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ORIGINAL ARTICLE

The prevalence of vitamin D deficiency in consecutive new patients seen over a 6-month period in general rheumatology clinics

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Abstract The objectives of this study are to assess: (a) the prevalence of vitamin D deficiency among new patients attending rheumatology outpatient departments, (b) the age profile of these low vitamin D patients and (c) whether any diagnostic category had a particularly high number of vitamin D-deficient patients. All new patients seen consecutively in general rheumatology clinics between January to June 2007 inclusive were eligible to partake in this study, and 231 out of 264 consented to do so. Parathyroid hormone, 25-hydroxyvitamin D, creatinine, calcium, phosphate, albumin and alkaline phosphatase levels were measured. We defined vitamin D deficiency as ≤53 nmol/l and severe deficiency as ≤25 nmol/l. Overall, 70% of 231patients had vitamin D deficiency, and 26% had severe deficiency. Sixty-five percent of patients aged ≥65 and 78% of patients aged ≤30 years had low vitamin D levels. Vitamin D deficiency in each diagnostic category was as follows: (a) inflammatory joint diseases/connective tissue diseases (IJD/CTD), 69%; (b) soft tissue rheumatism, 77%; (c) osteoarthritis, 62%; (d) non-specific musculoskeletal back pain, 75% and (e) osteoporosis, 71%. Seasonal variation of vitamin D levels was noted in all diagnostic groups apart from IJD/CTD group, where the degree of vitamin D deficiency persisted from late winter to peak summer. Very high prevalence of vitamin D deficiency was noted in all diagnostic categories (p=0.006), and it was independent of age (p=0.297). The results suggest vitamin D deficiency as a possible modifiable risk factor in different rheumatologic conditions, and its role in IJD/CTD warrants further attention.

Keywords Outpatient clinics · Prevalence · Rheumatology · Vitamin D deficiency

Background and introduction

Vitamin D deficiency is a health concern of all ages and races. It can be associated with an array of poor clinical outcomes for patients in many subspecialties, not just rheumatology. The major biologic function of vitamin D is to maintain normal blood levels of calcium and phosphorus, and osteomalacia is the classic vitamin D deficiency disease where bone becomes soft due to hypomineralisation. Osteomalacia predisposes to bone fracture, skeletal deformity, bone pain, persistent low-level muscle aching and weakness [1]. Vitamin D deficiency when less severe also has a role in causing sub-clinical osteomalacia without overt biochemical osteomalacia; this can also lead to muscle weakness and hard-to-diagnose chronic musculoskeletal pain [2, 3]. Inadequate serum vitamin D can be associated with secondary hyperparathyroidism with consequent increased bone turnover and secondary osteoporosis. In addition to maintaining calcium homeostasis, the role of vitamin D in muscle health is well documented. Receptors for 1,25(OH) vitamin D have been identified in skeletal muscle tissue [4]. There are several double-blind randomised controlled trials showing that vitamin D supplementation increased muscle strength and balance [5, 6]. Besides its effects on musculoskeletal system, 1,25-dihydroxyvitamin D is a potent modulator of

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immune function, inhibitor of cellular growth, stimulator of insulin secretion and inhibitor of renin production [2, 7]. The observations that vitamin D-deficient people are more prone to solid tumours, autoimmune diseases and hypertension have added to the importance of studying vitamin D deficiency [2, 7].

Poor awareness of this preventable and treatable condition exists, especially in rheumatology patients. It is widely recommended that there should be a routine use of vitamin D and calcium for all older housebound, sunlight-deprived/institutionalised people, but there are no guidelines for free living healthy dwellers, who undoubtedly belong to the vast majority of our rheumatology outpatient attendees. It is therefore imperative that we study not only the significance, but also the prevalence of this deficiency condition among our rheumatology patients. It is with this perspective that the current study was undertaken. The aims of this study were threefold: (1) to assess the prevalence of vitamin D deficiency in new patients at first visit to our rheumatology outpatient clinics, (2) to find out the age profile of the vitamin D-deficient patients and (3) to investigate whether any diagnostic category had a particularly high number of vitamin D-deficient patients.

