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Parathyroid hormone and optimal vitamin D status in postmenopausal women

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Aim: Low serum vitamin D and calcium levels as well as high parathyroid hormone (PTH) levels are the most important risk factors in osteoporosis. The aim of our study was to estimate the optimal vitamin D status needed to prevent a rise in PTH concentrations in postmenopausal women.

Materials and methods: A total of 197 postmenopausal women who were at the menopausal period for at least 1 year and who had body mass indexes (BMIs) <25 kg/m2 were recruited between November 2011 and February 2012. Patients were evaluated by dividing them into 4 age groups (39–50 years, 51–60 years, 61–70 years, and >70 years).

Results: The mean age of patients was 60.8 ± 10.9 years. Serum 25-hydroxyvitamin D3 [25(OH)D3] levels were lower than 10 ng/mL in 94 patients (47.7%) and lower than 20 ng/mL in 167 (84.8%) patients. The mean vitamin D level was lowest in group 2 (51–60 years), but the difference was not statistically significant (P = 0.57). PTH levels were higher than 75 pg/dL in 52 patients, and 65.4% of those patients (n = 34) had vitamin D insufficiency (<10 ng/mL).

Conclusion: Vitamin D insufficiency was very common in our study population (84.8%). Treatment should be aimed at achieving a 25(OH)D3 level, at which no further suppression of PTH occurs. Further studies are needed to increase awareness among physicians that with optimal vitamin D levels a rise in PTH and subsequent bone loss is prevented.

Key words: Osteoporosis, menopause, vitamin D, parathyroid hormone

1. Introduction

Osteoporosis is defined as a progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures. It is a common disease that may lead to serious disability, increased morbidity and mortality, and significant healthcare costs (1).

The clinical relevance of osteoporosis is due to the fractures that it causes (2). The decrease in bone mineral density (BMD) is the most important cause of fracture risk. Among other factors, calcium and vitamin D deficiencies are important risk factors for a decrease in BMD, which can consequently induce osteoporosis. Loss of BMD is related to hormonal imbalance, ageing, environmental factors, life-style, and genetic predisposition. The above causes account for 50%–80% of individual variability in bone mass (3). Loss of bone mass in women occurs predominantly in the postmenopausal period due to disturbances in the balance between bone resorption by osteoclasts and bone formation by osteoblasts (4). Loss of BMD in women consists of 2 stages. It starts after the menopause with a rapid decrease in BMD. This process is estrogen-dependent and lasts approximately 5–10 years. Subsequently, it is followed by a constant stage that is age-related. The sudden estrogen-dependent loss of bone mass after the menopause accounts for 50% of the total loss in the thoracic and lumbar spine, and it is responsible for fractures of the cancellous bone such as compression fractures of vertebral bodies. Age-related loss of bone mass causes thinning of the bone trabeculae and loss of bone tissue in the cortical layer. As a result of this process the cortex becomes porous, which increases the susceptibility to fractures in the femoral neck (5).

Approximately 30%–50% of postmenopausal women have osteoporosis (6), and more than one-third of adult women will suffer one or more osteoporotic fractures in their lifetime (2). According to a study conducted in Turkey, vertebral fractures were the most common form of osteoporotic fractures by 11%, and the overall rate of osteoporotic fractures was 20.8% (7).

Important modifiable factors involved in the optimization of BMD include adequate dietary calcium intake and vitamin D status and life-style factors, including

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activity levels, parity, and age of menarche and menopause (8). Calcium balance studies have concluded that low dietary calcium and/or low absorption of calcium may be a major risk factor for the development of osteoporosis (9,10). Vitamin D plays a key role in calcium absorption and homeostasis, and there is increasing evidence supporting the role of vitamin D supplementation in the prevention of falls and fractures in elderly postmenopausal women (11,12).

Body weight is also significantly correlated with increased BMD; there is an inverse association with postmenopausal bone loss and bone fracture, as stated in the wider literature (13,14). Such evidence as increased aromatization of androgen to estrogens in adipose tissue, decreased sex hormone binding globulin levels, and high free sex steroids in obese women may illustrate the higher BMD (15).

The aim of our study was to estimate the optimal vitamin D status needed to prevent a rise in PTH concentrations in postmenopausal women.

2. Materials and methods

Postmenopausal women that presented to the family medicine outpatient clinics of Ankara Dışkapı Training and Research Hospital between November 2011 and February 2012 were recruited. Included were women who fit the following criteria: women who were menopausal for at least 1 year with body mass indexes (BMIs) <25 kg/m^2 and kidney function tests within normal ranges. Levels of calcium, phosphorus, alkaline phosphatase (ALP), 25-hydroxyvitamin D_3 [25(OH)D_3], and parathyroid hormone (PTH) were evaluated by dividing the patients into 4 age groups (group 1: 39–50 years, group 2: 51–60 years, group 3: 61–70 years, group 4: >70 years).

