

Serum levels of vitamin D in women treated at rheumatology services in Lima

The objective of this study was to determine the vitamin D status in women ≥ 50 years of age who were treated at rheumatology services in Lima, Peru, and determine the proportion of patients who require correction of vitamin D deficiency.

A total of 157 women were evaluated; 25-hydroxyvitamin D [25(OH) D], intact parathyroid hormone (PTH), calcium and serum phosphorus were measured. The mean age was 63.3 ± 8.6 years, and most were diagnosed with fibromyalgia (50%) and osteoarthritis (30.57%). The mean [25(OH) D] value was 18.7 ± 6.7 ng/mL, and no differences in calcium, phosphorus, [25(OH) D] and PTH values were found between the subgroups stratified by age. No correlation was found between age and [25(OH) D] ($r = 0.099$; $P = 0.214$). We found a weak direct correlation between age and PTH ($r = 0.183$; $p < 0.05$) and a weak inverse correlation between [25(OH) D] and PTH values ($r = -0.179$; $p < 0.05$).

We found [25(OH) D] values < 20 , between 21-29 and ≥ 30 ng/mL in 58.6%, 36.9% and 4.5% of patients, respectively. The average [25(OH) D] values were lower in obese patients than in non-obese patients (16.94 vs. 19.42 ng/mL; $p < 0.05$). Vitamin D deficiency was prominent in rheumatic patients, and in approximately 60%, we found vitamin D values < 20 ng/mL, which require correction. Identifying and treating vitamin D deficiency is recommended because of the impact on different health parameters in these patients.

Keywords: Vitamin D • osteoarthritis • fibromyalgia • rheumatology

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Key points

Vitamin D deficiency is common among patients who attend a rheumatology service in Lima, and at least 60% of cases require corrective action.

Introduction

Vitamin D has a structure very similar to that of cholesterol, and the active form, 1,25(OH)₂ vitamin D₃ (calcitriol), is considered a steroid hormone involved in the regulation and homeostasis of mineral metabolism. The functions of vitamin D on mineral metabolism are exerted through the effect on 3 main organs: intestine, bone and kidney [1,2]. However, the discovery of vitamin D receptors in most tissues explains their multiple extraskeletal functions, and their role in reducing the risk of some chronic cardiovascular, autoimmune, neoplastic and infectious diseases is currently evaluated [2,3].

There are 2 forms of vitamin D, referred to as calciferols: cholecalciferol (vitamin D₃), which is of animal origin, and ergocalciferol (vitamin D₂), which is of plant origin; both share similar metabolic pathways, but the majority of animal

and plant species contain inactive precursors that require sunlight (UVB light) for conversion into calciferols [4]. Cholecalciferol and ergocalciferol have shown efficacy in correcting vitamin D deficiency, but cholecalciferol is more effective than ergocalciferol for increasing serum vitamin D levels [5,6].

Although humans can obtain vitamin D from nutritional sources, the greatest proportion and most important source comes from synthesis in the skin [7]. The synthesis of vitamin D in the skin depends on a number of factors, such as age, type of clothing, skin color and use of sunblock [8]. In darker-skinned individuals, synthesis is reduced because melanin efficiently absorbs ultraviolet B light photons and competes with 7-dehydrocholesterol to form pre-vitamin D [3].

Vitamin D status is determined by measuring 25-hydroxyvitamin D [25(OH)D] or calcidiol; although the cut-off points to differentiate adequacy and insufficiency are not uniformly established, recommendations have been based on different parameters, such as maximum PTH suppression, adequate intestinal calcium absorption and prevention of fractures. The U.S.

Endocrine Society defines vitamin D deficiency, insufficiency and sufficiency based on the following cut-off points: <20, 21-29 and ≥ 30 ng/mL, respectively; for the National Osteoporosis Society (NOS) and the Institute of Medicine (IOM), the cut-off points are <12, 12-20 and ≥ 20 ng/mL, respectively [9-11]. The objective of this study was to determine the prevalence of vitamin D deficiency in female patients ≥ 50 years of age who were seen in rheumatology services in the city of Lima and to determine the proportion that requires intervention to correct vitamin D deficiency.

Materials and methods

This study included 157 women ≥ 50 years of age who were treated on an outpatient basis at the rheumatology departments of the Maria Auxiliadora Hospital, the Higuiereta Clinic and the Diagnostic Center for Osteoporosis and Rheumatic Diseases (Centro Diagnóstico de la Osteoporosis y Enfermedades Reumáticas-CEDOR) between the months of August 2017 and August 2018. This study was approved by the Institutional Bioethics Committee-Vía Libre, and all patients signed an informed consent form before any study procedure.