Materials and methods

All new patients who attended rheumatology outpatient clinics were eligible to partake in this study. This was a cross-sectional observational study. All new patients seen consecutively between January to June 2007 inclusive were eligible for entry into this study. All new patients (all-comers) were assessed and asked for consent to partake in this study; 231 out of 264 patients gave their consent to do so. Baseline demographic details were recorded, along with other clinical and biochemical parameters, and the given diagnosis after rheumatologic opinion. Blood sampling was performed to analyse parathyroid hormone (PTH), 25-hydroxyvitamin D, serum creatinine, calcium, phosphate, albumin and alkaline phosphatase levels. A total of 33 patients did not give consent, and among them, 83% stated that they did not wish to participate in research and the rest of them refused due to hassle of having blood tests. Patients who did not consent for this study were comparable as regards the age, gender, diagnosis and quarterly distribution than those who consented ($p>0.05$). We defined hypovitaminosis D as ≤53 nmol/l (≤21 ng/ml) and severe deficiency as ≤25 nmol/l (≤10 ng/ml). The PTH normal range was 15–65 ng/l. We divided the rheumatologic diagnoses into five major categories: (a) inflammatory joint disease and connective tissue diseases, (b) soft tissue rheumatism: this mainly included chronic musculoskeletal pain syndrome (fibromyalgia) and other regional non-inflammatory conditions, (c) osteoarthritis, (d) osteoporosis/metabolic bone disease and (e) non-specific musculoskeletal back pain (excluding backache secondary to osteoarthritis, inflammatory joint disease and vertebral fractures). The study was conducted in adherence with the Declaration of Helsinki and International Committee on Harmonization good clinical practices. This study was conducted at the South Infirmary—Victoria University Hospital (SIVUH), which serves as a catchment area of approximately 500,000. It is located in Cork City at the very southern tip of Ireland. The SIVUH is a secondary referral centre where all referrals come from primary care physicians (i.e. general practitioners—'G.P.s'). Ireland has a temperate climate with a latitude of 53° north.

Definition of vitamin D deficiency

For the purpose of this study, vitamin D deficiency was defined as a level ≤53 nmol/l, i.e. ≤21 ng/ml. Our laboratory's normal range was: 53–150 nmol/l or 21–60 ng/ml. The actual cut-off to define vitamin D deficiency has not been elucidated yet and varying 25-hydroxyvitamin D thresholds have been used in different studies. However, there is at the very least enough evidence to support using a cut-off around the 50 nmol/l level as 25 (OH) D levels of <50 nmol/l generate a secondary hyperparathyroidism response which in turn influences bone metabolism [8, 9]. We divided our patients into three categories according to their serum 25-hydroxyvitamin D concentrations: those with severe vitamin D deficiency—level less than 25 nmol per litre [12 ng per millilitre], mild–moderate vitamin D deficiency–level 25 to 53 nmol per litre [12 to 21 ng per millilitre] and those with adequate vitamin D stores—level of 53 nmol per litre [21 ng per millilitre] or more. Serum 25(OH) vitamin D was measured by Diasorin Liaison chemiluminescence immunoassay, which measures both 25(OH) vitamin D2 and D3 levels. These tests were carried out by Claymon laboratories, an Irish National Accreditation Board accredited laboratory to ISO's 15189 Medical Testing Standard.

Results

The prevalence of vitamin D deficiency, both absolute and severe, was noted to be high in this study population of non-housebound rheumatology outpatient attendees. The patients' ages ranged from 19 to 91 years of age with a mean age of 53±16 years. Sixty-five percent of the cohort was female, and 98% of patients were white Caucasians. Seventy percent (162 patients) of the 231 patients had

vitamin D deficiency, and 26% (n=61) overall had severe vitamin D deficiency. Thirty-four patients were found to have hyperparathyroidism, and we noted that all of them were low in vitamin D and 70.5% (n=24) of them had severe deficiency. In other words, of patients with low vitamin D (n=162), 21% (n=34) had secondary hyperparathyroidism. Significant inverse relation was observed between serum parathyroid hormone and 25(OH) D levels (r=−0.32; p=<0.0001). The overall inverse relation between serum parathyroid hormone and 25(OH) D levels did not vary with the season—whether late winter or early to peak summer.

