

ORIGINAL ARTICLE

## Vitamin D deficiency in general medical inpatients in summer and winter

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### Abstract

**Background:** Vitamin D deficiency is common in various populations worldwide. Adverse effects of vitamin D deficiency are the development of bone disorders; however, other diseases such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis and certain cancers have also been linked to vitamin D deficiency. The general medical inpatient population is a group at increased risk of vitamin D deficiency. These patients often have coexistent risk factors for its consequences. This study aims to document a point prevalence of vitamin D deficiency in this population.

**Methods:** Two cross-sectional audits of patients admitted to general medicine units were carried out – the first in mid-November at the end of winter and the second in mid-April and May at the end of summer. Information regarding patients' comorbidities, medication usage, previous falls and fractures was obtained and serum 25-hydroxyvitamin D, parathyroid hormone and calcium levels were measured.

**Results:** A total of 129 patients was studied (65 in winter and 64 in summer). Ninety-four patients (74%) had 25-hydroxyvitamin D levels  $\leq 50$  nmol/L. Seven patients had severe deficiency (levels  $\leq 12.5$  nmol/L). Average vitamin D levels were lower at the end of winter (35 vs 43 nmol/L,  $P = 0.007$ ). Of the 37 patients receiving vitamin D supplements, 20 (54%) had 25-hydroxyvitamin D levels  $\leq 50$  nmol/L.

**Conclusion:** Low vitamin D levels were common in this general medical inpatient population. The average vitamin D level was lower in the patient group tested in November following winter. Supplementation of vitamin D did not uniformly prevent deficiency.

## Introduction

Vitamin D deficiency is common and has been identified in various populations in Australia and around the world, including nursing home patients and community-dwelling adults.<sup>1–4</sup> The consequences of vitamin D deficiency include the syndrome of osteomalacia,<sup>5</sup> accelerated bone loss<sup>6</sup> and an independently increased risk of falls.<sup>3</sup> However, other

diseases such as multiple sclerosis, type 1 diabetes and rheumatoid arthritis and certain cancers have also been linked to vitamin D deficiency.<sup>7</sup> Treatment with vitamin D retards bone loss and appears to reduce falls and fractures in some groups of individuals.<sup>8–10</sup> International studies have suggested that hospitalized general medical patients are a group at high risk of deficiency with between 26 and 66% of patients having levels less than 37.5 nmol/L.<sup>11–13</sup> They are also likely to be at higher risk of adverse health outcomes compared with a general aged population. This is because of poor general health status and the presence of complex medical comorbidities and medications that

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increase risk of low bone mineral density, falls and fracture.

## Methods

### Study subjects

The primary hypothesis of the study was that vitamin D deficiency is common in the general medical population.

We carried out cross-sectional surveys of general medical inpatients at the end of winter 2004 and the end of summer 2005. The populations studied were current general medical unit inpatients aged 60 years and above at the Royal Melbourne Hospital, a tertiary referral University teaching hospital. The patients studied were chosen arbitrarily as those under the general medical unit bed card as of 20.00 hours on the specified days. The surveys were undertaken on one day in November and one day in both April and May to increase numbers. These dates were chosen to show the vitamin D levels at the end of the winter and summer periods, respectively.

Demographic data from the general medical population for the 2004/2005 period were obtained from hospital admission and discharge records.

The study was approved by the Melbourne Health Human Research and Ethics Committee. Written consent was obtained. Patients unable to consent secondary to cognitive impairment were recruited with acknowledgement of the next-of-kin and the consent of the Victorian Civil Administration Tribunal.

### Evaluation of clinical characteristics

During the admission, the patients' clinical characteristics were gathered from the admission medical record. The data were recorded on a standard questionnaire by the resident staff of the medical unit. The data collected included age, sex and residential status. Diagnoses were recorded with emphasis on conditions traditionally associated with vitamin D deficiency and those that may reduce mobility and place patients at risk of falls. The presence or absence of conditions was collected without any indexation of severity or current activity of the problem. Falls histories were taken from either the patient record or the patients directly. Fractures were specified as low trauma. Medication charts were also reviewed with emphasis on medication associated with vitamin D deficiency, vitamin D supplements and medications potentially associated with falls and fractures. Medication information represented incident information and duration of medication use was not assessed.

No attempt was made to formally assess vitamin D intake from dietary sources or sun exposure data.

### Laboratory studies

Blood samples were obtained from the patients during the index admission. Assays were carried out within a week of blood collection.