Women in good general condition with musculoskeletal pathology (fibromyalgia, low back pain, osteoarthritis, or soft tissue rheumatism) but without greater difficulty in carrying out their normal daily activities according to their age and who did not require assistive devices (walking stick, crutches, etc.) were included.

Women with suspicion of diseases with the potential of altering mineral metabolism (hyperparathyroidism, idiopathic hypercalciuria, hepatic or renal failure, etc.) or with inflammatory arthropathies were excluded from participating in the study. Women who received calcium and vitamin D supplements and other medications that could alter bone mineral density (antiresorptive, hormone replacement therapy, thiazides, corticosteroids, etc.) in the last 12 months or those who received megadoses of vitamin D ($\geq 100,000$ IU) at any time during their life were also excluded.

Demographic data, history and the main diagnosis that led to requesting medical help at a rheumatology service were recorded. Weight and height were assessed using a Kendall adult stadiometer scale, and the calculation of Body Mass Index (BMI) was performed with

the established formula ($BMI = \text{weight [kg]} / \text{height [m]}^2$). Measurement of total 25(OH) D and intact parathyroid hormone (PTH) was performed using an electrochemiluminescent immunoassay on a Cobas e 601 analyzer. Calcium and phosphorus were measured by colorimetric methods and analyzed with Cobas equipment. All measurements were performed by a laboratory internationally certified by the College of American Pathologists.

All statistical analyses were performed with Stata1 v. 15.0. Numerical variables are described as the mean \pm standard deviation (SD), and categorical variables are described as absolute (n) and relative frequencies (%). For the comparison between continuous variables, such as age, calcium, phosphorus, [25(OH) D] and PTH, the Pearson correlation coefficient was used. To determine the difference between groups in the case of categorical variables, the Chi² test and Fisher's exact test were used; for continuous variables, Student's T-test was used when there were 2 groups, and analysis of variance with Bonferroni correction was used when there were more than 2 groups. $P < 0.05$ was considered significant.

Results

A total of 157 women, with a mean age of 63.3 ± 8.6 years (range of 50 to 90 years), were included. The average height was 147.6 ± 6.4 cm, the average weight was 61.9 ± 10.8 kg, and the average BMI was 28.4 ± 4.6 kg/cm². Most of the women evaluated were of mixed race (147 women); 8 were white, and 2 were black.

The mean [25(OH) D] value for the entire group was 18.7 ± 6.7 ng/mL, and the mean values distributed by age group, 50-59 years, 60-69 years and ≥ 70 years, were 17.97 ± 6.15 ng/mL, 19.53 ± 7.10 ng/mL and 18.29 ± 6.78 ng/mL, respectively. No significant difference was found between these groups for [25(OH) D] values.

The mean serum calcium and phosphorus values were 9.4 ± 0.3 mg/dl and 3.8 ± 0.4 mg/dl, respectively, and the average PTH value was 44.8 ± 14.6 pg/mL. The values stratified by age subgroups are shown in Table 1; no differences were found between the subgroups for calcium, phosphorus, [25(OH) D] and PTH values. We did not find a significant correlation between age and [25(OH) D] values ($r = 0.099$, $p = 0.214$) or between calcium and [25(OH) D] values ($r = 0.088$; $p = 0.274$). We found a direct but weak correlation between age and PTH values ($r =$

Table 1. Calcium, phosphorus, [25(OH) D] and PTH values.

Age	Calcium	Phosphorus	25(OH) D	PTH
	mean (± SD)	mean (± SD)	mean (± SD)	mean (± SD)
50-59 years	9.38 (0.32)	3.90 (0.35)	17.97 (6.15)	40.16 (10.19)
60-69 years	9.43 (0.31)	3.73 (0.46)	19.53 (7.10)	47.89 (15.41)
≥70 years	9.34 (0.34)	3.76 (0.38)	18.29 (6.78)	46.43 (17.16)

Table 2. 25(OH) D status by age in the study population.

	50-59 years n (%)	60-69 years n (%)	≥70 years n (%)
Sufficient (≥30 ng/mL)	2 (3.57%)	5 (7.35%)	0 (0%)
Insufficient (21-29 ng/mL)	16 (28.6%)	25 (41.2%)	13 (42.4%)
Deficient (<20 ng/mL)	38 (67.85%)	35 (51.5%)	19 (57.57%)

Referential value: U.S. Endocrine Society (p=0.230)

0.183; p<0.05) and a weak inverse correlation between the values of [25(OH) D] and PTH (r=-0.179; p<0.05).

