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ORIGINAL ARTICLE

Vitamin D status, dependence on age, and seasonal variations in the concentration of vitamin D in Croatian postmenopausal women initially screened for osteoporosis

Nadica Laktasic-Zerjavic · Mirko Korsic · Zeljka Crncevic-Orlic · Zdenko Kovac · Ozren Polasek · Dragica Soldo-Juresa

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Abstract Vitamin D deficiency is associated with secondary hyperparathyroidism, increased bone turnover, and bone loss, leading to increased risk for osteoporotic fractures. The objective of this study was to investigate the prevalence of inadequate (insufficient or deficient) serum vitamin D levels in Croatian postmenopausal women initially screened for osteoporosis. Assessment of 25-hydroxyvitamin D (25(OH) D) was performed in 120 Croatian postmenopausal women aged ≥50 years. Three cut-off levels of vitamin D inadequacy were investigated: <75, <50, and <30 nmol/L. Among the included patients, only 14.2% of women complied with diagnostic criteria for osteoporosis. A total of nine (7.5%) had vitamin D levels greater than 75 nmol/L, suggesting that 92.5% of postmenopausal women had inadequate vitamin D status. The prevalence of two different cut-off point groups was 63.3% (<50 nmol/L) and 14.2% (<30 nmol/L). Mean (±SD) serum level of 25(OH)D was 46.94 (16.77) nmol/L. Vitamin D was exhibiting declining values with increasing age (r=−0.28; P=0.002). The prevalence of vitamin D levels below 30 nmol/L was high in patient aged ≥65 years (23.8%). The highest mean level of vitamin D was detected in summer, with significant differences from spring and winter (P=0.015 and P=0.022, respectively). The results of this study indicate a high prevalence of vitamin D inadequacy in Croatian postmenopausal women initially screened for osteoporosis. High prevalence coupled with the rising recognition of potential clinical significance of the vitamin D inadequacy makes this highly interesting intervention

N. Laktasic-Zerjavic (✉)
University Department of Rheumatology,
Zagreb University Hospital Center,
Kispaticeva 12,
10000 Zagreb, Croatia
e-mail: nadica_laktasic@yahoo.com

M. Korsic
Department of Endocrinology,
University Department of Medicine,
Zagreb University Hospital Center,
Kispaticeva 12,
10000 Zagreb, Croatia

Z. Crncevic-Orlic
Department of Endocrinology,
University Department of Medicine,
Rijeka University Hospital Center,
Kresimirova 42,
51000 Rijeka, Croatia

Z. Kovac
University Department of Medicine,
Zagreb University Hospital Center,
Kispaticeva 12,
10000 Zagreb, Croatia

O. Polasek
Centre for Clinical Medical Research,
University Hospital "Sestre Milosrdnice",
Vinogradska 29,
10000 Zagreb, Croatia

D. Soldo-Juresa
University Clinic for Endocrinology and Metabolic Diseases
"Vuk Vrhovac",
Dugi dol 4,
10000 Zagreb, Croatia

target, suggesting that the attempts to increase the awareness on this issue are needed.

Keywords Body mass index · Osteoporosis · Postmenopausal women · Seasons · Vitamin D

Introduction

The past decade was marked by the increasing interest in vitamin D and its physiological functions. Results of various studies implicated that vitamin D has an important role in the skeletal and some nonskeletal functions in the human organism. Several stages of the lack of vitamin D were described, ranging from insufficiency to deficiency. Vitamin D insufficiency was described to cause an increase in the serum levels of parathyroid hormone (PTH), leading to increased bone resorption and consequently even osteoporosis. Severe vitamin D deficiency is known to cause rickets or osteomalacia. Poor vitamin D status in the body has also been implicated as a contributing factor to muscle weakness and propensity to falls, which together with negative influences on bone mineral density (BMD) increases the risk for osteoporotic fractures [1–4].

