doi: http://dx.doi.org/10.11606/issn.1679-9836.v97i4p378-384

Prevalence of hypovitaminosis D and secondary hyperparathyroidism in postmenopausal women

Prevalência de hipovitaminose D e hiperparatireoidismo secundário em mulheres na pós-menopausa

Camila Varotto Baroncini[1], Thalles Pereira Regalado[1], Victória Zeghbi Cochenski Borba[2], Carolina Aguiar Moreira[3]

Baroncini CV, Regalado TP, Borba VZC, Moreira CA. Prevalence of hypovitaminosis D and secondary hyperparathyroidism in postmenopausal women / *Prevalência de hipovitaminose D e hiperparatireoidismo secundário em mulheres na pós-menopausa*. Rev Med (São Paulo). 2018 jul.-ago.;97(4):378-84.

ABSTRACT: *Introduction:* Vitamin D and parathyroid hormone (PTH) are two major modulators of mineral metabolism and the maintenance of calcium and phosphorus homeostasis. Vitamin D insufficiency is characterized by serum 25-hydroxy-vitamin D [25 (OH) D] concentration under 30 ng / mL and deficiency under 20 ng / mL. Such deficiency also increases PTH secretion and bone demineralization. This study aims to evaluate serum 25 (OH) D concentrations in postmenopausal women and correlates them with serum PTH concentrations and bone mineral density (BMD). *Methods:* Clinical, laboratory and densitometric data were collected from 114 postmenopausal women who participated in a previous clinical study. The patients recruited had a diagnosis of osteopenia or osteoporosis without previous treatment. Statistical analysis was carried out by the Statistical-Statsoft® software. *Results:* Patients were divided in osteoporotic 82.9% (n = 92) and osteopenic 17.1% (n = 19). The mean values of 25 (OH) D were 26.21 ± 9.69 ng / mL. Deficiency (16.05 ± 2.81 ng / mL) was identified in 32.4% of patients (n = 37) and insufficiency (24.71 ± 3.18 ng / mL) in 33.3% (n = 38). PTH presented a mean of 53.7 ± 20.1 pg / mL and 25% (n = 29) were above the reference values. Concentrations of PTH correlated inversely with 25 (OH) D ($p < 0.01$; rho = -0.2971). There was a negative correlation of femoral neck T-score in two situations: history of fractures and diagnosis of spinal fractures ($p < 0.01$). *Conclusion*: Hypovitaminosis D has been shown to be prevalent among these postmenopausal women with no seasonal influence. There was a negative correlation between PTH levels and 25(OH)D. The correlation between the history of fractures and BMD was found out, therefore, femur BMD can predict risk of fractures in other sites.

Keywords: Vitamin D deficiency; Parathyroid hormone; Bone diseases, metabolic; Postmenopause.

RESUMO: *Introdução*: A vitamina D e o paratormônio (PTH) são os principais moduladores do metabolismo mineral, contribuindo para homeostase do cálcio e fósforo. Considera-se como insuficientes níveis séricos abaixo de 30 ng/mL de 25-hidroxi-vitamina D [25(OH)D] e deficientes quando abaixo de 20 ng/mL. Tal deficiência também ocasiona aumento da secreção de PTH e, assim, há aumento da desmineralização óssea. Este estudo visa avaliar os níveis séricos de 25(OH)D em mulheres na pós-menopausa e correlacioná-los com as concentrações de PTH e a densidade mineral óssea (DMO). *Materiais e métodos*: Foram coletados dados clínicos, laboratoriais e densitométricos de 114 mulheres na pós-menopausa que participaram de estudo clínico prévio. As pacientes incluídas apresentavam diagnóstico de osteopenia ou osteoporose sem tratamento prévio. A análise estatística foi realizada pelo software Statistica - Statsoft®. *Resultados*: As pacientes foram classificadas em osteoporóticas 82,9% (n=92) e osteopênicas 17,1% (n = 19). A média dos valores de 25(OH)D encontrada foi 26,21 ± 9,69 ng/mL. Identificou-se deficiência (16,05 ± 2,81 ng/mL) em 32,4% das pacientes (n =

Oral presentation as Works of the Medical Course of UFPR, November 5-11, 2017. Presentation as a poster on the Journey of Clinical Medicine at Hospital de Clínicas UFPR, on September 30, 2017.

