RESEARCH

Factors associated with vitamin D deficiency in a multicultural inflammatory bowel disease cohort

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ABSTRACT

Objective The aim of this study was to determine the prevalence of vitamin D deficiency in a multicultural inflammatory bowel disease (IBD) cohort and determine predictors of deficiency including ethnicity.

Design Patients with IBD were recruited into a dedicated database over a 6-month period and evaluated retrospectively.

Setting Department of Gastroenterology, St George's University Hospital, London, UK.

Outcomes measured Clinical data including demographics, ethnic group, disease phenotype by the Montreal classification, vitamin D level and season tested were recorded from clinical and electronic medical records. Vitamin D levels were classified as normal (≥ 50 nmol/l) and deficient (< 50 nmol/l).

Results 168 patients had a vitamin D level measured subsequent to diagnosis. There was no significant difference in the median vitamin D level between patients with Crohn's disease (CD) and ulcerative colitis (UC) (39 nmol/l (IQR 23–56) vs 28 nmol/l (IQR 17–51), $p=0.35$). Overall the median vitamin D level was significantly lower in non-Caucasians (Asian and Black) versus Caucasians (28 nmol/l (IQR 17–41) vs 41 nmol/l (IQR 25–63), $p<0.0001$). Multiple regression analysis revealed IBD related surgery (OR 2.9) and ethnicity (OR 6.0 non-Caucasian vs Caucasian) in CD and ethnicity (OR 5.0 non-Caucasian vs Caucasian) in UC were independently associated with vitamin D deficiency.

Conclusions Vitamin D deficiency is common in IBD patients; therefore, we suggest monitoring of vitamin D levels and correction with supplements especially in non-Caucasians and those with a history of IBD related surgery.

has become of increasing interest.¹ Identification of the vitamin D receptor in most tissues and cells in the body suggests an additional physiological function of vitamin D including recognition of a potential immunoregulatory role.^{2–3} Vitamin D also appears to have a regulatory effect on T cell development and function which may alter the immune response.⁴

There is an increasing body of evidence that vitamin D is associated with cancer, cardiovascular disease, autoimmune disease, diabetes mellitus and IBD.⁵ However, it was a murine model using IL-10 knockout mice where the vitamin D receptor was shown to alter outcome in experimental IBD by inducing diarrhoea, weight loss and fatalities in those mice rendered vitamin deficient compared with those that were vitamin D sufficient.^{6–7}

Several predictors of vitamin D deficiency in IBD patients have been identified including surgery and ileal involvement⁸ among others but there is a paucity of data regarding the impact of ethnicity on vitamin D status within the UK. Studies have reported an increased prevalence of vitamin D deficiency in African Americans and Bangladeshi IBD cohorts from the USA and UK but not determined whether ethnicity was an independent predictor.^{9–10}

The aim of this study was to determine the prevalence of vitamin D deficiency in our IBD cohort and determine predictors of vitamin D deficiency including ethnicity at a single centre.

INTRODUCTION

The emergence of vitamin D beyond its role in bone health as an immune regulator in inflammatory bowel disease (IBD)

METHOD

Study design

This was a single centre retrospective observational study conducted at the

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Department of Gastroenterology. Approval was obtained from the local ethics committee.

Study population

To avoid selection bias subjects attending the clinic between 1 January 2011 and 30 June 2011 were consecutively recruited into a database and evaluated retrospectively. The cohort comprised only those with a known diagnosis of IBD made using established criteria.¹¹ Anyone with a gastroenterological condition other than IBD was excluded. Demographic and clinical data were obtained by scrutinising medical records including disease characteristics and current or previous medical therapy for IBD. Surgical procedures were defined by intestinal resection, that is, small bowel resection, ileo-caecal resection and total/subtotal colectomy. Non-intestinal resection defined by peri-anal surgery, fistula repair and abscess drainage was not included. The follow-up period was from date of diagnosis as evidenced from medical records through to July 2011.

Outcome measures

The vitamin D level was obtained from the central pathology database (Electronic Patient Records) and the first level identified anytime subsequent to diagnosis was recorded. Electronic Patient Records was first set up in 1990 and patients diagnosed before this time were not included. The reference range at our hospital is from 75 to 200 nmol/l. Vitamin D analysis was carried out using the *Immunodiagnostic systems* total 25 hydroxy (OH) vitamin D₂ and D₃ assay according to the manufacturer's instruction. We grouped vitamin D levels as normal (≥ 50 nmol/l) and deficient (< 50 nmol/l) and severe deficiency (< 25 nmol/l). Ethnicity was defined as Caucasian (White) and non-Caucasian which included Asian (Indian, Pakistani, Bangladeshi, any other Asian background) and Black (Caribbean, African, any other Black ethnicity) patients. Those whose the ethnicity could not be identified from the medical records were excluded.

