenopausal women.

METHODS: This research is an observational analytic study with a cross-sectional study design conducted at University of North Sumatra Hospital and Network Hospital in Medan for 12 months on 40 postmenopausal women who met inclusion and exclusion criteria. The data will be analyzed descriptively to determine variables frequency distribution. Previously, normality test of numerical data is carried out. If the data is normally distributed, Pearson correlation test will be carried out, and if the data is not normally distributed, then Spearman correlation test will be used.

RESULTS: Mean Vitamin D of the sample was 23.11 ng/mL with a standard deviation (SD) 4.43 and median value 23.5 ng/mL, while the mean uric acid was 7.52 mg/dL with a SD 0.92 and median value 7.45 mg/dL. There is an inverse relationship between uric acid levels and Vitamin D, as evidenced by Pearson test correlation coefficient of –0.541 with p = 0.001.

CONCLUSION: There is an inverse correlation between Vitamin D and uric acid levels.

Introduction

Menopause is permanent cessation of menstruation as a result of decrease in follicular function and activity. Menopause is naturally defined after 12 consecutive months of amenorrhea, which is not due to any other pathological or physiological cause. Therefore, menopause can only be known with certainty after 1 year [1].

During menopausal transition, changes in estrogen levels affect not only vasomotor symptoms, sexual dysfunction, osteoporosis, and cardiovascular disease, but also uric acid levels. Serum uric acid is the end product of purine metabolism in humans. The most of circulating uric acid is filtered in kidneys, which excrete about 60–70% of total uric acid from body [2].

Serum uric acid levels increase substantially in postmenopausal women to nearly close to uric acid levels in men. However, hormone replacement therapy (HRT) in postmenopausal women causes a decrease in serum uric acid levels. High endogenous estrogen levels in premenopausal women or administration of exogenous estrogens in postmenopausal women are believed to increase uric acid clearance through efficient renal clearance thereby lowering serum uric acid levels [3].

Postmenopausal women have a high prevalence of diseases associated with Vitamin D levels, such as musculoskeletal disease and altered Vitamin D metabolism, reduced skin Vitamin D synthesis, or changes in body composition related to Vitamin D status and physiology [4].

Vitamin D deficiency and hyperuricemia are common global health problems. A previous clinical trial in postmenopausal women showed that parathyroid hormone (PTH) increased hyperuricemia incidence [5]. Impaired renal function can increase serum uric acid levels by decreasing renal excretion. This is due to reduced nephron mass and 1-α hydroxylase enzyme activity caused by decreased Vitamin D levels [2]. This indicated that there is a negative correlation between Vitamin D levels and increased uric acid levels in postmenopausal women. From description above, researchers wish to know correlation between Vitamin D and uric acid levels in postmenopausal women.

Methods

This research is an observational analytic study with a cross-sectional research design conducted at University of North Sumatra Hospital and Network Hospital in Medan city for 12 months. This research was carried out starting from ethical clearance approval from the ethics committee until number of samples was met.

The research sample was 40 menopausal women who met inclusion criteria, namely, women aged >50 years, women who had been menopause (no menstruation at least in 12 consecutive months), did not have a history of hysterectomy or oophorectomy that causes menopause, not pregnant or breastfeeding, willing to become a research subject after obtaining informed consent, and never received HRT; while not included in exclusion criteria, namely, not willing to be a research subject or loss to follow-up, patients with a history of gout arthritis or hyperuricemia since before menopause, patients with parathyroid and thyroid disease or disorders, patients taking drugs to lower uric acid levels in the last 14 days, patients taking Vitamin D supplementation in the last 14 days, patients taking drugs that affect Vitamin D levels (steroids and HMG Co-A reductase group) in the last 14 days, patients with a history of kidney disease, tumors, and heart disease.

Subjects interviewed included age, parity, menopause duration, sun exposure, use of sunscreen, and dress habits. Anthropometric data were also measured in form of weight, height, and upper arm circumference. Blood samples were taken to measure vitamin D levels and uric acid levels. All research data input into master table for further analysis using a computer statistical program.