Federal University of Paraná (UFPR). Service of Endocrinology and Metabolism of Paraná - part of the UFPR Clinical Hospital Complex.
1. Fift-year medical students in Federal Universit of Paraná. Email: camilavbaroncini@gmail.com, thallesregalado@gmail.com.
2. Profesor, Department of Clinical Medicine, Federal University of Parana. Physician of the Bone Metabolism Unit of the Endocrinology and Metabology Service of UFPR. Email: vzcborba@gmail.com.
3. Ptrofesor, Department of Clinical Medicine, Federal University of Parana. Physician of the Bone Metabolism Unit of the Endocrinology and Metabology Service of UFPR.
Correspondence author: Carolina Aguiar Moreira. Av.Agostinho Leão Junior, 285. Alto da Gira, Curitiba, PR, Brazil. CEP: 80030-110. Email: carolina.aguiar.moreira@gmail.com.

37) e insuficiência (24,71 ± 3,18 ng/mL) em 33,3% (n = 38). Os valores de PTH apresentaram média de 53,7 ± 20,1 pg/mL. Destes, 25% (n = 29) apresentaram-se acima dos valores de referência. Os valores séricos de PTH correlacionaram-se negativamente com os valores séricos de 25(OH)D (p < 0,01; rho = -0.2971). Houve uma correlação negativa do T-score de colo de fêmur em duas situações: histórico de fraturas e no diagnóstico de fraturas de coluna (p < 0,01). *Conclusão*: Neste grupo de mulheres pós-menopausadas houve uma alta prevalência de hipovitaminose D, a qual se correlacionou negativamente com o PTH, não sendo observado relação com as estações do ano. Houve uma correlação entre a história de fraturas e a DMO, evidenciando que a DMO de fêmur pode predizer risco de fraturas em outros sítios.

Palavras-chave: Deficiência de vitamina D; Hormônio paratireóideo; Doenças ósseas metabólicas; Pós-menopausa.

INTRODUCTION

Vitamin D and parathyroid hormone (PTH) are the main hormones in bone metabolism[1]. Both, through a controlled feedback system, contribute to the homeostasis of calcium and phosphorus in the body. Low serum levels of calcium stimulates the release of PTH by the parathyroid glands and it acts on the skeleton, releasing ionized calcium (Ca2 +) and phosphate (HPO42-) into the bloodstream. In the kidneys, PTH stimulates the reabsorption of Ca2 + and decreases the reabsorption of HPO42-, while exerting positive feedback for the synthesis of vitamin D. This favores the intestinal absorption of calcium and contributes to adequate bone formation. Normal levels of serum calcium and adequate vitamin D concentrations are both inhibitory factors to PTH secretion[1]. Thus, both hormones have an impact on bone density and prevention of osteoporotic fractures[2].

Currently, there is a discussion regarding serum reference values of 25 (OH) D. The Brazilian Society of Endocrinology and Metabolism proposes that for the healthy population adequate values are > 20 ng/mL and for patients with risk factors for osteoporosis, the adequate values are > 30 ng/mL[3,4]. It is important to emphasize that the expected level of 25(OH)D is the necessary to maintain PTH at normal levels and to avoid the bone consequences of secondary hyperparathyroidism[5].

However, there is a documented hypovitaminosis D epidemic in the world literature[6]. Vitamin D deficiency is common in the elderly and in patients with osteoporosis and correlates with loss of bone mass and increased risk of falls and consequently fractures[7].

Therefore, this study aimed to evaluate the prevalence of hypovitaminosis D in a group of women who were treated at the Bone Metabolism Unit of the Department of Endocrinology and Metabolism of the UFPR (SEMPR) and to correlate the values of 25 (OH) D with serum PTH levels and bone mineral density.