The main diagnoses were fibromyalgia in 79 patients (50%), osteoarthritis in 48 patients (30.57%), osteoporosis in 11 patients (7%), low back pain in 6 patients (3.8%), osteoarthritis plus fibromyalgia in 6 patients (3.8%) and other diagnoses in 7 patients (4.5%). Among the different diagnostic categories, no significant difference was found in the proportion of participants with vitamin D deficiency.

In the total group, there was seasonal variation in [25(OH) D] values, which were significantly higher in summer and autumn (22.9 ng/mL and 23.2 ng/mL, respectively) than in winter and spring (14.55 ng/mL and 18.79 ng/mL, respectively) (p<0.01).

Figure 1 shows the vitamin D status in the study population according to the cut-offs proposed by the U.S. Endocrine Society. The prevalence rates of [25(OH) D] deficiency, insufficiency and sufficiency in the studied population were 58.6%, 36.9% and 4.5%, respectively. In contrast, using as reference values those proposed by the IOM and the UK NOS, we found prevalence

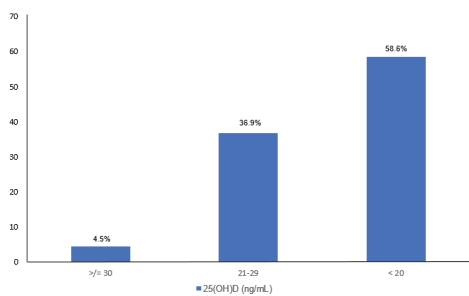


Figure 1. Vitamin D status in the study population.

Equivalence in mmol/L (conversion: 1 ng/mL=2.5 nmol/L): Deficiency (50 nmol/L), insufficiency (52.5-72.5 nmol/L), sufficiency (75 nmol/L).

rates of vitamin D deficiency, insufficiency and sufficiency of 16.6%, 42% and 41.4%.

In the total group, the proportion of patients with [25(OH) D] levels ≤20 ng/mL was approximately 60%. The distribution by age is shown in Table 2; there was no significant difference when comparing vitamin D status among the 3 age groups. Nevertheless, the proportion of patients with values ≤12 ng/mL increased from 10% for participants between 50 and 59 years of age to 17% for participants from 60 to 69 years of age and 24.3% for participants ≥70 years of age.

The mean [25(OH) D] values according to body mass index were 18.50 ± 7.28 ng/mL in participants classified as normal (BMI<25), 19.80 ± 6.87 ng/mL in participants classified as overweight (BMI ≥ 25) and 16.94 ± 5.62 ng/mL in participants classified as obese (BMI ≥ 30). The average [25(OH) D] values were significantly lower in obese participants compared to normal and overweight participants (16.94 ± 5.62 ng/mL versus 19.42 ± 6.99 ng/mL, p<0.05) (Figure 2). The proportion of participants with [25(OH) D] values <20 ng/mL was significantly higher in the obese participants compared to normal and overweight participants (73.3% vs. 52.7%; p<0.05).

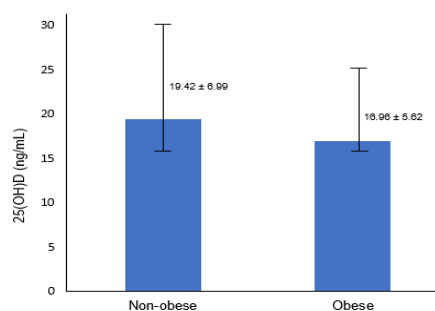


Figure 2. [25(OH) D] status according to body mass index.

Discussion

In recent decades, it has been recognized that vitamin D deficiency represents a global health problem, and it is estimated that between 20% and 100% of older adults living in the United States, Canada and Europe are vitamin D deficient [9]. [25(OH)D] values below 20 ng/mL (50 nmol/L) are associated with a reduction in the absorption of calcium and phosphorus, secondary hyperparathyroidism, and increased bone resorption with loss of bone mass and an increased risk of fractures [6,9]. Very low levels of vitamin D cause defective bone mineralization, generating osteomalacia in adults and rickets in children. Additionally, vitamin D deficiency is associated with an inadequate response to medications used for the treatment of osteoporosis [12,13].

In our study, we found a high prevalence of vitamin D deficiency, and approximately 60% of patients had [25(OH) D] values ≤ 20 ng/mL. This finding is a cause for concern regarding the implications on general and bone health and suggests taking appropriate measures to correct it. We did not find a correlation between age and [25(OH) D] values, which can be attributed to the fact that only women ≥ 50 years were included, not younger age groups, which would have allowed for assessing a broader age range. However, [25(OH) D] values ≤ 12 ng/mL increased progressively with age, and approximately one-quarter of the patients ≥ 70 years of age presented values in this range.

