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Vitamin D in menopause: a cross-sectional study on 471 women

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ABSTRACT

Introduction. Vitamin D is intensively studied during the last years. The most useful instrument to assess the vitamin D status is serum 25-hydroxy vitamin D (25-OH D).
Material and method. This is a cross sectional study in menopausal women, between 2008 and 2013 with inclusion criteria: at least 1 year since menopause, age between 40 and 80 years; exclusion criteria: specific therapy for osteoporosis, previous diagnosis of osteomalacia and rickets, primary hyperparathyroidism.
Results. 471 subjects were: group 1 with osteopenia and osteoporosis (N = 328) and group 2 with normal DXA (N = 143) which were statistically significant (SS) different regarding the age, body mass index (BMI), years since menopause, bone markers osteocalcin and CrossLaps, with no SS differences between 25-OH D. In group 1: the linear regression coefficient (r) between alkaline phosphatase and 25-OH D was -0.14 (p = 0.01). In group 2: the BMI distribution showed: normal weighted subjects (BMI ≤ 24.9 kg/m^2, N = 22, 15%, av. 25-OH D = 19.69 ng/mL), overweighed females (BMI = 25-29.9 kg/m^2, N = 56, 39%, av. 25-OH D = 15.11 ng/mL), obese (BMI ≥ 30 kg/m^2, N = 65, 46%, av. 25-OH D = 12.11 ng/mL), with SS differences between any 2 subgroups. 25-OH D is not SS different between the subgroups based on decades of years since menopause, regardless the DXA score.
Conclusion. Based on our observations, a prevalent low level of vitamin D is registered in menopausal women regardless they have or not osteoporosis and in women with normal DXA the vitamin D level is lower in obsesses versus normal or overweighed patients.

Keywords: vitamin D, menopause, osteopenia, osteoporosis

INTRODUCTION

Vitamin D is an essential element in various medical aspects as autoimmune diseases, cancers, metabolic syndrome ant its components, quality of life with wellbeing aspects, and, obviously, the muscle - skeletal status. This last aspect becomes even more important on menopausal women. Recent data suggests a higher prevalence of vitamin D deficiency than initially considered, as pointed by the assessment of 25-hydroxy vitamin D (25-OH D). The genetic, environmental/geographical, socio-economical factors have an important contribution to the vitamin D levels.

Special at risk groups for vitamin D deficiency are related to certain pathology as chronic renal failure or rheumatoid arthritis. (1,2) The extreme ages are also at risk for hypovitaminosis D. (3) The reports for the menopausal women with or without osteoporosis pointed a high prevalence of vitamin D deficiency. (4) Our observations are related to this type of results. (5,6)

The aim of our original study is to analyze the level of vitamin D as reflected by the serum level of 25-hydroxy vitamin D (25-OH D) in menopausal women related to different clinical factors and central Dual-energy X-ray Absorptiometry (DXA).

MATERIAL AND METHOD

This is a transversal study (cross-sectional) on women in menopause who were evaluated at "C.I. Parhon" National Institute of Endocrinology from Bucharest, Romania, between 2008 and 2013.

The including criteria were:

- Romanian population (Caucasian women)
- At least 1 year since menopause (12 months of secondary amenorrhea)

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- The age between 40 and 80 years
- The correct central DXA achievement (according to the international standards for the lumbar spine)
- The written informed consent of each patient regarding the investigations included in the study.
- The excluding criteria were:
- Previous or current therapy for osteoporosis or for osteoporotic fracture risk reduction, except for vitamin D and calcium supplements (bisphosphonates as zoledronic acid, ibandronate, alendronate, risendronate; selective estrogen receptor modulators; strontium ranelate; calcitonin; terparatide)
- Previous or actual diagnosis of metabolic bone diseases as Paget's disease, osteogenesis imperfect, cancer or bone metastases, multiple mieloma
- Previous diagnosis of osteomalacia or rickets
- Previous or current hormonal substitution therapy (estrogens or estro-progestatives)
- Endocrine causes of low bone mineral density as Cushing's syndrome, active, untreated hyperthyroidism, and primary hyperparathyroidism.
- The patients' evaluation included:
- Anamnesis data focusing on years since menopause (that were calculated based on the period of time since the last menstruation), the risk factors for osteoporosis and significant diseases for bone pathology; the body mass index or BMI (using the formula weight in kilos dived to the square of the height in m^2 (kg/m^2)
- Central DXA assessment (GE Lunar Prodigy) at the lumar level that allowed the using of WHO criteria for normal DXA/ostepenia/osteoporosis by using the T-score
- The blood tests were performed by venous a jeun assay in the morning: 25-OH D (chemiluminescence), bone markers of formation as alkaline phosphatase (AP; colorimetric assay, COBAS C501 SC ROCHE), osteocalcin (OC; electro-chemiluminescence, COBAS C6000, SC ROCHE), bone marker of bone resorption: CossLaps (CL, electro-chemiluminescence, COBAS C6000, SC ROCHE). The usual biochemistry parameters (hemograme, total calcium, phosphorus, creatinine, urea, liver enzymes) were also assessed.

