Vitamin D Status in Patients with Osteopenia or Osteoporosis – an Audit of an Endocrine Clinic

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Received for publication: October 19, 2005; Accepted for publication: May 3, 2006

Abstract: Vitamin D deficiency and insufficiency may further increase fracture risk in patients with decreased bone mineral density. We audited serum 25-hydroxyvitamin D (25OHD) concentrations in patients with osteopenia or osteoporosis attending endocrine osteoporosis clinics in North London between January 1998 and September 2001.

The total number of patients analyzed was 448 (age range 17–89 years), with 191 patients being < 50 years old (42.6%). The following cut-off points for serum 25OHD were used: levels ≤ 30 nmol/L for deficiency, > 30–50 nmol/L for insufficiency, and > 50 nmol/L for sufficiency.

The overall prevalence of vitamin D deficiency was 30.5% and of vitamin D insufficiency was 35.9%. Vitamin D deficiency was as prevalent in young patients as in older ones: the prevalence of serum 25OHD ≤ 30 nmol/L in those < 50 years of age was 33.0% (n = 63 of 191), compared with 31.1% (n = 80 of 257) in patients aged ≥ 50 years.

Our results indicate that vitamin D deficiency and insufficiency is a common problem in patients with osteopenia or osteoporosis. This situation persists despite dietary advice and prescription of vitamin D_3 supplementation. Vitamin D deficiency affects all age groups, not merely the elderly.

Key words: Osteoporosis, osteopenia, vitamin D, secondary hyperparathyroidism

Introduction

Secondary hyperparathyroidism, a feature of vitamin D deficiency and insufficiency, is the principal mechanism of vitamin D-related bone loss, aggravating any underlying osteoporosis [1]. Vitamin D status is dependent on several factors including exposure to UV radiation/season [2], dietary intake [3], age [4], ethnic origin [5, 6], and percentage of body fat content [7], although these factors can confound each other (e.g., ethnic origin can influence the degree of exposure to UV radiation [8], intake of vitamin D may be more important during winter than summer).

The role of vitamin D deficiency and insufficiency in osteoporotic/osteopenic patients has only recently come to light. Treatment with calcium and vitamin D has been shown to reduce the risk of hip fracture in institutionalized elderly women [9]. It also reduced the incidence of nonvertebral fractures in men and women 65 years of age or older who were living in the community [10], although this was not confirmed in a recent randomized placebo-controlled trial on secondary prevention of fractures in elderly people [11] . In our clinic we tend to routinely recommend calcium and vitamin D_3 supplementation along with lifestyle advice to all patients with osteopenia/osteo-

DOI 10.1024/0300-9831.76.5.307

porosis according to UK guidelines [12]. However, the actual vitamin D status may be critically affected by compliance of the patients and the implementation of the guidelines in daily clinical practice.

We therefore decided to audit the serum 25-hydroxyvitamin D (25OHD) levels, the accepted biochemical index of vitamin D status, in all patients with osteopenia or osteoporosis attending our clinic, both new referrals and follow-up patients, between January 1998 and September 2001.

Patients and Methods

Patients

General characteristics

The total number of subjects studied was 448 (414 women and 34 men). Almost all of them were Caucasians with the exception of 28 Asians and two blacks. The mean age of the group was 52.0 years (range 17–89 years). The number of those aged < 50 years was 191 (42.6%). There

Table I: General characteristics of patient groups and their treatment. Percentages shown in brackets. Where means are shown, standard deviations are denoted by «SD». *** $p < 0.001$ for difference between groups. The differences in primary diagnoses and types of treatment were not tested for statistical significance.