In other countries, similar results have been reported in rheumatic patients of both sexes who were treated on an outpatient basis at rheumatology clinics. Haroon evaluated 231 patients in Ireland and defined vitamin D status based on the following [25(OH) D] values: severe deficiency, <12 ng/mL; mild to moderate deficiency, 12-21 ng/mL; and sufficiency, >21 ng/mL. The authors found that 30% had values in the sufficiency range and 70% had vitamin D deficiency; in the latter group, 26% presented values within the severe deficiency range [14]. Cooles, in a cohort of 206 patients from an arthritis clinic in Newcastle, UK, and using the same reference values for [25(OH) D], found that 64% of the patients had levels in the deficiency range and 20% in the severe deficiency range [15].

Stoll, in 272 patients in Switzerland, found that 7% had 25(OH)D values <10 ng/mL, 79% had

values between 10-30 ng/mL, and 14% had values >30 ng/mL. A total of 38% of the patients received daily calcium supplements plus vitamin D (400 IU), in which the proportion of patients with normal [25(OH) D] values was significantly higher than the proportion of patients who did not receive supplements (25% *vs.* 6%; $p < 0.05$) [16].

Grazio, in 120 patients in Croatia with diagnoses of psoriatic arthritis, rheumatoid arthritis and osteoarthritis, found [25(OH) D] values ≤ 30 ng/mL in 74%, 94% and 97%, respectively, and values ≤ 10 ng/mL in 13%, 39% and 38%, respectively [17]. Maldonado, in 279 patients in Manta, Ecuador, found that 41.2% had [25(OH) D] values >30 ng/mL, 34.4% had values between 20-30 ng/mL, 23.3% had values between 10-20 ng/mL, and 1.1% had values <10 ng/mL [18]. In some of these studies, the proportion of vitamin D deficiency was high even among the youngest age groups [14,16,18].

In analyzing these figures, an initial hypothesis is that they could simply reflect a high population prevalence. Haaron compared his results with those of a healthy population from another study conducted in the same locality but with a higher average age. The prevalence of vitamin D deficiency was higher in rheumatic patients than in the healthy population [14,19]. If this finding is confirmed, it could suggest that other factors could contribute to aggravating the deficiency.

In patients with osteoarthritis and fibromyalgia, who formed the largest population in our study, pain or reduced physical capacity could restrict outdoor activities and decrease exposure to sunlight, affecting the synthesis of vitamin D from skin [20,21]. In the Grazio study, the highest vitamin D values were found in patients with psoriatic arthritis compared to those with rheumatoid arthritis and osteoarthritis; the psoriatic arthritis group was subjected to greater weekly exposure to sunlight, possibly because they considered it beneficial for psoriasis [17].

However, establishing a causal relationship between rheumatic diseases and an increased risk of vitamin D deficiency requires a more extensive analysis and properly designed and controlled clinical studies, in which risk factors are evaluated in comparison with the healthy population in the same geographical location.

The population we studied was composed mostly of women of mixed race, in which it has been reported that the most frequent type

of skin according to the Fitzpatrick classification are phototypes III and IV [22]; therefore, we cannot exclude an influence of skin color on the [25(OH) D] values in our study.

We found a significantly higher proportion of vitamin D deficiency in obese participants compared to normal and overweight participants. Vitamin D is fat-soluble and is stored in fat tissue, and obesity is associated with lower serum levels of [25(OH) D], most likely due to increased storage in adipose tissue [8,23]. The proportion of obese participants in our study was 28.66%, a value that is close to the upper limit of the range of obesity reported in women in the general population in Lima (12.2% to 29%) [24]; therefore, we cannot rule out some influence of obesity on our results.

Vitamin D deficiency is associated with deleterious health outcomes, such as secondary hyperparathyroidism, osteoporosis, osteomalacia, proximal muscle weakness, increased risk of falls and fractures, and an altered response to drugs used to treat osteoporosis [12,13]. Undoubtedly, for patients with rheumatic pathology, this deficiency represents additional detrimental effects to their health, in addition to those derived from the disease itself.

It is logical to propose on a theoretical basis that the consequences of vitamin D deficiency in patients with osteoarthritis and fibromyalgia could increase some of the risks inherent to the underlying disease or even generate new risks. It is also possible that they mimic or exacerbate some of the symptoms or that they have a negative influence on the tests designed to assess functional capacity [25-28].