Statistical analysis

The database was constructed using Excel 2010 (Microsoft Corp, Redmond, USA) and STATA V.11.0 was used for statistical analysis. Comparisons were made using Fisher's exact test and χ^2 test for categorical variables, and unpaired t test for normally distributed continuous variables. The median test was used within STATA V.11.0 to compare median vitamin D levels among groups. Predictors of vitamin D deficiency were evaluated using univariate and multivariate logistic regression. Vitamin D was recorded as a continuous variable but for this analysis factors associated with a level < 50 nmol/l were determined. The size of effect of each factor on vitamin D deficiency was measured by an OR. p Value was significant if < 0.05 .

Table 1 Demographic and clinical characteristics among those with deficient and normal vitamin D levels

Variable	Vitamin D deficiency (n=113)	Normal vitamin D level (n=55)
Age at diagnosis (years) Mean (SD)	34 (± 14)	37 (± 15)
Female n (%)	59 (52)	32 (58)
Disease duration (years) median (IQR)	8 (5–15)	7 (4–13)
IBD type		
CD	71 (63)	36 (65)
UC	42 (37)	19 (35)
IBD related surgery n (%)	0=68 (60) $\geq 1=45$ (40)	0=40 (73) $\geq 1=15$ (27)
Ethnicity n (%)		
Caucasian	67 (59)	47 (85)
Non-Caucasian	46 (41)	8 (15)
Smoking status at diagnosis n (%)	Never=103 (91) Ex-smoker=1 (1) Current smoker=9 (8)	Never=53 (96) Ex-smoker=0 (0) Current smoker=2 (4)
5ASA n (%)	86 (76)	40 (73)
Immunomodulator n (%)	68 (60)	33 (60)
Anti-TNF n (%)	11 (10)	6 (10)
Corticosteroids within 3 months of diagnosis n (%)	27 (24)	15 (27)

CD, Crohn's disease; IBD, inflammatory bowel disease; TNF, tumour necrosis factor; UC, ulcerative colitis; 5ASA, 5 aminosalicylic acid.

RESULTS

In all, 168 patients had at least one record of a vitamin D level subsequent to diagnosis. Demographic characteristics stratified by vitamin D level are presented (table 1). Overall, 107 patients had Crohn's disease (CD) and 61 had ulcerative colitis (UC). Of these, 68% were Caucasians and 32% non-Caucasian (23% Asians, 9% Black). The prevalence of at least one intestinal resection was significantly higher in those with vitamin D deficiency compared among those with a normal level (40% vs 27%, $p < 0.05$).

There was no significant difference in the median vitamin D level between CD and UC (39 nmol/l, IQR 23–56 vs 28 nmol/l, IQR 17–51, $p = 0.35$). Overall the median vitamin D level was significantly lower in non-Caucasians (Asian and Black) compared with Caucasians (28 nmol/l (IQR 17–41) vs 41 nmol/l (IQR 25–63), $p < 0.0001$) (figure 1). The median vitamin D level was significantly less in winter compared with autumn in CD and for spring in UC ($p < 0.05$) (figure 2).

The prevalence of vitamin D deficiency (< 50 nmol/l) and severe deficiency (< 25 nmol/l) was 66% CD, 69% UC and 27% CD, 36% UC respectively. Poor disease outcomes were significantly more prevalent in those with severe deficiency (level < 25 nmol/l) in comparison with those with a normal level (≥ 50 nmol/l) with regard to need for intestinal resection in CD (58% vs 36%),

Figure 1 Box plot of vitamin D levels stratified by disease type and ethnic group (n=168).

stricturing disease phenotype in CD (24% vs 14%), need for oral corticosteroids within 3 months of diagnosis in CD (24% vs 13%) and diagnosis of pancolitis in UC (72% vs 52%) ($p < 0.05$).

Regression analysis

Univariate analysis was used to identify factors associated with vitamin D deficiency defined as < 50 nmol/l. Since CD and UC are distinct diseases with distinct phenotypes and complications they were analysed separately to prevent any statistical interactions. Covariates entered into the model included: smoking status, season tested, disease location (CD) and disease extent (UC), and history of IBD related surgery, medication (antitumour necrosis factor, immunomodulators, 5ASA, oral corticosteroids within 3 months of diagnosis), gender, age, disease duration and ethnicity. Only those showing some association with vitamin D deficiency in the univariate analysis ($p < 0.2$) were included into the multivariate model using backward elimination.