MATERIALS AND METHODS

A retrospective cross-sectional observational study, in which the medical records of patients who participated in a selection for a clinical study performed during the period 2011 to 2012 at SEMPR were reviewed.

The inclusion criteria for both the clinical study and the present study were:

a) female gender above 50 years postmenopausal (absence of menstruation for at least 24 months);

b) osteopenia or osteoporosis detected by bone densitometry (osteopenia between -1.1 and 2.4 and osteoporosis below -2.5 of T-score).

As exclusion criteria, we considered:

a) patients with other osteometabolic diseases or history of medication use that interfere with bone metabolism (eg, corticosteroids, anticonvulsants, methotrexate);

b) patients who have received previous treatment for osteoporosis / osteopenia or vitamin D replacement.

The data collected included characteristics of the patients [age, weight, height, body mass index (BMI) and race], the history of atraumatic fractures (location and quantity) defined by the anamnesis, laboratory data (intact serum PTH, serum 25(OH)D, serum phosphate, serum calcium, total calcium corrected by albumin, urinary calcium, serum creatinine and urinary clearance), bone mineral density (BMD) of the total femur, femoral neck and lumbar spine, and the presence or absence of microfractures in the control spine radiography. The dates of blood collection for 25(OH)D dosage and the accomplishment of the exams were recorded and classified according to the season of the year. All data were recorded by the researchers in spreadsheet (Microsoft Excel®).

Statistical analysis was performed using the software (Statistica - Statsoft ®). The mean, standard deviation, maximum, minimum and median of the quantitative variables were calculated. Patients were classified separately according to bone densitometry and serum levels of 25(OH)D and PTH. Statistical tests were performed according to the nature of the variables and types of analyzes required. Spearman's correlation analysis was used to evaluate the correlation between 25 (OH) D and PTH concentrations, and each of them with laboratory and densitometric data. The Kruskal Wallis test was used to verify PTH and 25(OH)D in relation to qualitative variables. Fisher's exact and Chi-square tests correlated qualitative variables with each other. Student's and Mann-Whitney's t-tests correlated the quantitative variables of normal distribution [BMI, age, PTH, 25(OH) D and other laboratory and densitometric data] with the presence of fractures and BMD classification in osteopenia/ osteoporosis - each variable was analyzed separately. The level of significance was considered from 5% and the sample calculated to obtain at least 90% test power.

RESULTS

We selected 114 women, all of them Caucasian. The mean age observed was 70.4 ± 6.81 years and the mean BMI 26.32 ± 3.71 kg/m². Laboratory data are shown in Table 1. All patients had BMD reduction and were classified as osteoporotic 82.5% (n = 94) and osteopenic 17.5% (n = 20).

The exams were performed in the fall (n = 44, 38.6%) and winter (n = 43, 37.7%). There was no statistically significant correlation between the seasons of the year and serum PTH values (p = 0.332), 25 (OH) D (p = 0.338) and the T-score values in BMD.

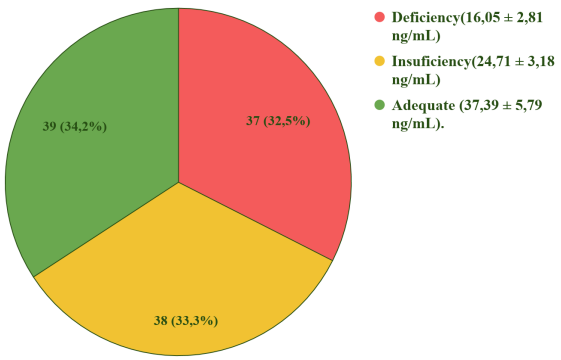
The mean values of 25(OH)D were 26.21 ± 9.69 ng/mL. Thirty-two percent of patients (n = 37) had vitamin D deficiency (16.05 ± 2.81 ng/mL), 33% (n = 38) insufficiency (24.71 ± 3.18 ng/mL) and 34% (n = 39) had adequate levels (37.39 ± 5.79 ng / mL), as shown in Graphic 1. The calculated Spearman correlations are shown in Table 2.