Table 1: Research subjects characteristics

Variables	n (%)
Age (Mean ± SD)	53.58 ± 3.94
<50 years old	5 (13.9)
≥50 years old	31 (86.1)
BMI (Mean ± SD)	23.27 ± 3.67
Underweight	2 (5.6)
Normal	18 (50.0)
Overweight	3 (8.3)
Obese I	13 (36.1)
Obese II	0 (0.0)
Parity	
Nulliparous	1 (2.8)
Primiparous	7 (19.4)
Multiparous	20 (55.6)
Grande Multiparous	8 (22.2)
Menopause duration	
1–5 years	15 (41.7)
6–10 years	15 (41.7)
>10 years	6 (16.7)
History of hormonal contraception	
Yes	17 (47.2)
No	19 (52.8)

Statistic analysis

The data will be analyzed descriptively to determine variables frequency distribution. Previously, normality test of numerical data will be carried out. If the data is normally distributed, then Pearson correlation test will be carried out, if the data is not normally distributed, then Spearman correlation test will be used. A logistic regression test was also performed to determine basic subjects characteristics to predicting serum uric acid levels in postmenopausal women. $p < 0.05$ is considered statistically significant.

Table 2: Vitamin D and uric acid levels in menopausal women

Levels	Mean ± SD	Median
Vitamin D	23.11 ± 4.43	23.50
Uric acid	7.52 ± 0.92	7.45

Results

Mean sample age in this research was 53.58 with a standard deviation (SD) 3.94 and median 53.0. Mean body mass index (BMI) was 23.27 with a SD 3.67 and median BMI 22.5. The most of samples were multiparous as much as 20 samples (55.6%) had experienced menopause >5 years, without history of using hormonal contraception, as many as 19 samples (52.8%). The research subjects characteristics were shown in Table 1.

According to the data from Table 2, samples mean Vitamin D serum levels were 23.11 ng/mL with SD 4.43 and median value 23.5 ng/mL. Mean uric acid was 7.52 mg/dL with a SD 0.92 and median value 7.45 mg/dL.

Table 3: Menopausal women characteristics with Vitamin D and uric acid levels

Variables	Vitamin D (ng/ml)	p-value	Uric acid (mg/d)	p-value
Age		0.014		0.274
<50 years old	28.80 ± 1.09		7.32 ± 0.70	
≥50 years old	22.19 ± 4.07		7.55 ± 0.95	
BMI		0.076		0.004
Underweight	24.00 ± 0.00		7.00 ± 0.00	
Normal	22.83 ± 4.63		7.48 ± 0.84	
Overweight	26.67 ± 2.88		7.33 ± 0.28	
Obese I	22.54 ± 4.68		7.69 ± 1.17	
Parity		0.679		0.725
Nulliparous	30.00 ± 0.00		8.50 ± 0.00	
Primiparous	26.29 ± 3.68		7.14 ± 0.65	
Multiparous	22.55 ± 3.91		7.41 ± 0.98	
Grande Multiparous	20.88 ± 4.67		8.00 ± 0.81	
Menopause Duration		0.009		0.206
1–5 years	25.87 ± 3.27		7.44 ± 0.52	
6–10 years	22.40 ± 4.29		7.10 ± 0.89	
>10 years	18.00 ± 0.89		8.76 ± 0.71	
History of hormonal contraception		0.493		0.098
Yes	23.06 ± 4.84		7.65 ± 0.70	
No	23.16 ± 4.18		7.40 ± 1.08	

*Chi-square test, *Data were presented in Mean ± SD.

Normality analysis result using Kolmogorov–Smirnoff test showed that data were normally distributed for Vitamin D and uric acid levels. Thus, Pearson correlation test was conducted to analyze data. From this test, correlation coefficient value is –0.541 with p = 0.001. This negative correlation coefficient indicates an inverse relationship between Vitamin D and uric acid levels, which is statistically significant ($p < 0.05$) as shown in Tables 3 and 4.

