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ORIGINAL ARTICLE

Prevalence of vitamin D inadequacy in European postmenopausal women

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ABSTRACT

Objective: Inadequate vitamin D level is associated with secondary hyperparathyroidism and increased bone turnover and bone loss, which in turn increases fracture risk. The objective of this study is to assess the prevalence of inadequate serum vitamin D levels in postmenopausal European women. There are no clear international agreements on what constitutes a level of vitamin D inadequacy, but recent publications suggest that the circulating level of vitamin D should be over 80 nmol/L or at least between 50 and 80 nmol/L.

Material and methods: Assessment of 25-hydroxyvitamin D [25(OH)D] was performed in 8532 European postmenopausal women with osteoporosis or osteopenia. European countries included France, Belgium, Denmark, Italy, Poland, Hungary, United Kingdom, Spain and Germany. Two cut-offs of 25(OH)D inadequacy were fixed : < 80 nmol/L and < 50 nmol/L.

Results: Mean (SD) age of the patients was 74.2 (7.1) years, body mass index was 25.7 (4.1) kg/m². Level of 25(OH)D was 61.0 (27.2) nmol/L. There was a highly significant difference of 25(OH)D level across European countries ($p < 0.0001$). The lowest level of 25(OH)D was found in France [51.5 (26.1) nmol/L] and the highest in Spain [85.2 (33.3) nmol/L]. In the whole study population, the prevalence of 25(OH)D inadequacy was 79.6% and 32.1% when considering cut-offs of 80 and 50 nmol/L, respectively and when considering patients aged less than 65 years, the prevalence reached 86% (cut-off of 80 nmol/L) and 45% (cut-off of 50 nmol/L).

Conclusion: This study indicates a high prevalence of vitamin D [25(OH)D] inadequacy in European postmenopausal women. The prevalence could be even higher in some particular countries. A greater awareness of the importance of vitamin D inadequacy is needed to address this public health problem.

Introduction

Osteoporosis is a chronic, progressive disease characterized by reduced bone mass and micro-architectural deterioration of bone. It is the major cause of fractures in middle-aged and elderly adults. The hallmark of osteoporotic fracture risk is a reduced bone mineral density (BMD). BMD is an indirect measure of calcium content of the bone, the most important regulator of which is the vitamin D-endocrine system.

Vitamin D, as cholecalciferol, is synthesised principally from 7-dehydrocholesterol in the epidermis of the skin, in a process dependent on ultraviolet radiation[1,2]. It then undergoes sequential hydroxylation in the liver and the kidney to produce 1,25-dihydroxy vitamin D[2,3]. Increasing plasma levels of vitamin D has been shown to lead to increased intestinal absorption of calcium[4] and normalisation of calcium balance, permitting a reduced requirement for bone resorption[5]. In the presence of diminished vitamin D levels, gut

absorption will decline and parathyroid hormone (PTH) secretion will increase[6], triggering a release of calcium from bone. If sustained, this will lead to a reduction in bone strength and increased risk of fragility fracture[7]. Vitamin D inadequacy has also been implicated as a contributing factor to muscle weakness and falls[8,9]. A positive relationship has also been shown between cognitive functioning and vitamin D level, which may also influence the risk of fall and fracture[10]. As a consequence, osteoporosis prevention and treatment guidelines developed by scientific authorities[11,12], contain recommendations for maintaining adequate vitamin D levels.

Sources of vitamin D are limited and include diet or synthesis in skin. Dietary sources of vitamin D are rare and include oily fish and fish liver oil. The majority of vitamin D is produced by photoactivation in the skin. However, the ability of the skin to synthesise vitamin D has been shown to decrease with age[1], as has the ability of the gut to absorb cholecalciferol[13]. Vitamin D deficiency is, therefore, to be expected in the elderly[14–16].

The objective of this study was to assess the prevalence of inadequate serum vitamin D levels in postmenopausal European women, in order to assess the extent of the problem and potential for improvement.

Methods

Postmenopausal women aged over 50 years were included in this study. These women were part of a run-in study aimed at normalizing the calcium and vitamin D status of patients prior to being included in a trial investigating the anti-fracture efficacy of a new anti-osteoporotic drug. Among the women included in this study, 24% already received vitamin D supplements. Patients were considered as osteoporotic if their lumbar spine or femoral neck BMD T-score was equal or less than –2.5 according to the centralized normative data. BMD was measured with a Hologic apparatus.

