Vitamin D deficiency in Crohn's disease: Prevalence, risk factors and supplement use in an outpatient setting

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Abstract

Background and aims: Vitamin D deficiency impacts on bone health and has potential new roles in inflammation. We aimed to determine the prevalence of and risk factors for vitamin D deficiency and to explore vitamin D supplement usage in patients with Crohn's disease (CD) in an outpatient setting, compared with controls.

Methods: Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured by radioimmunoassay in 151 participants, comprising 81 CD patients and 70 age-, sex- and socio-economic status-matched healthy controls. Levels of 25(OH)D <50 nmol/L were classed as deficient. Data on vitamin supplement usage were recorded for all participants at interview.

Results: Vitamin D deficiency was common in patients with CD (63%) and significantly higher in winter than summer (68% v 50%; p < 0.001, χ²). Notably, the deficiency rate remained high even in summer (50%). On regression analysis, 25(OH)D levels were inversely associated with winter season. Disease-specific factors for lower serum 25(OH)D levels were longer disease duration and smoking. Overall, 43% of patients reported using a vitamin D-containing supplement, primarily at low dosages (200–400 IU/d); however, this level of supplement did not prevent deficiency. For the majority of CD patients, 25(OH)D remained below optimal levels proposed to confer bone and immune health benefits.

Conclusions: Vitamin D deficiency was common in patients with CD and associated with longstanding disease, smoking and winter. While over 40% of patients used a vitamin D-containing supplement, the dosages were inadequate to prevent deficiency. Appropriate vitamin D screening and supplementation should be considered in the context of health promotion of outpatients with CD.

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KEYWORDS
Inflammatory bowel disease; Nutrition; Diet; Vitamin D deficiency; 25-hydroxyvitamin D
1. Introduction

Vitamin D is emerging as a multifunctional vitamin in Crohn’s disease (CD), with an established role in promoting bone health, and emerging anti-inflammatory and anti-cancer roles in the gut. The role of vitamin D in the prevention of osteoporosis in CD is well-evidenced, and current guidelines recommend daily vitamin D supplements (800 IU, 20 µg) during corticosteroid treatment, especially for therapy in excess of 12 weeks. Beyond bone, treatment with vitamin D appears to protect against the development of intestinal inflammation in animal models, mediated in part through effects on TNF-alpha and IL10. Clinically, augmenting 25(OH)D levels through high-dose vitamin D supplementation may have therapeutic potential and prevent relapse in CD, although this remains to be confirmed in further controlled trials.

In CD, vitamin D deficiency has been reported in both adults and children and is estimated to affect 18–70% of patients. Interpretation of prevalence rates for vitamin D deficiency across studies may be difficult as rates vary considerably depending on study designs, populations, geographic regions, seasonality and definitions of vitamin D deficiency applied. Taken together, the studies suggest that vitamin D deficiency is a problem likely to affect substantial numbers of CD patients worldwide.

Screening for vitamin D deficiency requires a blood sample for measurement of serum 25(OH)D levels and is practical and feasible in an outpatient setting. However, routine testing for 25(OH)D in this setting among CD patients not on corticosteroid therapy is reportedly low (11%). Understanding the factors associated with vitamin D status in CD may therefore help to identify patients most at risk of deficiency. Known risk factors for developing vitamin D deficiency are latitude and sunlight exposure. In countries of northern latitudes, such as northern Europe and Canada, the amount of ultraviolet B radiation in winter is inadequate to stimulate vitamin D production in the skin. Sunny regions, however, are not exempt from vitamin D deficiency, influenced by variables such as sun habits, skin pigmentation, indoor lifestyles and dietary intakes. For CD, the disease-specific factors associated with deficiency have not been extensively investigated. Small bowel disease has been identified, suggesting malabsorption of vitamin D; however, this may occur independently of disease location. Low usage of vitamin D supplements in CD has also been associated with deficiency. Vitamin D supplementation during corticosteroid treatment for CD may be expected; however, there are limited data on supplement usage and its effect on serum 25(OH)D levels in stable disease.

The aim of this prospective study was, firstly, to determine the prevalence of vitamin D deficiency in a CD outpatient setting compared with matched healthy controls. Secondly, to determine the disease- and non-disease-related factors associated with deficiency. Finally, to survey the use of vitamin D supplement usage and its effect on serum 25(OH)D levels.

2. Materials and methods

2.1. Study group and recruitment

Adult patients (≥ 18 years) with a confirmed diagnosis of CD for a minimum of 3 months were prospectively recruited from the Inflammatory Bowel Disease (IBD) outpatient clinics of the Adelaide & Meath Hospital, Dublin, Ireland. Healthy controls were recruited from local businesses and non-medical departments in the hospital and matched for age, sex and socio-economic status. Careful matching with healthy controls was considered an important component of the study design in order to reflect similar lifestyle and other variables in both cases and controls. The study was approved by the Federated Dublin Voluntary Hospitals’ Ethics Committee and written informed consent was obtained from all participants.