Table 1 - Anthropometric and laboratory data

Variables	Mean ± standard deviation
Age years)	70.4 ± 6.81
BMI (kg / m²)	26.3 ± 3.71
PTH (pg / ml)	53.7 ± 20.1
25 (OH) D (ng / mL)	26.2 ± 9.69
Corrected serum calcium (mmol/L)	2.29 ± 0.09
Urinary calcium (mg/dL)	2.32 ± 1.77
Serum phosphate (mmol/L)	1.19 ± 0.13
Serum Creatinine (mg/dL)	0.69 ± 0.16
Urinary Clearance (mL/min)	76.1 ± 28.6

Authors, 2017.

Graphic 1 - Concentrations of 25 (OH) D



Authors, 2017.

Table 2 - Correlations between 25 (OH)D and parameters

Parameter	p value
Age (years)	0.3888
BMI (kg/m²)	0.1233
PTH (pg/ml)	0.0013; rho = -0.297
Corrected serum calcium (mmol/L)	0.2986
Urinary calcium (mmol/L)	0.5857
Serum phosphate (mmol/L)	0,1289
Urinary Clearance (mL/min)	0.5861
T-score of L1-L4	0.2269
Femoral neck T-score	0.3017
Total femur T-score	0.9273

Authors, 2017.

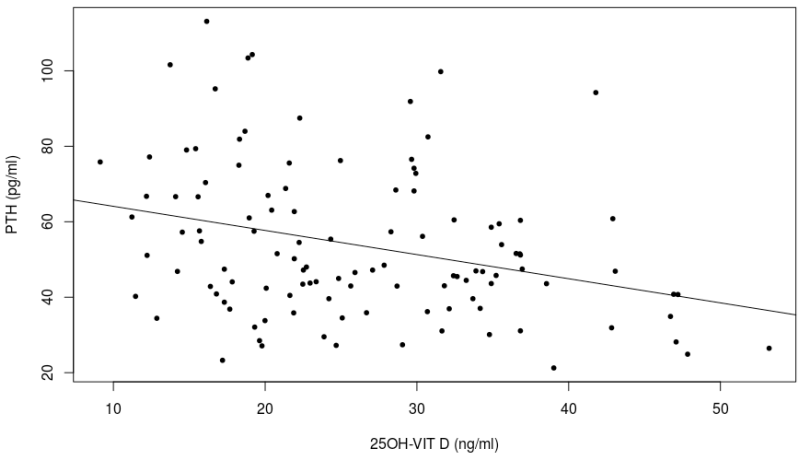
The observed PTH values had a mean of 53.7 ± 20.1 pg/mL. Twenty-five percent of the patients (n = 29) had PTH above the reference value (10-65 pg/mL or 10-65 ng/L). There was a negative correlation between serum PTH values with 25(OH)D values (p <0.01; rho = -0.2971), as shown in Figure 1. Through the multiple comparison test, the difference of serum PTH was statistically significant between the normal and deficient 25(OH)D group. There was no difference in the comparison between the normal group with the insufficient group and between the insufficient group with the deficient group.

Other laboratory data and their correlations are shown in Table 3. The only one with a significant inverse correlation was serum phosphate (p <0.01; rho = -0.28), as expected by PTH physiology.

Table 3 - Correlations between PTH and others parameters

Parameter	p value
Age years)	0,699
BMI (kg/m²)	0.517
Corrected serum calcium (mmol/L)	0.245
Urinary calcium (mmol/L)	0.153
Serum phosphate (mmol/L)	0.028; rho = -0.277
Urinary Clearance (mL/min)	0,409
T-score of L1-L4	0.167
Femoral neck T-score	0.592
Total femur T-score	0.407

Authors, 2017.



Test: Spermann correlation (p = 0.0013; rho = -0.2971)
The authors, 2017.