	Osteoporotic patients	Osteopenic patients
Number	193	255
Gender		
Females	171 (88.6%)	243 (95.3%)
Males	22 (11.4%)	12 (4.7%)
Age	60.9 [SD 16.3]***	45.3 [SD 17.6]
BMI	24.1 [SD 5.0]	24.1 [SD 4.1]
Diet		
Vegetarians	19 (9.8%)	22 (8.6%)
Non-vegetarians	116 (60.1%)	101 (39.6%)
Data missing	58 (30.1%)	132 (51.8%)
Smoking		
Smokers	34 (17.6%)	31 (12.1%)
Non-smokers	116 (60.1%)	94 (36.9%)
Ex-smokers	8 (4.2%)	12 (4.7%)
Data missing	35 (18.1%)	118 (46.3%)
Fracture history		
None	126 (65.3%) ***	215 (84.3%)
One fracture	30 (15.5%) ***	24 (9.4%)
Two or more fractures	37 (19.2%) ***	16 (6.3%)
Primary diagnosis		
Postmenopausal	56 (29.0%)	68 (26.7%)
Idiopathic	62 (32.1%)	39 (12.3%)
Premature ovarian failure	2 (1.0%)	9 (3.5%)
Turner's syndrome	12 (6.2%)	93 (36.5%)
Vitamin D deficiency	19 (9.9%)	20 (7.8%)
Hypogonadism	11 (5.7%)	7 (2.7%)
Pituitary disease	5 (2.6%)	3 (1.2%)
Bowel disease	8 (4.2%)	1 (0.4%)
Glucocorticoid therapy	8 (4.2%)	4 (1.6%)
Other	9 (4.7%)	3 (1.2%)
Not recorded	1 (0.5%)	8 (3.1%)
Treatment		
Calcium + vitamin D_3 alone	33 (17.1%)	70 (27.5%)
Estrogen replacement	87 (45.1%)	149 (58.4%)
Androgen replacement	4 (2.1%)	3 (1.2%)
Bisphosphonates	76 (39.4%)	22 (8.6%)
No bone-protective treatment	1 (0.5%)	5 (2.0%)
Not recorded	6 (3.1%)	11 (4.3%)

were 124 newly referred patients who were assessed at the time of their first visit [blood tests and bone mineral density (BMD) measurement], and 324 follow-up patients who have been attending our clinic at regular yearly intervals for between one and five years. The population was divided into osteopenic (n = 255) and osteoporotic (n = 193) groups based on their BMD assessed by dual-energy x-ray absorptiometry (DEXA), according to WHO criteria [13]. Only one quarter of osteoporotic patients and a third of those with osteopenia were postmenopausal women. Our cohort was also slightly unusual in that it contained many patients with hypogonadism secondary to Turner's syndrome and premature ovarian failure, which is why there was a significant proportion of those younger than 50 years. This is because the unit has a special interest in reproductive endocrinology. The patients' characteristics are summarized in Table I.

Bone protective treatment

The majority of osteoporotic patients had been prescribed and therefore were supposed to be taking calcium (1000 mg/day) and vitamin D_3 (800 IU/day) supplementation (Calcichew-D3® Forte (Shire) 2 tablets per day), but fewer subjects in the osteopenic group were similarly prescribed. A significant percentage of patients were taking this as the sole treatment. Approximately half of the patients in each group were prescribed estrogen or androgen replacement as appropriate. Bisphosphonate treatment was more prevalent in the osteoporotic group compared to the osteopenic group. A small number of patients were not taking any bone-protective treatment at all. Table I summarizes the bone-protective treatment taken by the patients included in this analysis.

Methods

Study design

This was an audit employing a cross-sectional design, which included all patients attending endocrine osteoporosis clinics at the Royal Free Hospital and University College Hospital in London (latitude 51° N) between January 1998 and September 2001.

New patients had their BMD measured on the day of the visit when blood samples were taken, whereas follow-up patients had their BMD measured either on the day of the visit when blood test was performed or within the previous two years.

Data collection

Our clinics are fully computerized and data are updated at each clinic visit. For the purpose of this audit our computerized database (FileMaker Pro 4, FileMaker, Inc., California, USA) was used. All the data were collected in accordance with the Data Protection Act.

Assessment of bone mineral density

BMD at the lumbar spine (L_1–L_4) and total hip were measured by dual-energy x-ray absorptiometry (QDR 4500, Hologic Inc., Bedford, MA). The precision (coefficient of variation) of this method was 0.5% for the lumbar spine BMD and 1.0% for the femoral neck BMD.

Biochemical assay

Only one blood sample was taken per patient, at different times of the year, depending on the time of clinic visit, in the morning after an overnight fast to assess the vitamin D status. The serum 25OHD concentration was measured using a ^{125}I radioimmunoassay (DiaSorin, Minnesota, USA). Specimens were separated as soon as possible after collection and stored at 4 °C for up to 3 days. The sensitivity of the method was 5 nmol/L, intra-assay imprecision 5.9 ± 8.9% (CV, coefficient of variation), and interassay imprecision 6.0 ± 9.0% (CV).