Figure 2 Box plot of vitamin D levels stratified by disease type and season (n=168).

CROHN'S DISEASE

In univariate analysis gender, smoking, season tested, ethnicity and disease duration were associated with vitamin D deficiency ($p < 0.2$). These variables were further analysed in the multivariate model and only IBD related surgery (OR 2.9 95% CI 1.2 to 8.7; $p = 0.03$) and ethnicity (OR_{Non-Caucasian vs Caucasian} 6.0 95% CI 1.6 to 21.7; $p = 0.007$) were independently associated with vitamin D deficiency (< 50 nmol/l) (table 2a).

ULCERATIVE COLITIS

In UC, only ethnicity (OR_{Non-Caucasian vs Caucasian} 4.5 95% CI 1.3 to 15.9; $p = 0.02$) and corticosteroid use (OR 0.5 95% CI 0.1 to 1.4; $p = 0.16$) associated with vitamin D deficiency ($p < 0.2$) were further analysed in the multivariate model. Ethnicity was found to be the only independent factor associated with vitamin D deficiency (OR_{Non-Caucasian vs Caucasian} 5.0 95% CI 1.4 to 18.2; $p = 0.02$) in the multivariate model (table 2b).

DISCUSSION

Principal findings

The prevalence of vitamin D deficiency defined by a cut-off value < 50 nmol/l was 68% in this cohort of IBD patients. This was significantly higher than other studies that have reported prevalence between 35% and 51%^{4 11 12} using the same cut-off; however, this is likely to be a reflection of our multicultural cohort. There is no agreed consensus on what defines a cut-off with regard to vitamin D deficiency; we chose < 50 nmol/l since The Endocrine Society¹³ has recently published a guideline defining deficiency as less than 50 nmol/l and in addition to allow comparison among other studies that used the same definition.^{4 11 12 14}

Although there was no significant difference in the median vitamin D level among those with CD compared with UC, the median level was significantly lower in non-Caucasians compared with Caucasians.

Multivariate regression analysis revealed that a history of IBD related surgery and ethnicity were independently associated with vitamin D deficiency (< 50 nmol/l) in patients with CD. The results for season tested were significant for spring (OR 4.2; 95% CI 1.2 to 15.3) for CD patients in the univariate analysis indicating a fourfold increased risk of vitamin D deficiency but this variable was not significant in the multivariate model. Other studies have reported seasonal variations with high prevalence of vitamin D deficiency in winter months but did not determine whether season was a predictor^{15 16} while a paediatric study found vitamin D deficiency was more likely to occur in winter months (OR 4.1; 95% CI 1.9 to 9.2).¹⁷

The odds for deficiency were nearly threefold in those with a history of IBD related surgery in those with CD but this was not an independent predictor in UC. Smaller studies evaluating impact of vitamin D

Table 2a Univariate and multivariate logistic regression: factors associated with vitamin D deficiency (<50 nmol/l) in CD (n=71)

Variable	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Gender						
Female _(reference)						
Male	1.4	0.6 to 3.1	0.45			
Age*	0.8	0.6 to 1.1	0.17	0.94	0.7 to 1.4	0.75
Smoking:						
Never _(reference)						
Smoker	5.1	0.6 to 41.7	0.13	6.4	0.7 to 59.3	0.11
Disease duration†	1.2	0.9 to 1.6	0.11	1.2	0.9 to 1.7	0.22
Ethnicity:						
Caucasian _(reference)						
Non-Caucasian	3.8	1.2 to 12.1	0.02	6.0	1.6 to 21.7	0.007
CD location:						
Colonic _(reference)						
Ileal	1.2	0.5 to 2.7	0.70			
Ileo-colonic	1.7	0.3 to 9.7	0.50			
Season:						
Summer _(reference)						
Spring	4.2	1.2 to 15.3	0.03	3.1	0.8 to 12.4	0.12
Winter	1.6	0.5 to 5.2	0.40			
Autumn	0.7	0.2 to 2.2	0.50			
IBD related surgery						
None _(reference)						
≥ 1	2.7	1.2 to 6.2	0.02	2.9	1.2 to 8.7	0.03
5ASA	1.1	0.5 to 2.6	0.81			
Corticosteroid‡	1.4	0.5 to 4.3	0.57			
Immunomodulator	0.8	0.4 to 1.8	0.54			
Anti-TNF	0.9	0.3 to 2.5	0.72			

*OR reported for every 10 year increase in age.