Examining the age profile of these patients, it was noted that 24% (n=55) of the 231 patients were aged ≥65 years; 65% of them were vitamin D deficient and 25% were severely deficient. The extent of vitamin D deficiency in the younger age group was quite striking. Although only 23 out of the 231 patients were ≤30 years, 78% of them were vitamin D deficient and 26% had severe deficiency (Table 1). Age distribution among the sample was as follows: ≤30 years, n=23, 11%; 31–50 years, n=69, 32%; 51–64 years, n=84, 39%; and ≥65 years, n=55, 24%. This reveals a wide distribution of age among the cohort; however, a significant majority of our patients belonged to relatively younger age spectrum—76% of the whole cohort was aged <65 years. Figure 1 demonstrates the vitamin D status of our cohort; for the ease of data interpretation, we have divided our patients in different subgroups according to their vitamin D titres. No correction of vitamin D level was made for the time of year the samples were taken, and the cut-off values remained the same throughout the study period, which was the first 6 months of 2007.

Table 2 shows the breakdown of data from the cohort and also a three-monthly overview of changes subdivided according to the five diagnostic categories. We noted that among patients in IJD/CTD group, the degree of vitamin D deficiency persisted from late winter to peak summer; this was directly in contrast with the other diagnostic groups, where vitamin D status improved significantly in the second quarter of year—IJD/CTD group: 68% of patients had vitamin D deficiency in the first quarter of the year versus 69% of patients in the second quarter; STR group: 84% versus 65%; OA group: 80% versus 46%. No case of biochemically proven osteomalacia (low serum calcium and phosphate, high alkaline phosphate) or chronic kidney disease was found in any patient in the cohort (i.e. alkaline phosphatase, serum phosphate, calcium and creatinine were within normal range). We carried out an analysis of variance to compare the means of vitamin D scores for each of the five diagnostic categories, and no difference of any statistical significance was found (F=2.04, p=0.090). Soft tissue rheumatism had the lowest mean but when the variation in the data was taken into account, there was no statistical evidence for any difference. We also compared PTH level results with the different diagnostic categories and, similarly, no statistically significant difference was noted (F=1.32, p=0.264).

Discussion

We have found a high prevalence of vitamin D deficiency in new patients attending our rheumatology outpatient clinics. These observations are a cause of concern. There are many reasons why rheumatologists should be interested in vitamin D: it is a major player in bone and muscle health, and its role in immunopathology is emerging. There are different lines of evidence supporting the important role of vitamin D in a rheumatology setting. Firstly, non-specific musculoskeletal pain is one of the common presentations in rheumatology outpatients, and its association with vitamin D deficiency is well described [3]. Similarly, in our cohort, the highest prevalence of vitamin D deficiency was noted in patients with soft tissue rheumatism. However, a high number of vitamin D-deficient patients with inflammatory joint diseases were also found. This could be linked to multiple immunosuppressive properties of vitamin D. In spite of the overwhelming evidence linking vitamin D deficiency to widespread pain, a recent meta-analysis of studies by the Cochrane Collaboration has concluded that there are insufficient randomised controlled trials to determine if intervention with vitamin D helps for widespread pain [10]. Secondly, the anti-fall efficacy of vitamin D is well documented. A 2009 meta-analysis of randomised

Table 1 The age-related findings in the while cohort

Age	Subjects with vitamin D deficiency [number (%)]	Subjects with severe vitamin D deficiency [number (%)]	Subjects with normal vitamin D status [number (%)]	Total [number (%)]
≤30 years	18 (78%)	6 (26%)	5 (22%)	23 (10% of the cohort)
≥65 years	36 (65%)	14 (25%)	19 (34.5%)	55 (24% of the cohort)
31–64 years	108 (70%)	41 (27%)	45 (29%)	153 (66% of the cohort)

This reveals that age of patients do not substantially influence the prevalence

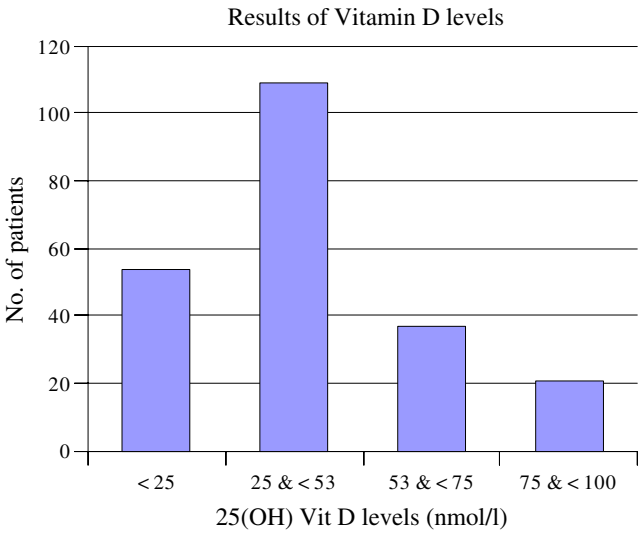

Fig. 1 Vitamin D status of the cohort. For the ease of data interpretation, we have divided our patients in different subgroups according to their vitamin D titres