Figure 1 - Correlation between PTH and 25 (OH) D levels

Age did not correlate significantly with PTH and 25(OH)D concentrations. There was a significant negative correlation with femoral neck T-scores ($p < 0.05$; rho = -0.225) and total femur ($p < 0.05$; rho = -0.189). Older women presented a tendency to present microfractures to the spine radiography, according to the student's t test ($p < 0.001$).

BMD values are presented in Table 4. According to the Spearman coefficient, BMI correlated positively with BMD [L1-L4: $p < 0.05$ and rho = 0.29; femoral neck: $p < 0.001$ and rho = 0.312; total femur: $p < 0.001$ and rho = 0.533). It was evidenced by the t-student test that osteoporotic patients present lower BMIs than patients with osteopenia ($p < 0.01$). There was no correlation between lumbar spine and femur BMD with serum concentrations of 25 (OH) D and PTH.

Table 4 - Densitometric data

Variables	Mean ± standard deviation
DMO L1-L4 (g/cm²)	0.812 ± 0.098
T-score L1-L4	-2.941 ± 0.845
BMD femoral neck (g/cm²)	0.724 ± 0.091
T-score Femoral neck	-2.195 ± 0.828
Total Femur BMD (g/cm²)	0.756 ± 0.108
T-score Femur Total	-1.934 ± 0.934

The authors, 2017.

The history of atraumatic fractures was positive in 70.8% of the patients (n = 80). The most frequent location was the forearm in 37% (n = 32); followed by the lower limb (22.8%, n = 26) and hip (9.6%, n = 11). It was evidenced that patients with previous fractures had a lower lumbar spine T-score than patients with a negative history for fractures, however, this was not significant for femoral neck and total femur T-scores. The relationship between the history of fractures and the classification of patients between osteoporotic and osteopenic was not significant ($p = 0.06$), as was the correlation with 25 (OH) D ($p = 0.39$) and serum PTH ($p = 0.39$).

A prevalence of 27% (n = 30) of morphometric fractures evaluated in the radiography of the control column was observed. A higher number of a traumatic fractures was identified with increasing age ($p<0.01$). In addition, patients with morphometric fractures at the x-ray had a lower T-score of the femoral neck.

DISCUSSION

In the present study, a high prevalence of hypovitaminosis D was demonstrated in a group of women from Curitiba, similarly with the international and national literature. In addition, a negative correlation with PTH was observed. In a global study[8] with 26 countries, 28.4% of vitamin D deficiency was reported in a population of 7564 postmenopausal women (<20 ng/mL). On the other hand, the percentage of postmenopausal women with osteoporosis who present serum 25(OH)D <30 ng/mL (insufficiency) during winter approaches 90-100% in Europe and 80% in Canada and the United States[9]. Even in Brazil, the country with the highest 25(OH)D status in the multicenter study, only 34.3% of the women had adequate serum levels in winter and 43% in summer[9]. In a

study conducted in São Paulo, a high prevalence of vitamin D insuficiency (41.9%) and vitamin D deficiency (15.4%) associated with secondary hyperparathyroidism (55%) was demonstrated in a population without risk factors[10]. In Belo Horizonte, a study of 180 outpatients found out a prevalence of 42.4% of vitamin D deficiency[11].

The main factors contributing to vitamin D insuficiency or deficiency are low sun exposure, presence of diseases or drugs that affect its metabolism, and poor dietary vitamin D[12,13]. In our study, patients' diet was not approached as calcium and vitamin D intake, but secondary causes that could affect vitamin D dosages were excluded. The probable causes of the geriatric population being more susceptible to hypovitaminosis D seem to be due less sun exposure, reduced production capacity of 25(OH)D (mainly due to decreased renal function), less vitamin absorption in the gastrointestinal tract, besides using multiple drugs that interfere in its absorption and metabolization[13,14].

It is known that the seasons also appear to exert an effect on vitamin D concentrations, especially in temperate regions[13,15-20]. In our study, this association was probably not observed because the majority of the patients had collected serum 25(OH)D in autumn and winter, presenting a lack of sample dispersion.