Vitamin D inadequacy has potential effects on other organ systems [5]. Presence of vitamin D receptor is detected in many tissues not directly involved in mineral metabolism. Adequate vitamin D status has been positively associated with better physical performance [6–8], lower cancer incidence and mortality [9, 10], decreased risk of cardiovascular and autoimmune diseases (such as diabetes type 1, multiple sclerosis, and rheumatoid arthritis) [11], and has beneficial effects in prevention of infection [5].

There are two main sources of the vitamin D in the organism. It can be obtained through the diet (plants are the source of the ergocalciferol, vitamin D2, while oily fish are the source of cholecalciferol, vitamin D3), or it can be synthesized in the skin, after exposure to the sun (vitamin D3). After hydroxylation in the liver into 25-hydroxyvitamin D (25(OH)D), second hydroxylation occurs in kidney into 1,25-dihidroxyvitamin D (1,25(OH)2D), forming the active metabolite which stimulates the calcium absorption from the gut [12].

25(OH)D is the main circulating metabolite of vitamin D, and it is considered as good indicator of the global vitamin D status in the body. Serum concentration of 25 (OH)D is under predominant influence of solar ultraviolet B (UVB) radiation (wavelength from 290 to 315 nm) [12].

There are no universally established guidelines as to which levels of 25(OH)D constitute adequacy. According to most surveys, adequate or sufficient vitamin D concentration is that equal or greater than 75 nmol/L (30 ng/ml), which is the lowest concentration of vitamin D able to prevent rise of PTH and may be necessary to optimize bone health. Concentrations between 50 and 75 nmol/L (20 and 30 ng/ml) are considered as vitamin D insufficiency, while concentrations below 50 nmol/L (20 ng/ml) are considered as vitamin D deficiency [13–15]. To assure bone health serum, 25(OH)D concentrations should be at least 50 nmol/L, which represents therapeutic target. Observational studies suggest that the optimal serum 25(OH)D level for nonskeletal benefits is greater than 75 nmol/L [16]. Additionally, previous studies have demonstrated that vitamin D status depends on the age, gender, and skin color and has a strong seasonal variation. Thus, old age, female sex, darker skin pigmentation, less sunlight exposure, improper dietary habits, and absence of vitamin D fortification are the main factors that are associated with lower 25(OH)D levels [17, 18]. All these results suggest that the possible extent of the 25(OH)D inadequacy may be greater than it was initially expected. Previous studies have demonstrated that the vitamin D status often shows inadequate levels in various populations, making this one of the highly interesting public health targets [18, 19].

The aim of this study was to investigate the prevalence of inadequate (insufficient or deficient) serum vitamin D levels in Croatian postmenopausal women, who were screened for osteoporosis.

Materials and methods

This study was based on the sample of adult, postmenopausal women (aged 50 years or over) from Croatia. Croatia is a European country located in southeast of Europe (latitude from 42° to 46°) with 4.7 million inhabitants. This study took place in Zagreb University Hospital Centre. We invited those patients for participation who were referred to our outpatient clinic for initial screening for osteoporosis. The patients were consecutively enrolled, with no influence on the referral by any of the researchers.

Women were eligible for this study if they had been postmenopausal for at least 1 year. Menopause was determined as the cessation of menstrual period either naturally or caused by bilateral ovariectomy. Women who previously received therapy for osteoporosis (bisphosphonates, strontium ralenate, selective estrogen receptor modulator, PTH, and hormone replacement therapy) were excluded from the study. Potential participants were ineligible if they had significant renal, hepatic, or bowel dysfunction (inflammatory bowel disease and malabsorption) and if they had uncontrolled thyroid or parathyroid gland dysfunction. After receiving information from the investigator, and being able to ask questions regarding all aspects of the study, all participants provided written informed consent before enrolment. The study was ap-

proved by the Ethical Board of the University Hospital Center-Zagreb, Zagreb, Croatia.