controlled trials has shown that fall prevention increased significantly with higher achieved 25-hydroxyvitamin D levels—60 to 95 nmol/l [11]. Furthermore, the rheumatology patients, in general, are more prone to have falls and/or fractures on account of the nature of their musculoskeletal diseases. Thirdly, the anti-fracture efficacy of vitamin D is now well established [12, 13]. A recent meta-analysis of randomised controlled trials has found a dose-dependent relationship of vitamin D and its anti-fracture efficacy starting at the level of 75 nmol/l. Moreover, it was noted that vitamin D reduced the risk of non-vertebral fractures by 20% and the hip fractures by 18%; this beneficial effect was achieved with vitamin D supplementation of at least 400 IU per day [12]. Fourthly, there is growing evidence linking the role of vitamin D as a potential contributor to immunopathology, and new evidence rather suggests its role in the aetiology of autoimmune diseases. Genetic polymorphism for vitamin D regulatory genes, such as for vitamin D receptor, has been found in patients with autoimmune diseases, and this has been correlated with accelerated bone loss in patients with rheumatoid arthritis [14, 15]. Few recent studies have also shown a possible immunomodulatory role of vitamin D in RA and an inverse relationship with disease activity and the risk of developing of RA [16, 17].

People in the younger age groups, who are otherwise healthy, are assumed not to require a dietary source of vitamin D. In our study group, there was a wide age spectrum (19–91 years with a mean age of 53±16 years) and it was noted that 78% of patients aged ≤30 years were low in vitamin D. The postulates to explain vitamin D deficiency in young adults gets complicated by the fact that in Europe there are very few foods which are fortified with vitamin D. One may argue that these results simply explain low vitamin D levels in Ireland—a country with only limited seasonal sun exposure. However, a recent study carried out in the same city where our research was done had shown that 48% of free living women were low in vitamin D, and only 7% had severe vitamin D deficiency [18]. Clearly, the prevalence and severity of vitamin D deficiency is quite striking among our rheumatology patients—70% were vitamin D deficient and 26% had severe deficiency. Moreover, it should be pointed out that compared with our study, which was carried out from late winter to the peak summer, the study of healthy reference

Table 2 shows vitamin D deficiency in each of the five diagnostic categories along with 3-monthly over view of changes in vitamin D levels

Diagnostic category	Number of patients	Vitamin D deficiency [number (%)]	Severe vitamin D deficiency [number (%)]	Vitamin D status in first quarter of year[a]	Vitamin D status in second quarter of year[b]
IJD/CTD	84	58 (69%)	21 (25%)	41 (28, 68%)	43 (30, 69%)
Soft tissue rheumatism	79	60 (77%)	28 (35%0)	44 (37, 84%)	35 (23, 65%)
Osteoarthritis	53	33 (62%)	7 (13%)	25 (20, 80%)	28 (13, 46%)
Osteoporosis	7	5 (71%)	2 (29%)	5 (3, 60%)	2 (2, 100%)
Non-specific backache	8	6 (75%)	3 (37%)	6 (4, 67%)	2 (2, 100%)
TOTAL	231	162 (70%)	61 (26%)	121 (92)	110 (70)

Among the cohort of 84 patients with IJD/CTD, 80 patients had inflammatory joint diseases (rheumatoid arthritis, psoriatic arthritis, spondyloarthopathies) and four patients suffered from connective tissue diseases. IJD = inflammatory joint diseases; CTD = connective tissue diseases

IJD inflammatory joint diseases, *CTD* connective tissue diseases

[a] First quarter of the year—January to March [values are the total number of patients (number of vitamin D-deficient patients and its percentage)]

[b] Second quarter of year—April to June [values are the total number of patients (number of vitamin D-deficient patients and its percentage)]

group from the similar geographic area was done only in late winter (February–March) with worse predicted vitamin D levels; however, rheumatology patients were noted to have worse vitamin D status. These findings have severe implications at a population level for their long-term health.