The prevalence of hyperparathyroidism secondary and hypovitaminosis D in this sample was 25%, unlike other Brazilian studies that observed a prevalence higher than 60%, which is probably due to the fact that the patients are older than the patients in this study. Saraiva[10] presented a 66% prevalence of hypovitaminosis D in a population over 65 years old, with 55% of secondary hyperparathyroidism associated. In 2007, in a comparison between institutionalized and outpatient patients, secondary hyperparathyroidism occurred in 61.7% of the patients in the institutionalized group and in 54% of the patients in the outpatient group[21].

However, our data demonstrated a significant negative correlation of 25 (OH) D and PTH, in agreement with other studies, despite different coefficient values[13,22-25]. This correlation, which is most evident when the level of 25 (OH) D is below 30 ng/mL, reinforces that the ideal value of 25OHD for patients with osteoporosis is greater than 30 ng/mL[9,13].

BMI was positively correlated with BMD, as patients with osteoporosis had significantly lower BMI than those with osteopenia. These data are consistent with the literature[26-29], which indicates that overweight stimulates osteogenesis by exerting mechanical force on the bones[30-31].

It was evidenced that patients with previous fractures had a lower L1-L4 T-score than patients with a negative history for fractures, however, this was not significant for femoral neck and total femur T-scores. This association of the history of fractures with BMD has also been documented[32-34].

The microfractures in the column radiography were presented in 1/3 of patients. Although they were not correlated significantly with the concentration of vitamin D, almost half of these patients had concentrations of 25(OH)D <30 ng/mL. This result is similar to one in a study conducted in Rio de Janeiro[22], which identified vertebral fractures asymptomatic in 20% of the postmenopausal women investigated, 57.7% of whom were deficient or insufficient in vitamin D. However, no significant correlation was found out with serum 25(OH)D. In our series, the atraumatic fractures were correlated with the increase in age and with a lower T-score value of the femoral neck, results consistent with the literature.

Our study has limitations. The sample was not representative of the general population, since the selection was restricted to women with altered BMD. Besides, we lacked a control group, patients without osteopenia and osteoporosis, to better evaluate the data.

CONCLUSION

We conclude that a high prevalence of hypovitaminosis D was observed in this sample of in this sample patients: postmenopausalwomen from Curitiba (southern Brazil) with low BMD. Vitamin D values correlated negatively with PTH concentrations, similarly to other studies in literature.

There was also a correlation between the history of fractures and morphometric fractures with BMD, proving the predictive value for fractures of the bone densitometry examination.

With these findings, we reinforce the importance of vitamin D sufficiency in the management of patients with low bone density, which will contribute to prevention of secondary hyperparathyroidism and increased risk of fractures.

REFERENCES

1. Khundmiri SJ, Murray RD, Lederer E. PTH and vitamin D. Compr Physiol. 2016;6(2):561-601. doi: 10.1002/cphy.c140071.

2. Reginster J-Y. Calcium and vitamin D for osteoporotic fracture risk. Lancet. 2007;370:632-4. doi: 10.1016/S0140-6736(07)61315-4.

3. Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? J Steroid Biochem Mol Biol. 2004;89-90(1-5):611-4. doi: 10.1016/S0140-6736(07)61315-4.

4. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int. 2005;16(7):713-6. doi: 10.1007/s00198-005-1867-7.

5. Castro LCG. O sistema endocrinológico vitamina D. Arq Bras Endocrinol Metabol. 2011;55(8):566-75. http://dx.doi.org/10.1590/S0004-27302011000800010.

6. Souberbielle J-C, Body J-J, Lappe JM, Plebani M, Shoenfeld Y, Wang TJ, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Autoimmun Rev. 2010;9(11):709-15. doi: 10.1016/j.autrev.2010.06.009.

7. Lips P, Hosking D, Lippuner K, Norquist JM, Wehren L, Maalouf G, et al. The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. J Intern Med. 2006;260(3):245-54. doi: 10.1111/j.1365-2796.2006.01685.x.