The statistical tests included the Excel database that was imported in SPSS21 (IBM C) where the actual analyze was performed. The statistical significance was at $p < 0.05$. The patients parameters was based on mean, standard deviation. The statistical functions included linear regression.

RESULTS

Three types of analyze were performed, based on three different types of groups:

A. The groups based on DXA results

B. The groups based on BMI values

C. The gropus based on years since menopause period of time

The entire cohort included 471 subjects.

A. Based on the lumbar T-score as revealed by lumbar DXA there was: group 1 with osteopenia or osteoporosis (T-score of less or equal to -1) included 328 patients (70%) and group 2 including patients with normal DXA included 143 subjects, representing 30% of the entire cohort. The patients' parameters from the two groups are listed in Table 1. The group with abnormal DXA results are statistically significant different from the group with normal DXA regarding the age, BMI, years since menopause (higher in group 2), and bone markers OC and CL, without any differences regarding the 25-OH D.

TABLE 1. *Anthropometric parameters and the bone metabolisms parameters in groups based on central DXA*

	Group 1	Group 2	Statistical significance
Age (years)	59.35 ± 7.88	54.08 ± 6.51	$p < 0.05$
BMI (kg/m^2)	27.98 ± 5.3	30.22 ± 6.17	$p < 0.05$
Years since menopause	12.9 ± 8.09	7.54 ± 5.49	$p < 0.05$
AP (U/L)*	78.65 ± 25.7	74.75 ± 6.16	p = NS
OC (ng/mL)**	0.52 ± 0.29	0.41 ± 0.24	$p < 0.05$
CL (ng/mL)***	25.51 ± 13.43	20.88 ± 12.8	$p < 0.05$
25-OH D (ng/mL) #	15.16 ± 7.87	14.81 ± 7.8	p = NS

*Normal: 38-105 U/L; **Normal: 15-46 ng/mL;
***Normal: 0.226-1.008 ng/mL; # Normal: 30-100 ng/mL)

In group 1: the linear regression coefficient (r) between the years since menopause and 25-OH D was -0.06 (p = 0.8); between AL and 25-OH D was -0.14 (p = 0.01), between OC and 25-OH D was -0.01 (p = 0.8), between CL and 25-OH D was -0.06 (p = 0.2). (Fig. 1)

In group 2: the linear regression coefficient (r) between the years since menopause and 25-OH D was 0.04 (p = 0.7); between AL and 25-OH D was