Assessment of vitamin D deficiency was based on measurement of serum levels of 25(OH)D_3 because of its long half-life. Serum 25(OH)D_3 was measured by using direct competitive chemiluminescence immunoassay (DiaSorin Liaison). The active metabolite, 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], was not used for this purpose, because levels decline only in severe deficiency and may not reflect levels in target tissues where it is generated. In order to avoid seasonal variations in vitamin D, the study was conducted in autumn and winter. Serum PTH was measured by using the intact-PTH 2-site sandwich immunoassay (Siemens Advia Centaur XP). Secondary hyperparathyroidism was defined as serum PTH concentration >75 pg/mL (upper limit of the reference range).

ALP, calcium, and phosphorus were measured by modified IFCC, Arsenazo III, and phosphomolybdate/UV, respectively (Siemens Advia 2400 Chemistry).

Statistical Package for the Social Sciences (SPSS) version 18.0 was used for statistical analysis. For normally distributed variables, descriptive analyses were performed, and values were expressed as mean ± standard deviation (SD). For variables that are not normally distributed [PTH, 25(OH)D_3], median and minimum–maximum values were used. Categorical data were expressed as percentages. For comparisons between 2 groups, comparison of means and independent samples t-test were used for normally distributed numerical variables. For the comparisons between multiple independent groups (the 4 age groups) 1-way ANOVA was used, and Tukey's test was used in post-hoc analysis. However, when the measurement variable was not normally distributed according to homogeneity of variances, the Kruskal–Wallis test was used. The chi-square test was used for categorical data. A P value of <0.05 was considered statistically significant.

3. Results

A total of 197 postmenopausal women were recruited. The mean age of the patients was 60.8 ± 10.9 (min.: 39, max.: 89) years. The BMIs of patients were between 18.5 and 24.9. Mean serum 25(OH)D_3, PTH, calcium, phosphorus, and ALP levels are shown in Table 1. Serum 25(OH)D_3 levels were lower than 10 ng/mL in 94 patients (47.7%) and lower than 20 ng/mL in 167 (84.8%) patients. The mean 25(OH)D_3 level was the lowest (11.6 ng/mL ± 6.8) in group 2 (51–60 years), but the difference was not statistically significant (P = 0.57) (Table 1).

Serum calcium levels were lower than 9 mg/dL in 23 patients, and among these patients 73.9% (n = 17) had vitamin D insufficiency (<10 ng/mL). The mean 25(OH)D_3 level of the patients with low serum calcium was 10.6 ± 10.9 mg/dL. That was lower than the mean 25(OH)D_3 level of the patients (13.5 ± 9.5 mg/dL) with normal serum calcium levels, but the difference was not statistically significant (P = 0.18).

PTH levels were higher than 75 pg/dL in 52 patients, and 65.4% of these patients (n = 34) had vitamin D insufficiency (<10 ng/mL). The mean 25(OH)D_3 level of the patients with high PTH was 10.3 ± 7.9. That was significantly lower than the mean 25(OH)D_3 level of the patients with PTH levels lower than 75 pg/dL (P = 0.01). The distribution of patients with vitamin D levels lower and higher than 10 ng/mL, according to PTH levels, is shown in Table 2.

Serum 25(OH)D_3 levels were between 10 and 20 ng/mL in 73 patients, and among these patients 18% (n = 11) had high PTH levels. On the other hand, almost all patients (98.1%) with high PTH had 25(OH)D_3 levels <25 ng/mL.

Table 1. Distribution of mean serum 25-hydroxyvitamin D_3 [25(OH)D_3], parathyroid hormone (PTH), calcium, phosphorus, and alkaline phosphatase (ALP) levels.

	Age groups ($\bar{X}$ ± SD)					
	Total (n = 197)	39–50 years (n = 36)	51–60 years (n = 70)	61–70 years (n = 50)	>70 years (n = 41)	P value
25(OH)D_3 (ng/mL)	13.1 ± 9.7	12.8 ± 10.4	11.6 ± 6.8	15.5 ± 13.6	13.2 ± 7.0	0.57
PTH (pg/mL)	65.3 ± 34.6	55.5 ± 25.9	62.8 ± 29.2	71.1 ± 36.9	71.0 ± 44.5	0.17
Calcium (mg/dL)	9.5 ± 0.6	9.3 ± 0.9	9.6 ± 0.4	9.5 ± 0.5	9.5 ± 0.5	0.15
Phosphorus (mg/dL)	3.5 ± 0.6	3.6 ± 0.7	3.5 ± 0.4	3.4 ± 0.5	3.5 ± 0.8	0.57
ALP (U/L)	85.1 ± 24.7	74.6 ± 29.4	90.4 ± 27.2	83.9 ± 18.9	87.0 ± 19.0	**0.01***

*Mean ALP levels were statistically significant in group 1 (39–50 years) and group 2 (51–60 years) (P = 0.01).