Serum 25-hydroxyvitamin D (25(OH)D) was measured by radioimmunoassay (Diasorin, Stillwater, MN, USA). Samples were analysed in multiple assays. Interassay coefficient of variation for the study period was between 8.1 and 13.1%. For the purposes of this prevalence study, the categories suggested in a position statement from the Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia are used.<sup>14</sup> Mild deficiency is categorized as 25(OH)D levels between 25 and 50 nmol/L. Moderate deficiency is categorized as levels between 12.5 and 25 nmol/L.<sup>15</sup> Severe vitamin D deficiency is categorized as levels of serum 25(OH)D of 12.5 nmol/L or less.

Serum parathyroid hormone (PTH) was measured by a chemiluminescent enzyme immunoassay (Immulite; DPC, Los Angeles, CA, USA). Normal range was 1.2–6.5 pmol/L taken from a normal serum patient pool at the Royal Melbourne Hospital in 2002.

Routine chemistries were measured by an Olympus 2700 autoanalyzer (Tokyo, Japan).

Calcium was corrected for serum albumin concentration and creatinine clearance was calculated using the Cockcroft–Gault equation.<sup>16</sup>

### Statistical analysis

Data from both end-of-summer and end-of-winter groups were analysed together. Exploratory analysis of associations of categorical variables with vitamin D status were examined using two-tailed Fisher's exact tests with vitamin D deficiency defined as 25(OH)D levels of 50 nmol/L or less. 25(OH)D levels were correlated to PTH levels as continuous variables. Multivariate analysis was carried out using stepwise linear regression. Adjustment for multiple comparisons was made.

All statistics were carried out using STATA version 7.

## Results

### Clinical characteristics

The winter survey included 65 patients. Nine eligible patients or their families declined to participate. The summer survey included 64 patients and 13 declined to participate. The 22 patients who did not participate were similar to those who did in respect to age and length of stay.

The characteristics of the combined groups are shown in Table 1. The patients were elderly with multiple

**Table 1** Patient characteristics

Age (years)	
Median	81
Interquartile range	74–85
Range	61–98
Days in hospital	
Mean $\pm$ SD	9 $\pm$ 10
Range	1–60
Weight (kg)	
Mean $\pm$ SD	68 $\pm$ 14.4
Sex	
Male/female	70/59
Percentage male/female	54/46
Residential status on admission, <i>n</i> (%)	
Home	106 (82)
Hostel	17 (13)
Nursing home	6 (5)
Gait aid used (%)	72 (56)
Visual Impairment (%)	28 (22)
Average no. medications used	8
Major medical problems, <i>n</i> (%)	
Hypertension	68 (53)
Ischaemic heart disease	52 (40)
Congestive cardiac failure	43 (33)
Atrial fibrillation	38 (29)
Osteoarthritis	29 (22)
Diabetes mellitus	26 (20)
Chronic obstructive airway disease	25 (19)
Stroke	24 (19)
Dementia	22 (17)
Chronic renal failure	21 (16)

comorbidities and were on multiple medications. Most were living in private residence before admission. The 10 most common major medical conditions are listed.

Hospital database information for the period July 2004 to June 2005 showed that general medical inpatients had an average age of 79.6 years with average length of stay of 7.8 days. Discharge information showed that 70% of patients were discharged home. The remainder were discharged to residential care, interim care or died.

### Prevalence of vitamin D deficiency

The prevalence of vitamin D deficiency was high overall with 95 patients (74%) with levels of 50 nmol/L or less (Table 2). The mean ( $\pm$ standard deviation (SD)) 25(OH)D level was 39  $\pm$  18 nmol/L.

Thirty-seven patients (29%) were receiving vitamin D supplements. All patients were taking ergocalciferol (Ostelin Boots Healthcare, Sydney, Australia) 1000 IU daily with one patient taking 3000 IU. Patients on vitamin D supplements had significantly higher vitamin D levels (46.2 vs 35.9 nmol/L,  $P = 0.002$ ). However, of those on vitamin D supplements, 20 (54%) remained in the defi-

**Table 2** Vitamin D status

	Total	Winter cohort	Summer cohort
Mild deficiency 25–50 nmol/L (%)	65 (50)	31 (48)	34 (53)
Moderate deficiency 12.5–25 nmol/L (%)	23 (18)	13 (20)	10 (16)
Severe deficiency <12.5 nmol/L (%)	7 (5)	7 (11)	0 (0)
Sufficient >50 nmol/L (%)	34 (26)	14 (22)	20 (31)

cient range. One hundred and twelve patients (87%) were either vitamin D deficient or taking supplements.