Table 4: Correlation of Vitamin D and uric acid in menopausal women

Variables	Mean Value	p-value	R
Uric acid	7.56 ± 0.96	0.001	–0.541
Vitamin D	23.20 4.66		

*Korelasi Pearson test, *Data were presented in Mean ± SD.

Discussion

Thakkinstian study showed that mean age and BMI were 39.9 (SD = 6.6) years and 23.9

(SD = 3.8) kg/m^2, respectively, with mostly male gender (74.3%) [6]. Chen *et al*. enrolled 9220 Chinese adults, including 3681 males (age 55.57 ± 13.23 years old) and 5539 females (age 54.31 ± 12.83 years old). Serum uric acid levels were 352.07 ± 79.25 nmol/L and 269.29 ± 64.68 nmol/L in men and women, respectively. The hyperuricemia group also had a higher BMI rate than normal group (26.33 ± 3.45 vs. 24.46 ± 3.56) [2]. Among 1726 women (54,000 + 10.39 years) in Peng *et al*. study, 858 (49.71%) postmenopausal participants were <55 years old and 868 (50.29%) postmenopausal participants were >55 years old. Premenopausal women with elevated serum uric acid (≥314 mol/L, 90th percentile SUA in premenopausal women) and 87 postmenopausal women with elevated serum uric acid [≥357 mol/L, rank to –90] SUA percentile in postmenopausal women). BMI in patients under <55 years was 23.6 kg/m^2 in normal group and 25.3 kg/m^2 in hyperuricemia group, while in patients aged >55 years, BMI of patients was 24.6 kg/m^2 in normal group and 25.9 kg/m^2 in hyperuricemia group, this difference showed a significant result ($p < 0.001$) [5]. Hansen *et al*. showed that mean patient age was 61 years with weight 81 kg and height 163 cm [7]. The mean participants age in Kang *et al*. study was 57.3 6.5 years old (range, 36–81 years old), and mean serum uric acid level was 4.6–1.0 mg/dL (range, 2.2–8.0 mg/dL) [8].

There have been many studies examining correlation between Vitamin D levels and uric acid. A meta-analysis including seven studies showed that individuals with normal Vitamin D levels had significantly lower serum uric acid levels than patients with Vitamin D insufficiency with combined MD (mean difference) –0.33 mg/dl (95% CI, –0.61, –0.04), and also had significantly lower serum uric acid levels than patients with Vitamin D deficiency with combined MD –0.45 mg/dl (95%CI,–0.82,–0.08). The statistical heterogeneity of this meta-analysis was high with I^2 78% and 89%, respectively. This study concluded that patients with Vitamin D insufficiency and deficiency had higher uric acid levels than normal patients [9].

Peng *et al*. study 2013 that examined same thing specifically in postmenopausal women showed that among postmenopausal women, 25-hydroxy Vitamin D levels in samples with high uric acid, were lower than those with normal uric acid (median [interquartile range]) (35[28–57] versus 40[32–58], g/L; p = 0.006). Elevated uric acid was more common in participants with Vitamin D insufficiency compared with those with normal Vitamin D levels (16.50% vs. 8.08%; $p < 0.001$). The association between Vitamin D insufficiency and elevated uric acid was not significant among premenopausal women. Study samples with Vitamin D insufficiency were more likely to have elevated uric acid than those without Vitamin D insufficiency among postmenopausal women (OR, 95% CI: 2.38, 1.47–3.87). In his study, Peng *et.al*. also mentioned that Vitamin D insufficiency can activate parathyroid to induce PTH release which is thought to increase serum uric acid levels, although mechanism is not clearly elucidated. Therefore, an intensive experimental study is needed to determine whether Vitamin D supplementation can reduce serum uric acid levels in hyperuricemic conditions [5].