Table 2. Distribution of patients with 25-hydroxyvitamin D_3 [25(OH)D_3] levels lower and higher than 10 ng/mL according to parathyroid hormone (PTH) levels.

		25(OH)D_3		P value
		<10 ng/mL (n, %*)	>10 ng/mL (n,%*)	
PTH	<75 pg/dL	60 (30.5)	85 (43.2)	0.01
	>75 pg/dL	34 (17.3)	18 (9.1)	
TOTAL		94 (47.7)	103 (52.3)	

*Of total.

4. Discussion

Several studies have shown that low serum 25(OH)D_3 and calcium levels and high PTH levels are the most important risk factors in osteoporosis (14–17). Vitamin D insufficiency (defined here as <20 ng/mL) is very common in our study population (84.8%).

The major causes of vitamin D deficiency and insufficiency are decreased renal hydroxylation of vitamin D, poor nutrition, scarce exposure to sunlight, and a decline in the synthesis of vitamin D in the skin. Studies show that clothing habits and degree of exposure to sunlight are the major factors for vitamin D insufficiency in Turkish women (18–20). According to a study from Central Anatolia, vitamin D deficiency is very common (54.1% of the subjects) in the Turkish elderly population, especially among those living in old people's homes where there is significantly low exposure to sunlight (18). In our study, almost half of our study population (47.7%) had serum 25(OH)D_3 levels lower than 10 ng/mL.

Age-related changes in vitamin D and calcium metabolism increase the risk of vitamin D insufficiency and secondary hyperparathyroidism. Although longitudinal data have suggested a role of vitamin D intake in modulating bone loss in perimenopausal women, studies of vitamin D and calcium supplementation have failed to support a significant effect of vitamin D and calcium during early menopause (21). There is a clearer benefit in vitamin D and calcium supplementation in older postmenopausal women. Vitamin D intake between 500 and 800 IU daily, with or without calcium supplementation, has been shown to increase BMD in women with a mean age of approximately 63 years (22,23). In our study group, although the oldest age group was expected to have the lowest vitamin D levels, the lowest vitamin D level was in group 2 (51–60 years). This finding suggests that in the first decade of menopause, calcium and vitamin D supplementation is not enough. In Turkey, according to a declaration of health care implementation, osteoporosis

medications can be prescribed when BMD results worsen. Vitamin D levels are better in older age groups and this suggests that doctors probably replace vitamin D along with osteoporosis treatment. Unfortunately, postmenopausal women who have not yet developed osteoporosis are deprived of vitamin D replacement.

Many investigators have estimated optimal vitamin D status by examining the relation between serum 25(OH)D_3, which is the best estimate of vitamin D status, and serum PTH (24,25). The concept behind these estimates is that there is a threshold for serum 25(OH)D_3 below which secondary hyperparathyroidism (and bone loss) occurs. The serum concentration of 25(OH)D_3 below which PTH begins to rise has been estimated to be between 10 and 49 ng/mL (25 and 122 nmol/L) (22–28). Among calcium-sufficient women in midlife, almost half of the studies in the literature reported a threshold of 20 ng/mL (50 nmol/L) 25(OH)D_3 is needed to prevent a rise in PTH concentrations; one-third reported thresholds between 16 and 20 ng/mL (40 and 50 nmol/L) (24). In our study, the optimal serum 25(OH)D_3 concentration below which PTH begins to rise seems to be 25 ng/mL. This result is in keeping with the relevant literature. The wide range of these estimates may be related to the varied ethnicity and ages of the populations studied, varied calcium intake, the presence of illness that may affect PTH concentrations in the elderly, renal insufficiency, and lack of standardization of assays for 25(OH)D_3.

In the literature, there are studies from Turkey that investigate the effects of endogenous hormones and vitamin D deficiency on osteoporotic hip fractures (2,12,16). However, our study is the first that estimates the optimal vitamin D status needed to prevent a rise in PTH concentrations. This is an important strength of the current work.

The major limitations of our study are as follows: BMD assessments and the effect of medications were not properly evaluated. Although we do not know whether our patients were taking calcium or vitamin D supplements, our study is important because it shows vitamin D insufficiency is still common in postmenopausal women. In the treatment and follow-up, vitamin D levels of 10 ng/mL would not be enough to avoid secondary hyperparathyroidism. Serum 25(OH)D_3 thresholds of 25 ng/mL should be achieved.

It must be stated that the establishment of an optimal vitamin D intake is also important in regard to the noncalcemic effects of vitamin D that are thought to influence the prevention of some cancers, type 1 diabetes, heart disease, and falls in the elderly (29–31). Treatment should aim for the 25(OH)D_3 level at which no further suppression of PTH occurs (32).

In conclusion, calcium and vitamin D supplements are cost-effective medications in the prevention and treatment of osteoporosis. It is apparent that awareness of the efficacy of calcium and vitamin D in osteoporosis is still low among physicians, and further work is needed to increase awareness in order to prevent the rise in PTH and prevent bone loss by providing optimal vitamin D levels.

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