Falls represent a health problem due to physical and psychological consequences. The risk of falls increases over 60 years of age and increases even more between 70 and 80 years. It is estimated that 30% of individuals over 65 experience an annual fall, and this proportion increases to 40% for individuals above 75 years of age [29]. The consequences of falls include fractures, ecchymoses, dislocations and musculoskeletal injuries, among which the former are associated with significant mortality [30].

The efficacy of vitamin D in optimizing muscle function and preventing falls and fractures has been widely reported, especially in individuals with [25(OH) D] values in the deficiency range and in individuals with a high risk of calcium and vitamin D deficiencies [31-33]. There

is controversial information in some recent meta-analyses on the relationship of vitamin D with falls and fractures [34,35]. In relation to falls, Tang comments that this discrepancy could be attributed to the heterogeneity of the included clinical studies because some have not incorporated all the important parameters in their design to analyze this association, such as the type of population studied (sufficient or deficient vitamin D patients), the form and dose of administration of the supplements and the way to collect information on falls [36].

In patients with osteoarthritis affecting the lower limbs, the risk of falls is increased due to alterations in body balance, pain and instability during ambulation, weakness of the periarticular muscular apparatus, difficulty in avoiding obstacles and alterations in gait [37-39], and an increase in the risk of fractures has also been reported [40].

In fibromyalgia, alterations in body balance control, probably mediated by disorders in the peripheral or central mechanisms of postural control [41], are associated with an increased risk of falls, compared to healthy controls and patients with rheumatoid arthritis [42].

Based on our literature review, we have not found literature that supports an additive effect of vitamin D deficiency on the risk of falls or fractures in patients with osteoarthritis and fibromyalgia; however, this possibility could not be excluded either, and correcting for vitamin D deficiency would be the most appropriate, in addition to taking general measures for the prevention of falls.

Although the role of vitamin D in osteoarthritis is not defined, weakness in the lower limb muscles is a recognized factor for the development and progression of osteoarthritis of the knees [43,44]. Quadriceps weakness is associated with poor neuromuscular control and impaired movement of this joint [45], and in patients with osteoarthritis, the strength of the quadriceps correlates with knee pain and [25(OH) D] levels [46]. Vitamin D supplementation could optimize functional parameters in patients with osteoarthritis in which there is also deficiency of this vitamin. Some authors recommend appropriate supplementation for patients with osteoarthritis and poor physical function [25]. The role of vitamin D in maintaining the integrity of articular cartilage, the effect on symptoms, the loss of joint space and the progression of the disease has been extensively

analyzed. A proportion of observational studies support a beneficial effect of vitamin D on some of the parameters mentioned, but the evidence is not conclusive enough to justify vitamin D supplementation to protect articular cartilage or change the course of the disease [47,48].

The association between pain, fibromyalgia and vitamin D is also a matter of debate. A recent meta-analysis concluded that reduced levels of vitamin D are found in patients with fibromyalgia compared to controls, but vitamin D supplementation has not shown a clinical benefit consistent with the symptoms [49].

Osteomalacia and myopathy are consequences of severe vitamin D deficiency and are associated with symptoms such as muscle weakness and generalized bone pain that could mimic the symptoms of fibromyalgia, representing a differential diagnosis problem [27,28]. It is possible that in patients with fibromyalgia and severe vitamin D deficiency, some of these symptoms may persist despite treatment for fibromyalgia, until vitamin D deficiency is also corrected.

The strengths of this study were the exclusion of women who received calcium and vitamin D supplements or other medications with the potential to alter bone metabolism; additionally, the study was conducted for 12 consecutive months. The limitations were its cross-sectional nature, and the study population was limited (women ≥ 50 years); additionally, patients with inflammatory arthropathies and details of diet and exposure to sunlight were not included.

Conclusions

We conclude that vitamin D deficiency is a problem with a very high prevalence in patients with rheumatic disease in Lima; we found values ≥ 30 ng/mL in approximately 5% of patients, levels between 21-29 ng/mL in 36.9% and levels < 20 ng/mL in 58.6%. According to these figures, at least approximately 60% of our patients require some therapeutic intervention aimed at correcting the deficiency.

It would be advisable to design clinical studies aimed at identifying additional factors that increase the risk of vitamin D deficiency in patients with musculoskeletal pathologies and assess the consequences on the functional capacity, quality of life and clinical picture of these patients.

These high prevalence rates suggest the need

to define criteria for serum [25(OH) D] values in patients with pathologies of the musculoskeletal system, in addition to providing recommendations on a healthy diet that includes adequate calcium intake and vitamin D supplementation. In deficient patients, it is necessary to take therapeutic measures to optimize vitamin D values. Correcting the deficiency would not only help prevent osteoporosis but also improve muscle function and optimize different health parameters in these patients.

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