2.2. Demographic and clinical information

Information on demographics, socio-economic status and smoking status was recorded at interview. Smoking status was classified as smoker or lifelong non-smoker. Height, weight and body mass index (BMI) were measured. Disease activity was determined using the Crohn’s Disease Activity Index (CDAI) where values under 150 represented clinical remission.

2.3. Measurement of serum 25-hydroxyvitamin D

A fasting blood sample was taken from all patients and stored at −80 °C until analysis. Serum 25(OH)D was measured by radioimmunoassay (DiaSorin Inc, Minnesota, USA). Vitamin D status was classified using a cut-off criterion where 25(OH)D levels below 50 nmol/L were considered inadequate and classified as ‘deficient’. As a secondary end point, we applied a higher cut-off criterion of less than 80 nmol/L to define deficiency.

Seasonality was defined as winter from October to March and summer from April to September. To interpret the prevalence rates in the present study, we set our results in the context of published studies. We selected studies that reported prevalence of vitamin D deficiency in adult CD, included a minimum of 20 CD participants, clearly defined deficiency, and were published in English in the previous 10 years (2001 onwards). Importantly, studies needed to distinguish rates of vitamin D deficiency for CD (as opposed to IBD in general) or have sufficient data to allow this to be computed from the paper. Data on season and matched controls were shown where available.

2.4. Vitamin D supplement use and intake

Information on the use of vitamin D-containing supplements was recorded at patient interview. In addition, a self-administered food frequency questionnaire was used to estimate the amount of vitamin D intake from food sources. Calculation of dietary vitamin D intake excluded vitamin D intake from milk, unless specifically stated, to correspond with an Irish setting where milk is not routinely fortified with vitamin D.

2.5. Statistics

Data were analysed using SPSS (version 14.0). Prevalence of vitamin D deficiency according to group and season was analysed using Fisher’s exact test. Student’s t-tests were used for
parametric data. Descriptive data were presented as mean and standard deviation or median and quartiles for non-parametric data. Linear regression analysis (backwards elimination) was performed to determine factors associated with serum 25(OH)D levels. Disease variables (CDAI, CRP, disease duration, disease location, corticosteroid usage and previous surgery) and generic variables (age, gender, season, BMI, vitamin D intake with and without supplements) were entered into the linear regression model.

3. Results

3.1. Characteristics of the study group

Patients and controls were matched for age, gender and socioeconomic status. Demographic and clinical characteristics are shown in Table 1. All participants were Caucasian and living in Ireland. The majority of patients (68%) were in clinical remission (median CDAI score of 92) with longstanding disease (median 6 years), reflecting an outpatient cohort.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the study group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>n = 81</td>
<td>n = 70</td>
</tr>
<tr>
<td>Age, yrs, mean ± sd</td>
<td>36.43 ± 11.00</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>60%</td>
</tr>
<tr>
<td>Ethnic origin, % Caucasian</td>
<td>100%</td>
</tr>
<tr>
<td>Smoking status, % current smokers</td>
<td>27%</td>
</tr>
<tr>
<td>Body mass index, mean ± sd</td>
<td>25.02 ± 5.43</td>
</tr>
<tr>
<td>Disease site</td>
<td></td>
</tr>
<tr>
<td>Small bowel only</td>
<td>47%</td>
</tr>
<tr>
<td>Large bowel only</td>
<td>28%</td>
</tr>
<tr>
<td>Small and large bowel</td>
<td>22%</td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>3%</td>
</tr>
<tr>
<td>Disease duration, yrs, median (quartiles)</td>
<td>6 (3, 12)</td>
</tr>
<tr>
<td>Age at diagnosis, mean ± sd</td>
<td>28.81 ± 11.09</td>
</tr>
<tr>
<td>Family history of IBD</td>
<td>20%</td>
</tr>
<tr>
<td>CDAI, median (quartiles)</td>
<td>92.09 (39.01, 164.50)</td>
</tr>
<tr>
<td>CRP, mg/L, median (quartiles)</td>
<td>3.85 (2.90–9.62)</td>
</tr>
<tr>
<td>Previous surgery for CD</td>
<td>28%</td>
</tr>
<tr>
<td>Current medications</td>
<td></td>
</tr>
<tr>
<td>5ASAs</td>
<td>79%</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>44%</td>
</tr>
<tr>
<td>Biologics</td>
<td>15%</td>
</tr>
<tr>
<td>Steroids (prednisolone 11%, budesonide 10%, other 1%)</td>
<td>22%</td>
</tr>
<tr>
<td>Any steroid usage in past 12 months</td>
<td>48%</td>
</tr>
<tr>
<td>sd: standard deviation. CDAI: Crohn’s Disease Activity Index. CRP: C-reactive protein. Median and quartiles shown for non-parametric data.</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1  Prevalence of vitamin D deficiency overall, and according to season, in CD and matched control groups. Vitamin D deficiency <50 nmol/L. No statistically significant differences in deficiency rates in CD v controls (p = 0.226, χ²). A significantly higher prevalence of deficiency among patients with CD in winter compared with summer (p < 0.001, χ²).