Another meta-analysis involving 32 studies also showed a similar relationship with two previous studies. This meta-analysis showed a significant combined beta-coefficient of serum uric acid levels at serum 25 (OH) D levels from three studies 0.512 (95% CI: 0.199, 0.825) and a significant combined probability ratio between Vitamin D deficiency and hyperuricemia 1.496 (95% CI: 1.141, 1.963). The combined mean difference in serum 25 (OH) D between groups with hyperuricemia and normouricemia was not significant which is 0.138 (–0.430, 0.707) ng/ml, and the mean difference in serum uric acid between categories 25 (OH) D was also not significant which is 0.072 (–0.153, 0.298) mg/dl between deficiency and normal group, 0.038 (–0.216, 0.292) mg/dl between insufficiency and normal group, and 0.034 (–0.216, 0.283) mg/dl between deficiency and insufficiency group. This study conclusion is increased, serum uric acid may lead to an increase in 25 (OH) D levels due to compensatory mechanisms, while Vitamin D deficiency is associated with hyperuricemia [10], [11].

A study conducted in Turkey stated that hyperuricemic patients had significantly lower serum Vitamin D levels than patients with normal uric acid levels ($p < 0.001$).This study also stated that there was an inverse and significant correlation between serum uric acid levels and Vitamin D (r = –0.060, p = 0.018). In this study, it is stated that there is some experimental evidence that serum uric acid can suppress alpha 1 hydroxylase action, an enzyme required to convert 25 (OH) Vitamin D to its active form, 1,25 (OH) 2 Vitamin D. The mechanism underlying the interaction this appears to be mediated through NFkB pathway [12].

Different results were obtained by Nimitphong *et al*. (2021) which based on regression analysis showed that changes in serum 25 (OH) D were not significantly correlated with changes in serum uric acid during period of Vitamin D supplementation (p = 0.76). However, changes in serum levels of 1,25-dihydroxy Vitamin D [1,25 (OH) 2D] concentrations were negatively correlated with changes in serum uric acid concentrations during Vitamin D supplementation after controlling age, BMI, baseline uric acid concentration, type of supplementation, Vitamin D, and changes in the concentration of 25 (OH) D variables (r = –0.33; p = 0.01). In his research, mechanism underlying the negative effects of uric acid due to Vitamin D is still unclear. Vitamin D is known to affect many physiological functions through its role in number of target genes. Genomic association studies have identified a number of genes that affect circulating uric acid concentrations, including ABCG2 gene, which encodes a high-capacity urate transporter gene in intestinal epithelium and in renal proximal tubular luminal surface cell epithelium. Other genes that have been reported to be associated with circulating uric acid concentrations are primarily renal urate transporters, such as SLC2A9, SLC17A3, and SLC22A12. Although it is thought that Vitamin D will affect the expression of these uric acid-regulating genes, there are no studies that support or deny possibility of this mechanism. It is also mentioned that decrease in uric acid that occurs during Vitamin D supplementation may be mediated through decrease in PTH concentration [10].

Chen *et al*. stated that increased levels of PTH can also reduce renal urate excretion, although exact mechanism is still unclear. PTH can also induce CYP27B1 expression and inhibit CYP24A1, as a result, 1,25 (OH) 2D production is increased. Therefore, hyperparathyroidism or PTH replacement therapy can affect uric acid and Vitamin D levels. In addition, Chen *et al*. also stated metabolic effect of estrogen on Vitamin D and serum uric acid. There is a different relationship between Vitamin D and serum uric acid levels in premenopausal and postmenopausal women. It is hypothesized that estradiol (E2) can affect uric acid levels through mechanisms involving excretion, secretion, and reabsorption in kidneys. High uric acid levels are thought to be associated with impaired kidney function. Impaired renal function may increase circulating serum uric acid concentrations by decreasing renal excretion. Reduced nephron mass and/or 1α-hydroxylase enzyme activity have been shown to be associated with decreased 1,25 (OH) 2D levels in patients with chronic kidney disease. As a 1,25 (OH) 2D substrate, 25 (OH) D levels may be increased [2].

Conclusion

There is an inverse relationship between Vitamin D and uric acid levels. A decrease in ovarian function causes decrease hormone estrogen production and physiological changes result in decrease of various organ functions and quality of life. Serum uric acid levels increase substantially in postmenopausal women due to decreased estrogen levels. High uric acid levels are thought to be associated with impaired kidney function which can lead to decreased levels of Vitamin D due to reduced nephron mass and 1-α hydroxylase enzyme activity.

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