Fasting blood samples were centrally analyzed. Enzyme-linked immunosorbent assay was used for assessment of 25 (OH)D. Commercial immunodiagnostic kit (immunodiagnostic systems-IDS Ltd, from UK represented by IASON Zagreb d.o.o, Croatia) with direct assay technology was used eliminating the inconvenience of solvent precipitation and centrifugation. It enables quantitative determination of 25(OH)D (vitamin D2 and D3) in human serum or plasma with very high sensitivity (5 nmol/L from a small sample size) and good assay precision (intra-assay variability, <8%; inter-assay variability, <10%) and has wide measuring range (6–360 nmol/L).

Three different cut-off values of 25(OH)D inadequacy were assigned: <75, <50, and <30 nmol/L. Values of 25 (OH)D ≥75 nmol/L were considered as sufficient or adequate, indicating normal vitamin D status.

Additionally, BMD was measured to all patients. BMD at the lumbar spine (L1–L4) and proximal femur (total hip and femoral neck) was measured by dual-energy x-ray absorptiometry using a Delphi W (S/N 700483) instrument (Hologic, Inc., Waltham, MA, USA). BMD measurements were converted into T-scores. According to the World Health Organization guidelines, osteoporosis was defined as a value for BMD that is 2.5 standard deviations (SDs) or more below the young adult mean value for women (T-score ≥−2.5 SD), and osteopenia is defined as a T-score that lies between −1 and −2.5 SD.

All participants were asked about their physical activity in the past year if they are independent in activities of daily living and if they usually spend some time of the day outdoors. They were also asked about their smoking habits and educational level.

Statistical analysis

The data were presented as the absolute numbers and percentages for categorical variables, and averages and means for numerical data. Independent samples *t* test was used for the analysis of the numerical values in two investigated groups, while the analysis of variance was used if more than two groups were analyzed, with Tukey's post hoc test. The correlations were calculated using the Pearson's test. The critical age for the decline in vitamin D was calculated using the classification tree with age as a predictor and vitamin D concentration as the outcome variable (age was forced into the model, in order to classify even in case there are no significant cut-off points). The model was set at ten cross-validations and was based on the Chi-squared automatic interaction detector algorithm. The analysis was performed using Statistical Package for Social Sciences (SPSS) version 13, with significance set at $P<0.05$. Odds ratios for hypovitaminosis D across age groups were calculated by comparing the two elderly groups of examinees (60–69 and ≥70 years) with the youngest group (50–59 years). In case of the eldest group, since all cases had recorded hypovitaminosis, Peto odds ratio was calculated. This approach allows the calculation even if the cell frequency in one cell is zero, and it is suitable for unmatched case control studies [20]. The analysis was performed using SPSS version 13 (SPSS Inc, Chicago, IL, USA), with significance set at $P<0.05$.

Results

A total of 120 postmenopausal women were included in this study with an average age of 61 years (Table 1). Average menopause duration was slightly over 10 years (Table 1). Majority of women had osteopenia or normal BMD, while only 14.2% of women had osteoporosis (Table 1). The average BMI was 28.8 kg/m^2 (Table 1). All participants were independent in activities of daily living, and they usually spend some time of the day outdoors (data not shown). Most of participants were physically active in the past year (77.5%); thus, only 22.5% of them reported sitting as predominant type of daily activity last year. Mean serum concentration of 25(OH)D was below 50 nmol/L (46.94±16.77; Table 1).

The prevalence of 25(OH)D inadequacy among Croatian postmenopausal women was 92.5%, 63.3%, and 14.2% considering cut-offs of 75, 50, and 30 nmol/L (Table 2). All women with osteoporosis had inadequate 25(OH)D levels (<75 nmol/L; Table 2).