This particular European study involves 1195 patients from Belgium (mean age 76.9 years), 327 from Denmark (74.6), 1292 from France (79.6), 373 from Germany (73.1), 353 from Hungary (72.1), 1235 from Italy (71.1), 1544 from Poland (72.1), 590 from Spain (74.6) and 1623 from the United Kingdom (72.9).

Assessment of 25-hydroxyvitamin D [25(OH)D] was performed with a commercial radioimmunoassay (DiaSorin) and consists of a two-step procedure. In the first step the 25(OH)D and other hydroxylated metabolites are rapidly extracted from serum or plasma with acetonitrile. The extract is then assayed by RIA using a polyclonal antibody with specificity to 25(OH)D. The sample, the antibody and the tracer are incubated for 90 min at room temperature (20–25°C). The complexes (antigen–antibody) are separated after 20 min incubation at RT with a second antibody precipitating complex. This radioimmunoassay is a competitive binding assay with a limit of detection of 4 ng/mL and a within and between assay precision lower than 8%.

There is no clear international agreement on what should constitute a diagnostic serum level of vitamin D deficiency. Recent publications suggest that circulating levels of 25(OH)D should be between 50 nmol/L (≈ 20 ng/mL) and 80 nmol/L (≈ 32 ng/mL)[17], or at least 80 nmol/L[18]. Indeed, it has been demonstrated that calcium absorption is reduced in patients with vitamin D levels below 80 nmol/L[4]. In this particular study, two cut-offs of 25(OH)D inadequacy were fixed : < 80 nmol/L and < 50 nmol/L. However, we also used the threshold of 75 nmol/L that has been recommended by a consensus expert panel[17].

Results

Baseline characteristics of the 8532 women included in this study are presented in Table 1. The majority (97%) of the women were considered as osteoporotic.

The mean (SD) level of 25(OH)D was 61.1 (27.2) nmol/L. There was a highly significant difference of 25(OH)D levels across European countries ($p < 0.0001$). The lowest mean level of 25(OH)D was found in France [51.5 (26.1) nmol/L] and the highest in Spain [85.2 (33.3) nmol/L]. In the whole study population, the prevalence of 25(OH)D inadequacy was 79.6%, 72.7% and 32.1% when considering cut-offs of 80, 75 and 50 nmol/L, respectively. The prevalence of low 25(OH)D (< 80 nmol/L) reaches 90.4% in France and 45.8% in Spain (Figure 1).

There was a highly significant difference of 25(OH)D level between months of sampling ($p < 0.0001$), the lowest being found in March and the highest in September. In March, 83.8% of the women were in

Table 1. *Baseline characteristic of the study population (n = 8532)*

Variable	Mean (SD)
Age, years	74.2 (7.1)
BMI, kg/m²	25.7 (4.1)
25(OH)D level, nmol/L	60.1 (27.2)
Lumbar BMD, g/cm²	0.771 (0.135)
Femoral neck BMD, g/cm²	0.554 (0.079)

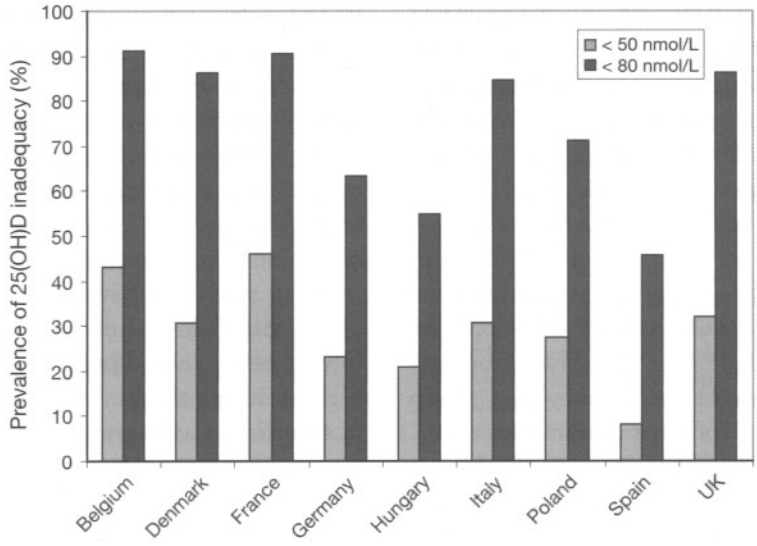

Figure 1. *Prevalence of vitamin D inadequacy across nine European countries* (n = *8532)*

25(OH)D inadequacy (80 nmol/L cut-off) compared to 71.6% in September (Figure 2). We found also a significant difference in 25(OH)D level across seasons ($p = 0.004$), with the lowest level in winter and the highest in summer.