For the purpose of this audit vitamin D deficiency was defined as serum 25OHD levels ≤ 30 nmol/L [14, 15]. Serum 25OHD levels of > 50 nmol/L were considered sufficient. An intermediate category of «insufficiency» therefore fell in between, with levels between > 30 and 50 nmol/L [16].

Analysis of the data

Differences between two groups were tested using *t*-test for numeric variables and chi-squared test for categorical variables. The data are presented as means with standard deviations (SD) or percentages.

All patients were also divided into three groups according to the season when blood sample was taken (February-May, June-September, and October-January). For comparing these three groups (seasons) regarding numerical outcome (serum 25OHD level), one-way ANOVA was used with Tukey's *post hoc* comparisons.

Statistical analysis was carried out using GraphPad Prism version 4.00 for Macintosh, GraphPad Software, San Diego, California USA, www.graphpad.com.

Results

Patient general characteristics

Results of BMD measurement, which are not shown, served to separate the cohort into osteopenic and osteoporotic groups. Clinical data of patients in both groups

are presented in Table I. Patients in the osteoporotic group were significantly older than those in the osteopenic group ($p < 0.001$). As expected, there was a significantly higher prevalence of one or more fractures in the osteoporotic group ($p < 0.001$). There was no significant difference in body-mass index (BMI) between the osteopenic and osteoporotic groups. The proportion of declared vegetarians was similar between the two groups. There seemed to be a slightly larger proportion of smokers in the osteoporotic than in the osteopenic groups, but data on smoking were missing in over 40% of osteopenic patients.

Vitamin D

Vitamin D deficiency (serum 25OHD level ≤ 30 nmol/L) was found in 30.5% of all patients (136 out of 448 patients) or 32.6% of the osteoporotic group and 28.6% of the osteopenic group. Further 161 patients (35.9% of all) or 33.2% of the osteoporotic group and 38.0% of the osteopenic group had serum 25OHD levels in the insufficiency range. Therefore, 297 out of 448 patients (66.3%) or 65.8% of the osteoporotic group and 66.7% of the osteopenic group had serum 25OHD levels that were suboptimal (≤ 50 nmol/L). No statistically significant difference in the numbers of patients in each serum 25OHD category was found between the osteopenic and osteoporotic groups.

When all patients were stratified into age groups (Figure 1), the prevalence of vitamin D deficiency (serum 25OHD ≤ 30 nmol/L) was between 25.0–35.8% in different age groups. Vitamin D deficiency was as prevalent in young patients (< 50 years) as in older ones (≥ 50 years): 33.0% (n = 63 of 191) and 31.1% (n = 80 of 257) respectively.

The prevalence of 25OHD deficiency in newly referred patients was 27.4% vs. 31.5% in follow-up patients. The prevalence of 25OHD insufficiency was slightly albeit insignificantly higher in newly referred patients compared to follow-up patients, 41.9% vs. 33.6% respectively.

The serum 25OHD measurements were also partitioned into three «seasons»: February to May, June to September, and October to January (Figure 2). There was a statistically significant difference in serum 25OHD levels between seasons. The highest levels were recorded during the season (June–September) with the highest sun exposure.

Serum 25OHD levels were significantly lower in declared vegetarians (37.61 ± 21.78 nmol/L) compared to declared non-vegetarians (44.76 ± 24.31 nmol/L; $p = 0.031$).

The majority of vitamin D-deficient osteoporotic patients (87.4%) and a smaller proportion of vitamin D-deficient osteopenic patients (64.9%) were supposed to have been taking calcium and vitamin D_3 supplementation.

Discussion

The most important finding of this audit was that of high prevalence of vitamin D deficiency (30.5%) in patients attending our endocrine osteoporosis clinics. If we take into consideration an even greater prevalence of vitamin

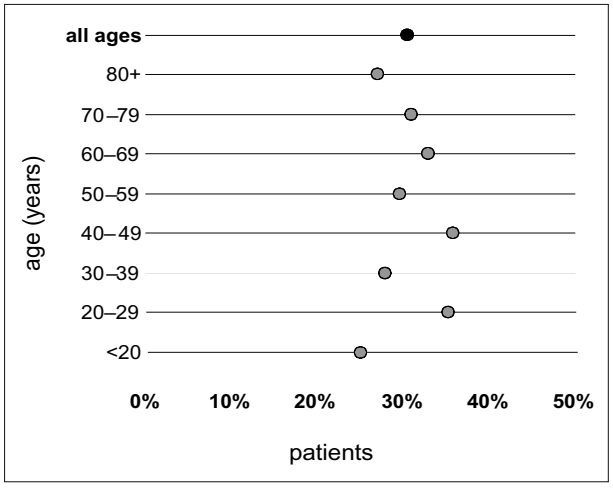

Figure 1: Proportions of patients (expressed as percentage) with serum 25OHD levels ≤ 30 nmol/L stratified by age group.