Vitamin D concentration declined with increasing age (Fig. 1); thus, correlation between age and serum 25(OH)D concentration was significant and negative ($r=-0.28$; $P=0.002$). The critical age at which the concentration declined most strongly was 59 years, with an average value of mean (±SD) 50.95±17.40 nmol/L for those who were younger or equal to 59 years and 41.87±14.34 nmol/L for those who were older than the critical age ($t=3.11$, $P=0.002$). When all patients were divided in three age groups (50–59, 60–69, and ≥70 years), 25(OH)D concentration differed significantly across the entire sample ($F=7.05$; $P=0.001$), being the lowest in group of patient aged 70 years or more (Table 3). Prevalence of vitamin D inadequacy was significantly higher in the eldest age group compared to the youngest age group (Fisher's exact test, $P=0.010$; Fig. 2). When considering only patients aged 65 years and more vs. the rest of the sample, prevalence of vitamin D deficiency reached 23.8% and 73.8% vs. 14.2% and 63.3% (cut-off of 30 and 50 nmol/L), and prevalence of vitamin D insufficiency reached 100% vs. 92.5% (cut-off of 75 nmol/L).

Table 1 The basic characteristics of the 120 Croatian postmenopausal women

Characteristic	Mean ± SD	Range	*N*	%
Age (years)	61.19±8.84	50–88		
Years since menopause (years)	11.40±8.89	1–44		
Body weight (kg)	74.80±12.02	49.0–114.2		
Body height (cm)	161.1±6.8	140.0–185.0		
Body mass index (kg/m^2)	28.86±4.74	19.1–44.0		
Serum 25-hydroxyvitamin D (nmol/L)	46.94±16.77	10.0–110.9		
Serum calcium (mmol/L)	2.43±0.10	2.15–2.73		
Lumbar BMD (g/cm^2)	1.01±0.18	0.60–1.46		
Lumbar BMD (T-score)	−0.65±1.43	−3.9–2.4		
Femoral neck BMD (g/cm^2)	0.83±0.15	0.59–1.32		
Femoral neck BMD (T-score)	−0.50±1.18	−3.3–3.9		
Total hip BMD (g/cm^2)	0.95±0.15	0.65–1.45		
Total hip BMD (T-score)	−0.06±1.22	−2.9–4.1		
Bone mineral density status				
Osteoporosis			17	14.2
Osteopenia			44	36.6
Normal BMD			59	49.2
Physical activity in the past year				
Predominately sitting			27	22.5
Predominately standing or walking			87	72.5
Predominately climbing or lifting			5	4.2
Predominately hard physical work			1	0.8
Smoking				
Never smoked			100	83.3
Past smoker			7	5.8
Current smoker			13	10.9
Education level				
Without primary school			1	0.8
Primary school			47	39.2
Secondary school			60	50.0
College or faculty			12	10.0
Total			120	100.0

The analysis of the seasonal pattern of vitamin D was performed using season rather than the month as the analyzed variable, due to the insufficient sample size for more detailed analysis. When all patients were divided into the four groups based on either spring, summer, autumn, or winter, measurement of vitamin D suggested significant differences across the entire sample (F=4.03, P=0.009), while the post hoc test indicated significant differences between spring and summer (P=0.015) and winter and summer (P=0.022), while the remaining pairwise comparisons were insignificant. The averages and SDs for the measured vitamin D concentrations were as follows: spring

Table 2 Prevalence of vitamin D inadequacy among Croatian postmenopausal women

Vitamin D group	All patients		Patients with osteoporosis		Patients with osteopenia or normal BMD	
	N=120		*N*=17		*N*=103	
	N	%	*N*	%	*N*	%
<30 nmol/L	17	14.2	5	29.4	12	11.7
<50 nmol/L	76	63.3	12	70.6	64	62.1
<75 nmol/L	111	92.5	17	100.0	94	91.3
≥75 nmol/L	9	7.5	0	0.0	9	8.7