8. Lips P, Duong T, Oleksik A, Black D, Cummings S, Cox D, et al. A global study of vitamin d status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the Multiple Outcomes of Raloxifene Evaluation Clinical Trial. J Clin Endocrinol Metab. 2001;86(3):1212-21. doi: 10.1210/jcem.86.3.7327.

9. Kuchuk NO, van Schoor NM, Pluijm SM, Chines A, Lips P. Vitamin D status, parathyroid function, bone turnover, and BMD in postmenopausal women with osteoporosis: global perspective. J Bone Miner Res. 2009;24(4):693-701. DOI: 10.1359/jbmr.081209

10. Saraiva GL, Cendoroglo MS, Ramos LR, Araújo LMQ, Vieira JGH, Kunii I, et al. Influence of ultraviolet radiation on the production of 25 hydroxyvitamin D in the elderly population in the city of São Paulo (23 degrees, 34'S), Brazil. Osteoporos Int. 2005;16(12):1649-54. doi: 10.1007/s00198-005-1895-3

11. Silva BCC, Camargos BM, Fujii JB, Dias EP, Soares MMS. Prevalência de deficiência e insuficiência de vitamina D e sua correlação com PTH, marcadores de remodelação óssea e densidade mineral óssea, em pacientes ambulatoriais. Arq Bras Endocrinol Metabol. 2008;52(3):482-8. doi: 10.1590/S0004-27302008000300008.

12. Holick MF, Chen TC, Lu Z, Sauter E. Vitamin D and skin physiology: a D-lightful story. J Bone Miner Res. 2007;22(S2):V28-33. doi: 10.1359/jbmr.07s211.

13. Maeda SS, Saraiva GL, Hayashi LF, Cendoroglo MS, Ramos LR, Corrêa M de P, et al. Seasonal variation in the serum 25-hydroxyvitamin D levels of young and elderly active and inactive adults in São Paulo, Brazil. Dermatoendocrinol. 2013;5(1):211-7. doi: 10.4161/derm.24476.

14. Russo LAT, Gregório LH de, Lacativa PGS, Marinheiro LPF. Concentração plasmática de 25 hidroxivitamina D em mulheres na pós-menopausa com baixa densidade mineral óssea TT - concentration of 25-hydroxyvitamin D in postmenopausal women with low bone mineral density. Arq Bras Endocrinol Metabol. 2009;53(9):1079-87. doi: 10.1590/S0004-27302009000900004.

15. Brot C, Vestergaard P, Kolthoff N, Gram J, Hermann AP, Sørensen OH. Vitamin D status and its adequacy in healthy Danish perimenopausal women: relationships to dietary intake, sun exposure and serum parathyroid hormone. Br J Nutr. 2001;86(S1):S97. doi: 10.1079/BJN2001345.

16. Bozkurt S, Alkan BM, Yildiz F, Gümüş S, Sezer N, Ardiçoğlu 2 Özge, et al. Age, sex, and seasonal variations in the serum vitamin D3 levels in a local Turkish population. Arch Rheumatol. 2014;29(1):14-9. doi: 10.5606/tjr.2014.3968.

17. Kroll MH, Bi C, Garber CC, Kaufman HW, Liu D, Caston-Balderrama A, et al. Temporal relationship between vitamin D status and parathyroid hormone in the United States. PLoS One. 2015;10(3):e0118108. doi: 10.1371/journal.pone.0118108.

18. Vuistiner P, Rousson V, Henry H, Lescuyer P, Boulat O, Gaspoz J-M, et al. A Population-based model to consider the effect of seasonal variation on serum 25(OH)D and vitamin D status. Biomed Res Int. 2015;2015:1-9. doi: 10.1155/2015/168189.

19. Klingberg E, Oleröd G, Konar J, Petzold M, Hammarsten O. Seasonal variations in serum 25-hydroxy vitamin D levels in a Swedish cohort. Endocrine. 2015;49(3):800-8. doi: 10.1007/s12020-015-0548-3.