3.2. Prevalence of vitamin D deficiency in CD compared with controls

Sixty-three percent of patients with CD were vitamin D deficient28 (Fig. 1). Deficiency rates were higher in patients than controls but this difference was not statistically significant. We observed a high background level of deficiency (51%) in matched healthy controls from the same catchment area (Fig. 1) and mean serum 25(OH)D values were similar for patients and controls (47.76±27.27 nmol/L v 51.86±24.53 nmol/L; NS) (Fig. 2). Analysis by gender did not significantly alter the rates of vitamin D deficiency in CD. Both men (69%) and women (59%) with CD had high rates of deficiency. Applying the higher cut-off criterion for deficiency (<80 nmol/L) that defined our secondary end point, the majority of patients [90% (73/81)] were classed as vitamin D deficient. Table 2 illustrates our results in the context of published studies of vitamin D deficiency in CD, taking into account season and control data where available.

3.3. Factors associated with serum 25(OH)D levels in CD and controls

Vitamin D deficiency, as anticipated, was influenced by season. In the CD group, significantly more patients with CD were...
vitamin D deficient in winter than summer (68% vs 50%; \( p < 0.001, \chi^2 \)), with a similar trend in the control group (58% vs 46%; \( p = 0.08 \)). Correspondingly, mean serum 25(OH)D was significantly lower in winter than summer respectively in CD (mean±SE, 43.42±3.11 v 58.03±6.52 nmol/L; \( p = 0.01 \)) and in controls (46.68±3.89 v 58.09±4.15 nmol/L; \( p = 0.049 \)) (Fig. 2). Serum vitamin D levels were classified as summer and winter season for 27 and 59 of the CD group, and 39 and 31 of the controls, respectively. Regression analysis (Table 3) identified winter as the only common generic predictor of low 25(OH)D levels in both groups, significantly so in CD patients (\( p = 0.004 \)) with a trend noted in the controls (\( p = 0.07 \)). Notably, half of CD patients were vitamin D deficient in summer.

Based on regression analysis, lower serum 25(OH)D was associated with longer disease duration (\( p = 0.01 \)) and smoking (\( p = 0.05 \)) in CD, in addition to winter season (\( p = 0.004 \)). A trend was further observed for an association between lower serum 25(OH)D and lower total dietary vitamin D intake (\( p = 0.079 \)), but this did not reach statistical significance (Table 3). Other variables, namely CDAI, CRP, disease location, corticosteroid usage, previous surgery, age, gender and BMI did not significantly contribute to the regression model. In this sample, the data suggest that longer disease duration, cigarette smoking and winter season were significantly associated with lower 25(OH)D levels for outpatients with CD.

### 3.4. Vitamin D supplement use and contribution to 25(OH)D levels

Overall, 43% (35/81) of CD patients and 16% (11/70) of healthy controls reported taking a vitamin D-containing supplement. Multivitamin preparations were the most common form of vitamin D-containing supplement reported, which provided on average 225 IU (200–400 IU) vitamin D daily. High dose vitamin D supplement usage (\( \geq 800 \) IU) in this outpatient setting was uncommon, reflecting the predominance of quiescent CD. Among CD supplement users (\( n = 35 \)), only five patients regularly consumed a high dose vitamin D supplement.

Supplements contributed 64% and 32% respectively to total vitamin D intake among patients and controls who consumed a supplement. Median vitamin D intake from diet alone (without supplements) was significantly lower in CD patients than controls [1.0 μg/day (95% CI 0.6–1.9) v 1.6 μg/day (1.0–2.5); \( p < 0.001 \)], but was similar between groups when supplements were taken into account [2.1 μg/day (0.8–6.0) v 1.8 μg/day (1.1–3.4); NS]. The main food source of vitamin D was oily fish for both patients and controls (38% v 48%; NS, \( \chi^2 \)) followed by eggs (27%) for CD and breakfast cereals (26%) for controls.