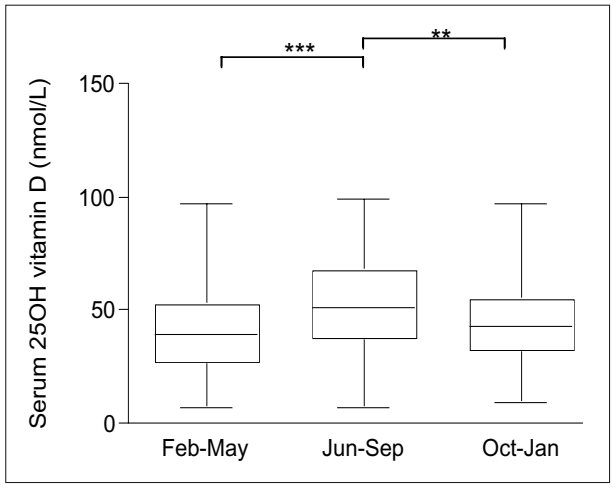

Figure 2: Serum 25OH vitamin D status according to season ($p < 0.001$ overall; ** $p < 0.01$ and *** $p < 0.001$ for *post hoc* comparison).

D insufficiency, it is obvious that almost two-thirds of our patients had suboptimal serum 25OHD levels. This appears to be unexpectedly high in a population of predominantly white, nonhousebound, noninstitutionalized outpatients, with almost half of them being younger than 50 years. The prevalence of 25OHD deficiency in our clinic population was similar across all age groups. This is one of the few reports of serum 25OHD status in patients younger than 50 years in age attending osteoporosis clinic. Our findings of high prevalence of vitamin D deficiency and insufficiency in those younger than 50 are in agreement with a study from Boston, which included an outpatient thyroid clinic population and found that patients' age was not among the predictors of serum 25OHD concentration [17]. Nakamura *et al* found that vitamin D insufficiency might be prevalent among healthy young women [18] and Haney *et al* recently reported that medical residents were at risk for vitamin D insufficiency [19]. Thomas *et al* found that vitamin D deficiency was as high as 57% in unselected general medical inpatients in Boston. The patients studied were younger and more representative of the general population than those in many previous studies [20]. Plotnikoff and Quigley found in their study that younger patients had even significantly lower serum 25OHD levels than older patients [21]. In contrast to these statements, Rucker *et al* measured serum 25OHD in healthy Canadians and found that age is a major determinant of vitamin D status [22]. Isaia and co-workers studied the prevalence of 25OHD deficiency in a population drawn from osteoporosis clinics in Italy and likewise found that serum 25OHD levels are inversely correlated with age [23]. This is likely to be multifactorial in origin. Elderly patients have low intakes of vitamin D [24]. They are more likely to cover up their skin, especially in the colder weather of northerly latitudes. Even if their skin is exposed to sun, there may be less efficient synthesis of vitamin D in aged skin [25]. Moreover, higher serum 25OHD concentrations are required in older people to avoid secondary hyperparathyroidism, perhaps because declining renal function causes decreased conversion of 25OHD to $1,25\,OH_2D$ [26, 27]. Generally, vitamin D status is more troublesome in elderly subjects in comparison with young adults (reviewed in [28]). There is a possibility that some additional unrecognized cause for vitamin D deficiency and insufficiency might be present in our younger patients. First of all, there is some evidence to suggest that vitamin D metabolism in patients with Turner's syndrome is abnormal. For example, Gravholt *et al* found reduced serum 25OHD levels in patients with Turner's syndrome when compared to controls, suggesting either diminished intake or uptake of the compound [29]. This finding can at least partly explain significant prevalence of low vitamin D levels in our younger population, which included a significant proportion of patients with Turner's syndrome.