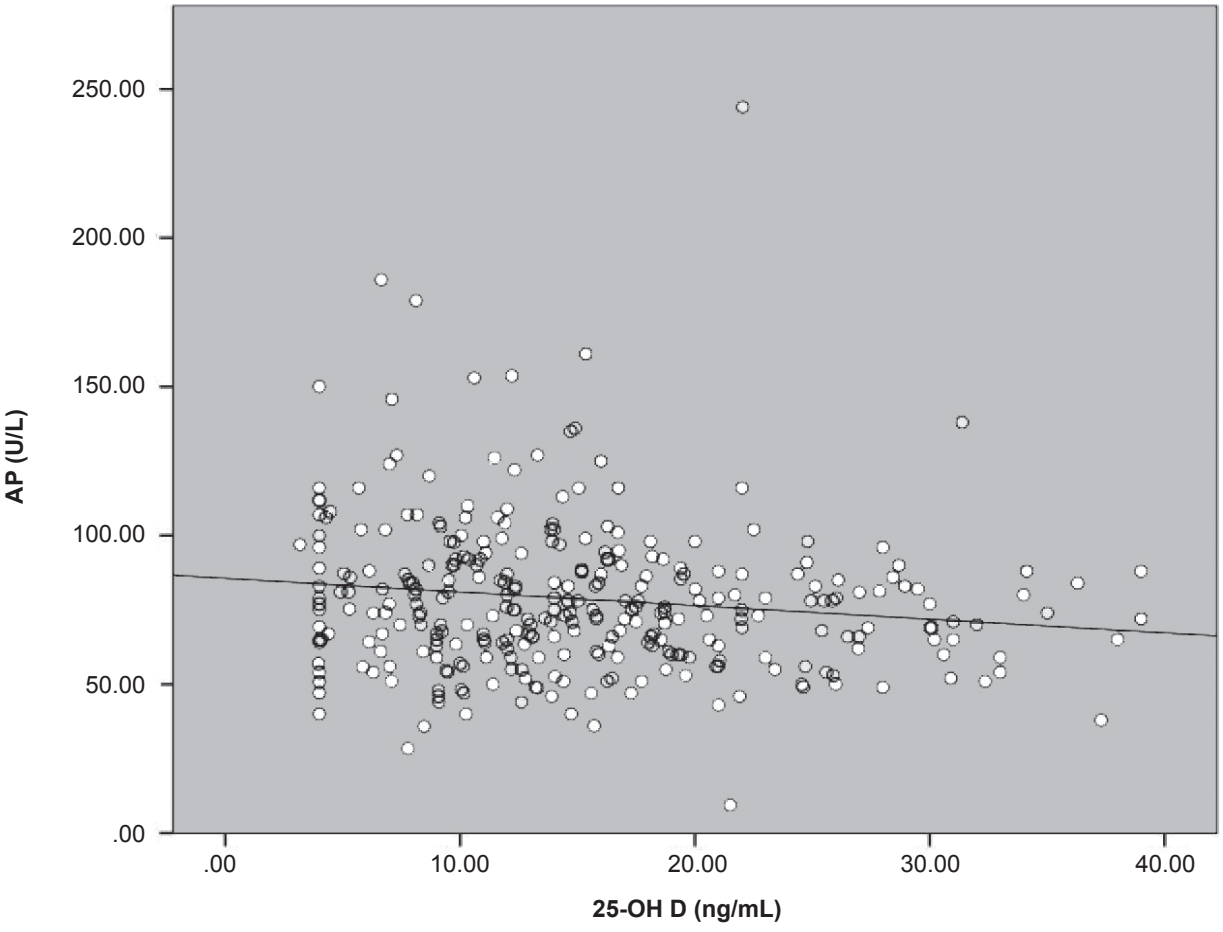

FIGURE 1. *The correlation between alkaline phosphatase and 25-hydroxy vitamin D in the group of osteopenia + osteoporosis (N = 328; r = -0.14, p = 0.01)*

0.15 (p = 0.1), between OC and 25-OH D was 0.17 (p = 0.06), between CL and 25-OH D was 0.13 (p = 0.17).

B. In group 1 (N = 328) the subgrops based on BMI showed: normal weighted (BMI ≤ 24.9 kg/m^2, N = 99, 30%, av. 25-OH D = 15.45 ng/mL), over weighted (BMI = 25-29.9 kg/m^2, N = 127, 39%, av. 25-OH D = 15.22 ng/mL), obese (BMI ≥ 30 kg/m^2, N = 102, 31%, av. 25-OH D = 14.8 2 ng/mL). The differences between 25-OH D in each BMI group were not statistically significant (p > 0.05).

In group 2 (N = 143) the subgroups based on BMI showed: normal weighted (BMI ≤ 24.9 kg/m^2, N = 22, 15%, av. 25-OH D = 19.69 ng/mL), over weighted (BMI = 25-29.9 kg/m^2, N = 56, 39%, av. 25-OH D = 15.11 ng/mL), obese (BMI ≥ 30 kg/m^2, N = 65, 46%, av. 25-OH D = 12.11 ng/mL). The differences between the 25-OH D levels in normal and over weighted groups was p = 0.01; between overweight and obese was p = 0.03; between normal weight and obese was p = 0.01.