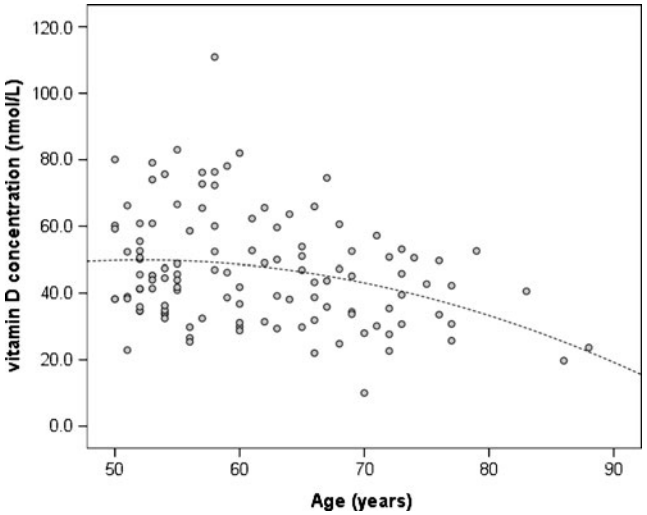

Fig. 1 Effect of age on serum 25(OH)D concentration. *Dashed line* is the quadratic trend line, showing progressively decreasing vitamin D concentrations with increasing age

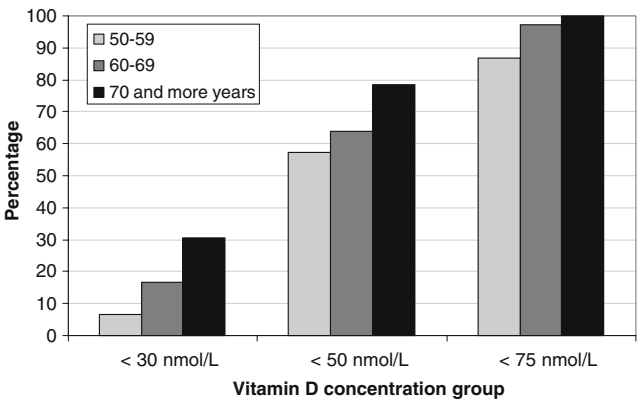

Fig. 2 Effect of age on prevalence of vitamin D inadequacy

41.35±15.82, summer 54.51±18.85, autumn 45.87±13.62, and winter 43.38±14.78. Thus, highest level of vitamin D was detected in summer.

We did not detect a significant correlation between BMI and serum 25(OH)D concentration (r=−0.13, P=0.157).

Discussion

The results of this study show rather high prevalence of the vitamin D inadequacy in Croatian postmenopausal women. This is interesting especially as the vitamin D concentrations seem to have different and sometimes unexpected patterns across various populations. The highest prevalence of vitamin D deficiency (levels below 25 nmol/L) was reported in South Asia and Middle East [18, 19], while Scandinavian countries within Europe have the highest concentrations, and the Southern Europe the lowest, contrary to what should be expected [19, 21]. This is probably caused by different exposure to sunshine, differences in the dietary intake of vitamin D, and the use of supplements. Difference in vitamin D status of postmenopausal women within European countries was confirmed in the recent study [22]. In that study, assessment of 25(OH)D was performed in 8,532 postmenopausal women with osteoporosis and osteopenia from nine European countries. Mean concentration of 25(OH)D was 61.2±27.2 nmol/L, with the lowest concentration detected in France and the highest in Spain. There was highly significant difference in 25(OH)D levels across all nine European countries (P>0.001). In the whole study population, the prevalence of vitamin D deficiency (levels below 50 nmol/L) was 32.1% [22].