It is important to mention the issues of terminology and cut-offs to define vitamin D deficiency, specifically with regard to use of the terms 'inadequacy, insufficiency or suboptimal states'. We believe that these latter three terms are both confusing and of no major clinical or research benefit. We favour using the term 'deficiency' and then subdividing further according to the degree of severity. Although, majority of recommendations favour using the cut-off value of 75 nmol/l, there are still some clinicians who favour conservative approach of using the cut-off value of 50–55 nmol/l [19]. In this study, which was designed in late 2006, we used the then perceived wisdom to define hypovitaminosis D, i.e. a cut-off of 53 nmol/l (21 ng/ml). Clearly, our results show a very high prevalence of vitamin D deficiency even using a conservative cut-off of 53 nmol/l. Had we used what we now believe should be the cut-off, i.e. 75 nmol/l (30 ng/ml), 87% of our cohort of 231 patients would have been deficient in vitamin D. Seasonal and latitudinal variations of 25-hydroxyvitamin D levels have long been described with the lowest levels reported in the late winter season. However, we noted that apart from some predicted improvement in vitamin D levels in early to peak summer, a significant proportion of patients had low vitamin D levels—48% of the whole cohort in the month of June. Reviewing the quarterly changes in vitamin D levels among different diagnostic categories, we noted remarkably similar degree of deficiency in IJD/CTD group from January to June; however, in other diagnostic categories, a significant improvement of vitamin D levels was noted in early to peak summer. This possibly is related to some of its anti-inflammatory and immune-modulating properties. Moreover, we noted that nearly one quarter of our patients with vitamin D deficiency had secondary hyperparathyroidism, and these results are comparable to patients with cystic fibrosis [20]. We know that there are clear guidelines recommending vitamin D supplementation with 800 IU/day to cystic fibrosis patients aged >1 year and to monitor 25(OH)D concentrations in the late autumn or winter [21, 22]; however, there are no such consensus statement or recommendations for our rheumatology patients. We also observed a significant negative correlation between parathyroid hormone and 25-hydroxyvitamin D ($r=-0.32$; $p=<0.0001$), and our results are quite similar to the published literature—negative correlation in the range of −0.15 to −0.45 [23]. Furthermore, in rheumatology outpatient settings, a recent retrospective study in UK has shown that vitamin D deficiency is significantly more prevalent amongst general rheumatology outpatients than osteoporotic or osteopaenic patients, irrespective of whether they were receiving vitamin D supplementation at the time of measurement [24]. These findings lend weight to the impression that rheumatology patients should be regarded as a high-risk group to have vitamin D deficiency, given its increasingly recognised role in the pathogenesis of chronic pain, autoimmunity and inflammatory diseases. Moreover, many of our patients would have limited sun exposure either due to poor mobility secondary to joint deformities, or avoidance from sun, such as in SLE.

Among the strengths of our study is its prospective nature with three clearly defined objectives. In an attempt to minimize selection bias, we attempted to recruit all consecutive patients over a 6-month period. The participants of this study were free living, and none of them were institutionalised. All our subjects were new outpatient referrals (all-comers) with no confirmed rheumatologic diagnosis at first presentation to us. All 231 studied patients were immunosuppressive naïve at the time of vitamin D assessment. This limited the bias of any interaction of rheumatologic drugs with vitamin D metabolism. Furthermore, none of our patients had chronic kidney disease (estimated GFR of <60 ml/min per m^2 for ≥3 months), or the symptoms suggestive of malabsorption or celiac disease. In our centre, there is separate office to deal with referrals for DEXA scanning, and this explains the low number of patients referred to us with osteoporosis alone. There are limitations to this study: there was no control population, full data collection detailing current and past calcium and vitamin D supplementation was not done, no dietary history was documented and no documentation of outdoor activities/sun exposure was made. However, these notable limitations were never meant to be the focus of this small study or among the objectives of this study. Rather, we wanted to get a prolonged snapshot of vitamin D status in our general rheumatology clinics.

In summary, we have found a very high prevalence of hypovitaminosis D in our cohort of new rheumatology patients, extending well beyond the traditional risk categories of the older housebound, sunlight-deprived or institutionalised person. The results underscore the fact that all physicians, not just rheumatologists, must be vigilant in identifying and treating this vitamin-deficient state, a state which has protean deleterious effects on the well-being and health of not just rheumatology patients. It is now time for rheumatologists to take the lead in drawing up formal guidelines with regard to when to investigate for vitamin D deficiency and how to treat it most effectively.

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Disclosures None

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