There was a slight not clinically significant inverse correlation between the age of the patients and the level of 25(OH)D ($r = -0.10$; $p < 0.0001$). In women aged less than 70 years old ($n = 1631$), the prevalence was 80.3% and 37.6% when considering cut-offs of 80 and 50 nmol/L, respectively. The prevalence reaches 80% (cut-off of 80 nmol/L) and 36% (cut-off of 50 nmol/L) when considering patients aged less than 65 years ($n = 746$) (Figure 3). The prevalence of 25(OH)D inadequacy reaches 78.9% (cut-off of 80 nmol/L) and 38.2% (cut-off of 50 nmol/L) in patients aged less than 60 years old ($n = 285$).

Among the study population, 257 were osteopenic. In this subgroup, the prevalence of 25(OH)D inadequacy was 88% and 57% when considering cut-offs of 80 and 50 nmol/L, respectively. The prevalence reaches 86% (cut-off of 80 nmol/L) and 45% (cut-off of 50 nmol/L) when considering patients aged less than 65 years (Figure 3).

Discussion

The results of this study confirm high vitamin D [25(OH)D] deficiency amongst 8532 elderly European women, regardless of whether a 50 nmol/L, 75 nmol/L or 80 nmol/L threshold is used to diagnose deficiency and regardless of age of the patient. We have also shown that the prevalence of vitamin D inadequacy could be even higher in some particular countries.

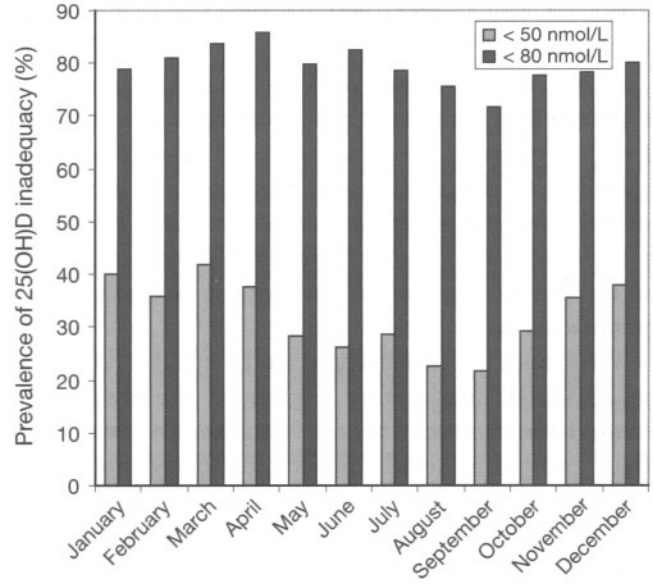

Figure 2. *Prevalence of vitamin D inadequacy stratified for months of sampling* (n = *8532)*