### Seasonal difference

There was a difference in the mean 25(OH)D level between winter and summer groups (35 vs 43 nmol/L,  $P = 0.007$ ). Indeed there were no severely deficient patients in the summer cohort (Table 2). This difference was not accounted for by either age or vitamin D usage in multivariate analysis.

Although there seemed to be some protection against severe deficiency in summer, most of those patients still had levels of 25(OH)D of 50 nmol/L and less (Table 2).

### Univariate associations with vitamin D deficiency

None of the categorical variables was significantly associated with vitamin D deficiency (25(OH)D levels  $\leq$ 50 nmol/L) on univariate analyses. This remained the case when the analysis was repeated excluding those on vitamin D replacement. In particular, age, residential status and length of stay were not significantly associated in this population. Of the continuous variables, albumin was significantly lower in patients with low vitamin D levels (Table 3).

### Conditions associated with Vitamin D deficiency

Few patients had histories of conditions traditionally related to vitamin D deficiency (malabsorption, nephrotic

**Table 3** Biochemical associations with vitamin D deficiency

	Vitamin D <50 nmol/L	Vitamin D >50 nmol/L	<i>P</i> -value
Creatinine (mmol/mL)	0.123 (0.095)	0.121 (0.041)	0.9
Creatinine Clearance (mL/min)	48 (2.5)	42 (2.4)	0.2
Corrected calcium (mmol/L)	2.35 (0.14)	2.39 (0.12)	0.2
Parathyroid hormone (pmol/L)	7.3 (4.9)	8.0 (8.0)	0.54
Albumin (g/L)	34.5 (5.9)	37.6 (4.8)	0.007
Alkaline phosphatase (IU/L)	121 (126.1)	124 (74.9)	0.9

syndrome, gastrointestinal disorders). Nine patients (7%) were taking anti-epileptic medications. There was no significant difference in the 25(OH)D levels between those taking and those not taking anti-epileptic drugs. Seven of the nine patients on anti-epileptic medications were taking vitamin D tablets.

### Vitamin D, falls and fractures

Thirty-four patients (26%) in the study had had a previous low trauma fracture, 16 of whom had a previous fractured hip. Falls were common with 57 patients (44%) having had a previous fall. Twenty-seven (21%) had had a fall requiring hospitalization.

Of the patients with any previous fracture, 26 of 34 (76%) were vitamin D deficient. Twenty-one of the 34 (62%) patients were on vitamin D replacement. Of the patients with any history of falls, 42 of 57 (74%) were vitamin D deficient and 22 of 57 (39%) were on vitamin D supplements. Vitamin D status was not significantly associated with fracture or fall in this group.

### Vitamin D and PTH

There was no significant correlation between 25(OH)D levels and the natural logarithm of PTH level in a multivariate analysis with creatinine clearance, calcium level and diuretic use. All of these parameters were independently correlated to PTH levels. There was a significant correlation when the patients taking vitamin D supplements were excluded ( $R^2 = 0.28$ ,  $P = 0.04$ ), which may be explained by more limited sensitivity of the Diasorin assay to detect vitamin D2. The association of PTH levels and diuretic use was only present with loop diuretics. Thiazide diuretic users ( $n = 10$ ) showed no significant correlation.

Mean (SD) PTH level across the entire cohort was 7.5 pmol/L (5.8 pmol/L) (normal range 1.2–6.5 pmol/L). Fifty-eight patients (45%) had PTH levels above the upper limit of the normal range. There were no cases of primary hyperparathyroidism.

## Discussion

This study shows that a significant proportion of patients admitted under general medical units had low vitamin D levels. Vitamin D levels were lower in winter but deficiency as defined in this study was common throughout the year. Overall, two-thirds of the general medical patients were deficient and 23% had moderate to severe vitamin D deficiency. These rates are similar to Australian populations in residential care and in other general medical inpatients around the world.