In the study of Kraljevic et al., very high prevalence (97%) of vitamin D inadequacy was detected (levels below 75 nmol/L) in Croatian postmenopausal women receiving osteoporosis therapy (N=75) [23]. A total of 75% of women had vitamin D deficiency (levels below 50 nmol/L). Our study indicates a similar and high prevalence of vitamin D inadequacy in Croatian postmenopausal women who were initially screened for osteoporosis. The prevalence of 25(OH)D insufficiency (levels below 75 nmol/L) was 92.5%. The prevalence of vitamin D deficiency (levels below 50 nmol/L) was 63.3%, and the prevalence of more pronounced deficiency of vitamin D (levels below 30 nmol/L) was 14.2%, all being much higher than in most European countries. In only 14% of women, osteoporosis was detected which is rather low

Table 3 Effect of age on mean serum 25(OH)D concentration

Age (years)	25(OH)D nmol/L mean ± SD	Range	P value[a]
50–59	50.95±17.40	22.9–110.9	0.002
60–69	45.21±14.59	22.0–82.0	0.582
70 and more	36.64±12.51	10.0–57.2	0.001

[a] Each group vs. the remaining two

Statistical difference (F=7.05, P=0.001), age 50–59 vs. age 70+ (P=0.001), age 50–59 vs. age 60–69 (P=0.197), age 60–69 vs. age 70+ (P=0.108)

considering that they were referred for initial screening for osteoporosis. We did not influence the referral.

In conclusion, both studies indicate poor vitamin D status in population of Croatian postmenopausal women (initially screened for osteoporosis or being treated for osteoporosis). We can speculate on reasons. Croatia is located above 35° of latitude, which prevents the production of vitamin D in skin from October to March. Food is not fotificated with vitamin D in Croatia, and average dietary intake of oily fish is very low in general population. Also, supplements of vitamin D are usually prescribed only to the patients with established osteoporosis, and compliance is low. In our study, detected serum level of 25(OH)D was mean (±SD) 46.94 (±16.77) nmol/L, which is concordant with results of study conducted in Italy on similar study population, free-living postmenopausal women referred to an osteoporosis outpatient clinic for initial screening. They detected mean 25(OH)D level of 45± 20 nmol/L [24].

Generally, vitamin D status is negatively related to age. Older persons are at increased risk of vitamin D inadequacy due to the reduced capacity of older skin to synthesize vitamin D under the influence of ultraviolet light. The risk of vitamin D inadequacy could even be increased in institutionalized persons due to the lower sunshine exposure [25, 26]. In our study, correlation between age and serum 25(OH)D concentration was significant and negative ($r=-0.28$; $P=0.002$). The critical age at which the concentration declined most strongly was 59 years, and the prevalence of more pronounced deficiency of vitamin D (<30 nmol/L) was very high in patient aged 65 years and more (23.8%).

Seasonal variations in vitamin D status are expected in countries distant from equator. There is seasonal variation in UVB exposure because of the lower angle of the sun. Highest prevalence of 25(OH)D deficiency can be expected in late winter and early spring, thus concentrations of 25 (OH)D are highest in summer and early fall [27]. We also detected the highest level of vitamin D in summer with significant statistical difference between spring and summer and winter and summer ($P=0.015$ and $P=0.022$).

Obesity has been found to be associated with lower levels of serum 25(OH)D [27, 28] and higher levels of serum PTH [29, 30]. Underlying causes that have been suggested are less sun exposure due to the limited mobility in obese persons and higher storage of vitamin D in adipose tissue. The association between serum 25(OH)D and obesity is weaker if only anthropometric measures are used indicating specific role of adipose tissue [30]. In our study, only anthropometric measures were used (weight, height, and BMI), and we did not detect a significant correlation between BMI and serum 25(OH)D concentration ($r=-0.13$, $P=0.157$), which may be also due to the small sample size.

The results of this study are prone to several limitations. Firstly, the study was based on the relatively small sample size that had several implications, including the lack of possibility to assess seasonal variation based on the monthly data. Furthermore, the sample that was included in the present study and analyzed might not be representative for the entire population of Croatian postmenopausal women.

Conclusion

The results of this study suggest very high prevalence of inadequate vitamin D concentrations in Croatian postmenopausal women. Since the inadequate concentration of vitamin D may affect skeletal and nonskeletal physiological functions, this has to be considered as an important health risk factor, thus making this one of the public health priorities requiring a careful approach and widespread intervention efforts.

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