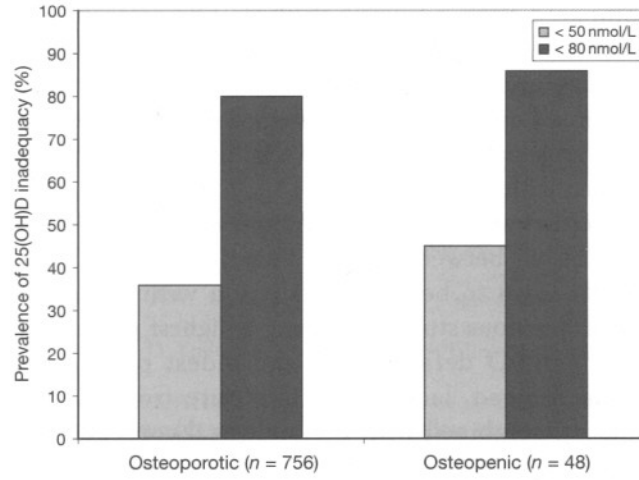

Figure 3. *Prevalence of vitamin D inadequacy in women aged less than 65 years*

Various studies have found that adults who have had osteoporosis or fractures associated with osteoporosis are more likely to have serum 25(OH)D levels below the normal range[16,19–23]. For example, in the UK, in 400 consecutive patients with a history of fractures or falls, 72.5% had very low serum 25(OH)D levels below 20 ng/mL (48 nmol/L)[24]. In a US population, very low vitamin D levels (below 12 ng/mL) were observed in 50% of postmenopausal, free-living women hospitalized for acute hip fracture with no secondary cause of bone loss[25]. A recent study carried out in Glasgow[26] prospectively investigated vitamin D inadequacy in a group of non-vertebral fragility fracture patients (n = 50). In this non-vertebral fracture group 82% of patients had 25(OH)D levels below 70 nmol/L and 90% had levels below 80 nmol/L. Other studies in osteoporotic populations (with or without fractures) have reported a prevalence of 25(OH)D inadequacy of 50–80% below 30 ng/mL (72 nmol/L) and 17–56% below 20 ng/mL (48 nmol/L)[16,20,23].

In our study, we analysed the vitamin D status of a population screened prior to being included in a trial investigating the anti-fracture efficacy of an anti-osteoporotic drug. Because of the criteria of inclusion/exclusion of patient in this particular study, our study population could not be considered as representative of the general population but more as an osteoporotic population starting a treatment.

We found, in this particular study, a high prevalence of 25(OH)D inadequacy. However, the prevalence observed in this study cohort was generally lower than that reported in healthy adult and elderly subjects in previous studies. The women enrolled in this clinical trial were fairly healthy and free of diseases other than osteoporosis. In addition, volunteers for clinical trials may be more conscious about their health than the general population. Both of these factors may have contributed to the lower overall prevalence of vitamin D deficiency observed in this study compared with previous studies. The same trends have been reported with the analysis of the baseline characteristics of patients included in the international Multiple Outcomes of Raloxifene Evaluation study, a large prospective intervention trial in postmenopausal women with osteoporosis[27].

In our study, we did not observe any strong clinical correlations between age and vitamin D levels. These results seem to be in contradiction with some but not all previous studies, showing a highest prevalence of vitamin D deficiency in the oldest population group. Indeed, lack of sun exposure from staying indoors, combined with the biological consequences of ageing, may contribute to a higher prevalence of vitamin D inadequacy in the elderly[28]. However, PTH levels are higher in the elderly than in younger people at similar serum 25(OH)D levels, which may adversely affect the skeleton[29,30], suggesting that higher vitamin D supplementation may be needed in the elderly population. It should also be pointed out that the prevalence of 25(OH)D inadequacy was high, irrespective of BMD status (osteoporotic or osteopenic).

In our study, we have also shown a strong difference of vitamin D level between months of sampling, the lowest being seen during the winter months and the highest during the summer months. These findings are in accordance with previous studies and especially with results of the recent systematic review on vitamin D inadequacy in postmenopausal women[16]. However, in our study, it should be pointed that the 25(OH)D inadequacy is still high (over 75% with the 80 nmol/L threshold) even during the summer months. These results suggest that a vitamin D supplement may be necessary in osteoporotic postmenopausal women, independent of the season.

With sunshine exposure being the most important source of vitamin D, one should expect that vitamin D status varies depending upon geographic location relative to the equator, with vitamin D status being better in residents closer to the equator compared with those living at higher latitudes. Such a relationship was reported for the general adult urban population living in various regions of France[31]. Moreover, epidemiological work carried out in the late 1980s and early 1990s have suggested that there is a clear link between latitude of residence and hip fracture risk, with Norway, Iceland and Sweden having the greatest hip fracture risk in the developed world[32]. However, when considering all countries represented in this study, there was no apparent relationship between either serum 25(OH)D levels or the prevalence of low levels and latitude of the country of origin. Inadequate serum 25(OH)D could be a global problem, irrespective of latitude. It may well be that extreme dietary deficiencies are sufficient to override any differences in sunlight exposure. However, while dietary sources of vitamin D are rare they include oily fish, fortified margarine and spreads, fortified breakfast cereals, meat, eggs and milk. Other factors, such as time spent outdoors, clothing habits, and skin type and pigmentation may influence differences in vitamin D status between countries[33].

Our results suggest that most postmenopausal women will require supplementation to maintain a high level of 25(OH)D. However, it should be pointed out that the exact role of vitamin D supplementation on fracture prevention is still a much debated issue[34–40].

Conclusion

This study confirms the high prevalence of vitamin D inadequacy in osteoporotic European postmenopausal women, regardless of the age of the women. This leads to a strong conclusion that a greater awareness of the importance of vitamin D inadequacy is required in order to address this public health problem.

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