There were no clinical or biochemical factors that strongly predicted those patients who were vitamin D deficient in this group. These included surrogate markers of mobility (residential status or gait aid use), demographic data and comorbid conditions. Previous studies have attempted to find predictors of vitamin D deficiency. Some authors have identified independent associations with housebound and mobility status, dietary intake, sun exposure, alkaline phosphatase levels, calcium and PTH. The derived predictive models, however, have had only modest positive predictive value.<sup>4,11,17</sup>

The other result of interest was the prevalence of increased PTH levels in this population. Recent studies have suggested that PTH level may be an independent predictor not only of time to fall<sup>18</sup> but also of mortality in elderly populations.<sup>19</sup> This elevation in PTH level is only partly explained by vitamin D status with important contributions from renal function, diuretic use and calcium level. This has been also observed in larger population studies.<sup>20</sup> The role of PTH measurement in assessment of vitamin D deficiency and overall bone health remains to be established. The potential beneficial effects on bone of the thiazide diuretics<sup>21</sup> and deleterious effects of loop diuretics<sup>22</sup> need to be considered. The association with albumin and vitamin D levels has been observed in other studies in similar populations. The nature of this association is currently unclear.

The decision to test vitamin D levels should be considered in the context of the evidence for the efficacy of replacement in preventing adverse events – namely falls and fractures. There are substantial epidemiological data supporting the adverse effects of having low vitamin D levels on falls and bone density.<sup>3,6</sup> The evidence for vitamin D supplementation in fracture prevention remains mixed. A Cochrane Review from 2005 found that vitamin D alone did not significantly reduce fractures. The combination of vitamin D and calcium did result in a reduction of hip and non-vertebral fractures, primarily in frail elderly patients.<sup>23</sup>

Three recent studies have emphasized the lack of significant fracture prevention efficacy with vitamin D and calcium supplementation. Limitations of these studies include no recording of baseline vitamin D levels,<sup>24,25</sup> poor adherence rates and inadequate dosing of vitamin D.<sup>26</sup> Per-protocol analysis of the Women's Health Initiative Study, which excluded participants whose adherence rates were <80%, showed a significant reduction in hip fractures. A recent systematic review suggested that fracture prevention efficacy is only seen in studies with patients treated with 700–800 IU/day with smaller doses not improving fracture risk.<sup>27</sup> A meta-analysis has shown that vitamin D (including activated forms) reduces the risk of falls among ambulatory or institutionalized older individuals by 22%.<sup>11</sup> A recent randomized controlled trial of

700 IU of cholecalciferol with calcium reduced the odds ratio of falling in women by 46% regardless of baseline vitamin D level.<sup>28</sup> Fractures and falls were both common in the patient group of this current study although we were unable to correlate lower vitamin D levels to previous falls or fractures. This analysis was limited because of case numbers and the potential complicating factor of vitamin D replacement in these patients. Notably, the uptake of vitamin D supplements was not uniform in patients with previous falls and fractures.

Another question regarding testing concerns the accuracy of the test, particularly in patients on vitamin D replacement. Most patients in this study receiving vitamin D supplementation remained vitamin D deficient. This may reflect difficulties in assaying vitamin D2. The Diasorin assay is said to detect vitamin D2 and D3 with equal sensitivity (Diasorin Product Information) although a recent study has questioned its accuracy.<sup>29</sup> No formal intra-assay coefficient of variance between testing batches was carried out nor was the assay compared with a vitamin D3 standard. Alternatively this could be explained by the lack of efficacy of ergocalciferol (vitamin D2) to treat vitamin D deficiency<sup>30</sup> or inadequate dosing.

Cost-effectiveness is an important consideration when suggesting testing in larger groups of patients. The cost of vitamin D testing is not insubstantial. The cost of replacement is not great but the number of patients needing to be treated to prevent adverse events is high. A high prevalence in a population like this might obviate the need to test at all and treat empirically. Further studies are needed to clarify these important points.

Limitations of the study included the lack of assessment of dietary vitamin D intake, sunlight exposure and formal assessments of mobility and housebound status. Acute phase lowering of vitamin D levels is likely of minimal importance. One prospective study on perioperative acute phase changes in vitamin levels showed a statistically but not clinically significant decrease in vitamin D levels in women but not men following elective surgery.<sup>31</sup> Assessments of associations with vitamin D deficiency were limited by the number of patients in the study and remain exploratory only. The study was not powered to estimate effects on fractures or falls. The other limitation included adjusting for the moderate rate of vitamin D supplementation.

In conclusion, this study found a high prevalence of vitamin D deficiency in a sample of general medical inpatients. The prevalence of deficiency was similar to that found in similar settings internationally and in residential care settings in Australia. Measurement of 25(OH)D levels remains the only way to document patients' vitamin D status. Testing vitamin D levels in general medical inpatients should be strongly considered. Previous falls and fractures were also common and vitamin D supplementa-

tion was neither uniform nor adequate in this group. More than half of those receiving ergocalciferol still had vitamin D levels in the deficient range.

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