In further analysis, we investigated if the use of a vitamin D-containing supplement altered 25(OH)D levels, especially in winter. Patients who consumed a supplement in winter tended to have higher mean serum 25(OH)D levels than patients who did not (48.89±4.52 nmol/L v 39.11±4.19 nmol/L; \( p = 0.08, \) mean±SE). Notably, the mean 25(OH)D remained below the cut-off for deficiency (<50 nmol/L) and therefore did not prevent deficiency.

### 4. Discussion

In this prospective study we identified vitamin D deficiency in 63% of CD patients in an outpatient setting, rising to 90% when a higher cut-off criterion was applied. Our data highlight that vitamin D deficiency is common in CD even when the disease is well-controlled and managed in an outpatient setting, and remained high even in summer (50%). The reported prevalence of vitamin D deficiency in adults with CD varies considerably, from an estimated 18–100%, even when viewed using the same cut-off criterion [25(OH)D <50 nmol/L] (Table 2), although this may be partly due to different countries, seasons and study designs. The present study showed that deficiency rates (50%) remain a substantial concern throughout summer in CD. Consistent with our data, Bours et al. showed...
D levels in CD14,18,36 and is generally associated with disease levels. Smoking has previously been linked to lower vitamin specific variables were also important, with longer disease most well-known predictor of vitamin D status. Disease-only predictor identified in the control group. Lack of sun—strongest predictor of low 25(OH)D levels in CD, and the context of the high background level of deficiency in the (Table 2).

Populations living in sunny climates23 are not exempt from exposure. In CD, Jørgensen et al.7 recently noted that a high serum 25(OH)D of 50 nmol/L,21,36 depending on sunlight exposure. In CD, Jørgensen et al.7 recently noted that a high dose vitamin D (1,200 IU) supplement resulted in mean serum 25(OH)D of 96 nmol/L and a trend for reduced relapse rates at 12 months (13% v 29%, p=0.06). Importantly, oral intake of vitamin D is a modifiable factor. With in excess of 40% of patients taking a vitamin D supplement in this study, this offers an opportunity to augment the dose and usage rate to a level better evidenced to influence 25(OH)D status.

While the present study highlights rates and risk factors for vitamin D deficiency in CD, we did not aim to explore the health impact of deficiency, nor any association with incidence of CD. We report that 63% of CD had 25(OH)D levels below 50 nmol/L, and 90% below 80 nmol/L. To put this in context, levels <40–50 nmol/L of 25(OH)D21,28 are generally considered insufficient/inadequate, but many experts propose that levels of 75–80 nmol/L, or most probably 75–100 nmol/L,21,36 are required to confer bone, anti-inflammatory or anti-cancer benefits. In our study, 25(OH) D concentrations were below levels considered to promote bone health and substantially below levels proposed to confer immune benefits.21,36 Larger studies, that include incident cases, are required to more fully understand the role of vitamin D status in CD.

In conclusion, vitamin D deficiency was common in CD in an outpatient setting, with serum 25(OH)D below levels proposed to confer bone or anti-inflammatory benefit. There was a higher risk of low 25(OH)D levels in patients with longstanding disease, in smokers, and particularly in winter, although deficiency rates remained strikingly high in summer. In excess of 40% of patients used a vitamin D supplement, but the dose consumed was too low to prevent deficiency. There is a need for awareness raising around vitamin D status, screening, and adequate supplementation in the management of CD patients attending outpatient clinics.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Linear regression model of factors associated with serum 25(OH)D in CD and controls.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
</tr>
<tr>
<td><strong>Crohn’s disease</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.32 (−0.95; 0.31)</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.06 (−11.10; 13.23)</td>
</tr>
<tr>
<td>Season (winter)</td>
<td>−21.06 (−35.18; −6.95)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>−1.19 (−2.18; −0.19)</td>
</tr>
<tr>
<td>Smoking status: non-smoking</td>
<td>13.09 (−0.14; 26.33)</td>
</tr>
<tr>
<td>Total vitamin D intake (μg/d) including supplements</td>
<td>1.09 (−0.13; 2.32)</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td></td>
</tr>
<tr>
<td>Seasonality (winter)</td>
<td>−11.84 (−24.79; 1.09)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.13 (−0.59; 0.86)</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>7.85 (−4.96; 20.68)</td>
</tr>
<tr>
<td>Vitamin D intake (μg/d)</td>
<td>−0.36 (−1.68; 1.60)</td>
</tr>
</tbody>
</table>

B, coefficient; CI, confidence interval. * p<0.05 was considered statically significant.
Authors’ contributions

TNS contributed to the study design, carried out the studies, performed data analysis and interpretation, and co-wrote the paper.

GC and MH participated in the study design, carried out the vitamin D assays, and contributed to data interpretation and drafting the paper.

COM contributed to study design, data acquisition and drafting the paper.

MOS contributed to the study design, performed data analysis and interpretation, and co-wrote the paper.

All authors read and approved the final manuscript.

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