20. Serdar MA, Batu Can B, Kilercik M, Durer ZA, Aksungar FB, Serteser M, et al. Analysis of Changes in Parathyroid Hormone and 25 (OH) Vitamin D Levels with Respect to Age, Gender and Season: A Data Mining Study. J Med Biochem. 2017;36(1):73-83. doi: 10.1515/jomb-2017-0002.

21. Saraiva GL, Cendoroglo MS, Ramos LR, Araújo LMQ, Vieira JGH, Maeda SS, et al. Prevalência da deficiência, insuficiência de vitamina D e hiperparatiroidismo secundário em idosos institucionalizados e moradores na comunidade da cidade de São Paulo, Brasil. Arq Bras Endocrinol Metabol. 2007;51(3):437-42. doi: 10.1590/S0004-27302007000300012.

22. Need AG, Morris HA, Horowitz M, Nordin C. Effects of skin thickness, age, body fat, and sunlight on serum 25-hydroxyvitamin D. Am J Clin Nutr. 1993;58(6):882-5. doi: 10.1093/ajcn/58.6.882.

23. Oliveri MB, Mautalen C, Bustamante L, Gómez García V. Serum levels of 25-hydroxyvitamin D in a year of residence on the Antarctic continent. Eur J Clin Nutr. 1994;48(6):397-401.

24. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, et al. Hypovitaminosis D in Medical Inpatients. N Engl J Med. 1998;338(12):777-83. doi: 10.1056/NEJM199803193381201.

25. Mori H, Okada Y, Tanaka Y. Incidence of Vitamin D Deficiency and Its Relevance to Bone Metabolism in Japanese Postmenopausal Women with Type 2 Diabetes Mellitus. Intern Med. 2015;54(13):1599-604. doi: 10.2169/internalmedicine.54.3638.

26. Arantes HP, Kulak CAM, Fernandes CE, Zerbini C, Bandeira F, Barbosa IC, et al. Correlation between 25-hydroxyvitamin D levels and latitude in Brazilian postmenopausal women: from the Arzoxifene Generations Trial. Osteoporos Int. 2013;24:2707-12. doi: 10.1007/s00198-013-2366-x.

27. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk Factors for Hip Fracture in White Women. N Engl J Med. 1995;332(12):767-74. doi: 10.1056/NEJM199503233321202.

28. Bonnick SL, Harris ST, Kendler DL, McClung MR, Silverman SL. Management of osteoporosis in postmenopausal women. Menopause. 2010;17(1):25-54. doi: 10.1097/gme.0b013e3181c617e6.

29. Mazocco L, Chagas P, Mazocco L, Chagas P. Association between body mass index and osteoporosis in women from northwestern Rio Grande do Sul. Rev Bras Reumatol. 2017;57(4):299-305. doi: 10.1016/j.rbre.2016.10.002.

30. Sugiyama T, Yamaguchi A, Kawai S. Effects of skeletal loading on bone mass and compensation mechanism in bone: a new insight into the "mechanostat" theory. J Bone Miner Metab. 2002;20(4):196-200. doi: 10.1007/s007740200028.

31. Rodrigues Filho EA, Santos MAM, Silva ATP, Farah BQ, Costa MC, Campos FACS, et al. Relation between body composition and bone mineral density in young undregraduate students with different nutritional status. Einstein (São Paulo). 2016;14(1):12-7. doi: 10.1590/S1679-45082016AO3569.

32. Lips P, Obranr KJ. The pathogenesis and treatment of hip fractures. Osteoporosis Int. 1991;1:218-31. Available from: https://link.springer.com/content/pdf/10.1007/BF03187466.pdf.

33. Lips P. Vitamin D deficiency and osteoporosis: the role of vitamin D deficiency and treatment with vitamin D and analogues in the prevention of osteoporosis-related fractures. Eur J Clin Invest. 1996;26(6):436-42. https://doi.org/10.1046/j.1365-2362.1996.176290.x

34. Stephen AB, Wallace WA. The management of osteoporosis. J Bone Joint Surg Br. 2001;83(3):316-23.

Received in: July 17, 2018
Accept in: September 11, 2018