C. The analyze based on the years since menopause allowed the re-ordering the patients in subgroups on decades of years since menopause. In group 1 (osteopenia + osteoporosis; N = 328): 1-10 years since menopause 149 patients, 11-20 years since menopause 119 patients, 21-30 years since menopause 51 subjects, 31-40 years since menopause 9 women. The parameters according to the subgroups based on years since menopause in Table 2. The statistical analyze between these groups did not find statistical significant differences between any of the two groups (p > 0.05). In group (normal DXA; N = 143): 1-10 years since menopause, 104 patients; 11-20 years since menopause with 33 patients, 21-30 years since menopause including 5 subjects, 31-40 years since menopause included one patient. The values corresponding to each decade of years since menopause are listed in Table 3. The statistical analyze between these groups did not show any relevant differences between any of the two subgroups (p > 0.05), except for the last subgroup which

was excluded from the analyze because of the small number of subjects.

TABLE 2. *The values of the 25-OH vitamin D based on groups of years since menopause (ng/mL) in patients with central DXA detecting osteopenia+osteoporosis (N = 328)*

Years since menopause	1-10	11-20	21-30	31-40
25-OH D (ng/ml, mean)	15.64	15.56	13.18	13.15

TABLE 3. *The values of 25-OH vitamin D based on groups related to the years since menopause (ng/mL) in patients with normal DXA (N = 143)*

Years since menopause	1-10	11-20	21-30	31-40
25-OH D (ng/ml, mean)	14.59	15.09	18.4	11.95

DISCUSSION

Based on this study, we noticed:

- The increased number of patients who were pre-selected in order to be bone diseases free (who were evaluated at "C.I. Parhon" National Institute of Endocrinology for different diseases, not necessarily for bone pathology) increases the accuracy of the data.
- The mean level of 25-hydroxy vitamin D is insufficient and is not different if the patient has normal DXA or not. These data are partially overlapped to those from literature based on different menopausal populations with a high frequency of hypovitaminosis D. (7)
- The only statically significant differences were found between the 25-OH D levels in normal DXA subjects related to the BMI: the women with normal weight have higher 25-OH D than women overweighed and obese while the overweighed subjects have higher 25-OH D than obese. These results confirm the theoretical and practical observations that associate the metabolic syndrome to the hypovitaminosis D, considering than obesity is the most frequent component of the metabolic syndrome. (8) In our study we did not extended the analyze to the others components of the metabolic syndrome.
- The analyze based on the decades of years since menopause shows values of 25-OH vitamin D that are not statistically significant different between any of the two proximate subgroups of years since menopause. There is not a trend line regarding the mean 25-OH D according to each decade of years since menopause (regardless normal DXA or not). The data from literature show a higher prevalence of hypovitaminosis D in older subjects possible correlated to food habits, malabsortion, co-morbidities, drugs that interfere with the vitamin D metabolism and reduced sun exposure. (9)
- The relationship between 25-OH D and bone markers shows a lack of correlation, except for alkaline phosphatase and 25-OH vitamin D in the group with osteopenia + osteoporosis ($N = 328$; $r = -0.14$, $p = 0.01$), a week negative correlation suggests that in patients with decreased bone mineral density, the lower vitamin D is, the higher alkaline phosphatase is. The results based the published studies show a high variability of the bone turnover markers pattern in the management of osteoporosis or hypovitaminosis D without any clear correlations. (10)

As limits of our study we mention that we did not have enough data regarding the parathormon levels in order to appreciate the secondary hyperparathyroidism in very low levels of vitamin D. Also, our study design did not included the analyze based on prevalent fragility fractures.

CONCLUSIONS

This cross sectional study of 471 women in menpause reveals a low level of 25-hydroxyvitamin D regardless the normal results of lumbar DXA; statistically significant lower levels of 25-hydroxyvitamin D in obese versus normal or overweighed subjects (with normal DXA); the levels of 25-hydroxyvitamin D are not correlated in a specific pattern to the bone remodeling markers

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