The definition of vitamin D deficiency and insufficiency may, of course, influence estimates of its prevalence. It is difficult to clearly define cut-off values for each stage, partly because of incomparable serum 25OHD values from different laboratories, using different assays [30]. There is no doubt that serum 25OHD levels below 12.5 nmol/L can result in osteomalacia and there is also evidence that levels below 25 nmol/L lead to osteomalacia in the long run (reviewed in [28]). Consequently, some researchers used an even higher threshold of 30 nmol/L [14, 15] for the vitamin D deficiency and that was the cut-off point we used in this audit. Having in mind the definition of vitamin D insufficiency as the level of serum 25OHD that causes serum parathyroid hormone (PTH) increase with deleterious effect on the skeleton [31] via increased turnover of bone [16], serum 25OHD levels of > 30 to 50 nmol/L were considered insufficient. Two studies of more than 7700 patients using the same radioimmunoassay that we used in this audit showed increased levels of serum PTH with serum 25OHD levels of 50 nmol/L or less [32, 33]. However, it seems that this definition of vitamin D insufficiency is quite conservative, as some other investigations suggested that the true cut-off value might be as high as 80 nmol/L [34, 35]. Moreover, one cannot ignore the opinion that only serum 25OHD levels between 100 and 200 nmol/L are adequate, where no disturbances in vitamin D-dependent body functions occur (reviewed in [28]).

Similar prevalence of 25OHD deficiency and insufficiency was found in newly referred patients and the follow-up patients. This was a surprising finding since the latter group had received standardized advice on lifestyle and diet modification and had been prescribed and were supposed to be taking calcium (1000 mg) and vitamin D_3 (800 IU/day) supplementation. It is disappointing that our advice and the recommended supplementation did not make any significant impact on vitamin D status of patients attending our clinics.

It is possible that a proportion of our patients were not compliant with recommended calcium and vitamin D_3 supplementation because of side effects and poor patient tolerance of calcium and vitamin D_3 supplementation. Combined oral supplements are associated with constipation, dyspepsia, and nausea, and the tablets are relatively large. Unfortunately, this audit based on information from the database had limitations in terms of assessing compliance to recommended therapy or supplementation. It is less likely that the recommended supplementation with 800 IU of vitamin D_3/day was not enough to replace the deficit, as there are some data

which suggest that even supplements containing a median of 280 IU of vitamin D_3/day lead to significantly higher vitamin D status in postmenopausal women [36]. On the other hand, Glerup and colleagues suggest that in absence of sunlight, 1000 IU/day of vitamin D_3 is necessary to maintain adequate serum 25OHD concentrations [8].

In London and its surroundings at 51 °N latitude there is no production of previtamin D in skin from October through March [37]. Our audit data, showing a statistically significant difference in serum 25OHD status between seasons, with the highest levels recorded during the season June-September, is consistent with this observation. Therefore, serum 25OHD status in autumn and winter is mostly dependent on oral intake of vitamin D-rich foods such as meat, meat products, and fish, which means that certain groups, for example vegetarians, have an increased risk of deficiency, as this audit clearly showed.

A widespread increase in vitamin D intake is likely to have a greater effect on osteoporosis and fractures than many other interventions [38]. It is not clear what should exactly be the recommended daily dose, but the margin of safety is probably substantial. Excess vitamin D causes hypercalciuria and hypercalcemia, but these complications do not occur unless the daily dose exceeds at least 2400 IU [39]. Recently Vieth *et al* confirmed the safety and efficacy of even 4000 IU/day vitamin D_3 in patients who needed additional vitamin D [40]. Such high doses of vitamin D are probably needed only in special circumstances, although some authors believe that a daily supplement of 1000 IU of vitamin D_3 is advisable for all adults [41].

In summary, our audit showed that 25OHD deficiency and insufficiency represents a significant problem in patients attending an endocrine osteoporosis clinic, despite detailed advice regarding changes to lifestyle and prescription of calcium and vitamin D supplementation. It seems, however, that compliance is a bigger issue than a potentially insufficient amount of vitamin D in the prescribed supplements. More intensive education of patients and strict implementation of clinical guidelines are required to ensure that patients with osteoporosis or osteopenia are vitamin D-replete. This is essential in order to optimize their treatment by preventing secondary hyperparathyroidism and increased bone turnover.

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