†OR reported for a 5 year increase in disease duration.

‡Oral corticosteroids within 3 months of diagnosis.

CD, Crohn's disease; TNF, tumour necrosis factor; 5ASA, 5 aminosalicylic acid.

deficiency in IBD cohorts have demonstrated an association with long-term disease, small bowel resection, ileal involvement, high disease activity in CD and smoking.^{8 18 19}

To our knowledge, there are limited data assessing impact of ethnicity on vitamin D status in IBD. A study from Canada demonstrated higher percentage of South Asians had hypovitaminosis D when compared with Caucasians. Furthermore, disease severity trended

towards an inverse relationship with vitamin D status in all South Asian and Caucasian CD patients but this was not statistically significant.¹⁴ A smaller study from India demonstrated vitamin D levels were significantly lower among CD patients as compared with age and sex matched controls and low levels were associated with increased disease activity in those with CD.²⁰ Finally, mean vitamin D levels were 52.6% lower among patients with dark skin complexion in a cohort of children and young adults from the USA.²¹ In our study, we determined the OR using multivariate analysis as to whether ethnicity impacts on vitamin D deficiency. Compared with Caucasians the risk of deficiency was sixfold and fivefold in non-Caucasians in CD and UC, respectively, which is a cause for concern given that a recent review article concluded vitamin D therapy may offer additional benefits to IBD patients including improving bone health, reducing the risk of colorectal cancer and treating depressive symptoms.²¹ Furthermore, vitamin D deficiency correlates with a poorer health related quality of life.⁴ Many

Table 2b Multivariate logistic regression: factors associated with vitamin D deficiency (<50 nmol/l) in UC (n=42)

Variable	OR	95% CI	p Value
Corticosteroid*	0.4	0.1 to 1.3	0.12
Ethnicity			
Caucasian _(reference)			
Non-Caucasian	5.0	1.4 to 18.2	0.02

*Oral corticosteroids within 3 months of diagnosis.

UC, ulcerative colitis.

factors are likely to contribute to deficiency including malabsorption secondary to surgery or mucosal inflammation, reduced sunlight exposure, lack of physical activity, and inadequate dietary intake.

Study limitations

First, this study has the inherent bias of any retrospective design; however, one of the strengths is based on the diverse ethnic characteristics of the study population and large number of patients with a measured vitamin D level. Second, there is heterogeneity among studies with no consensus on what constitutes a low vitamin D level and therefore our results can only be applied to those populations using a similar definition. We chose a cut-off of <50 nmol/l since The Endocrine Society has defined vitamin D deficiency by a cut-off of <50 nmol/l and this definition has been used in other studies. Third, we had no control group; however, we compared markers of severe disease among those with severe deficiency as compared with a vitamin D level and adjusted for any potential confounding factors. Finally, our study was conducted in an ambulatory single-centre where there is the potential for selection bias and hospitalised patients were not captured.

Further studies are required to determine the exact nature of the relationship between vitamin D deficiency and IBD and whether it is a simple association or causal relationship. Our data suggest that vitamin D deficiency is common among non-Caucasians with IBD, although the mechanism of deficiency appears to be more complicated. Ideally a placebo controlled randomised controlled trial would be required to define whether treatment of vitamin D deficiency impacts on disease course. However, ethical considerations may limit the ability to set up such a trial where patients with severe vitamin D deficiency were left untreated due to potential adverse outcomes with regard to IBD and bone health.

What is already known on this topic

- ▶ Vitamin D deficiency is common in patients with inflammatory bowel disease (IBD) and studies have reported a higher prevalence in non-Caucasians.

What this study adds

- ▶ Ethnicity was found to be independently associated with vitamin D deficiency. Compared to Caucasians the risk of deficiency was 6 fold and 5 fold in non-Caucasians in CD and UC respectively

How might it impact on clinical practice in the foreseeable future

- ▶ Vitamin D measurement and replacement should be part of routine management in IBD especially in non-Caucasians.

Conclusions and implications

Vitamin D deficiency is common in IBD patients and may be associated with markers of severe disease. Vitamin D measurement and replacement should be part of routine management especially in non-Caucasians and those with a history of IBD related surgery. However, further studies are needed to evaluate whether correction has a favourable outcome in IBD.

Contributors SC, AP, VC wrote the article. SC and RH collected the data. SC performed the statistical analysis. PN, J-YK, RCP reviewed and edited the article.

Competing interests None.

Ethics approval St George's Hospital Ethics Committee.

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