ORIGINAL ARTICLE

B-vitamin status in relation to bone mineral density in treated celiac disease patients

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Abstract

Objectives. Patients with celiac disease (CD) are at increased risk of osteoporosis and compromised B-vitamin status. Emerging evidence supports a beneficial role of folate and the metabolically related B-vitamins in bone health in generally healthy adults, but no previous study has investigated this in CD patients. The aim of the current study was to examine the relationship of folate, vitamins B12, B6 and B2 (riboflavin), and the related metabolite homocysteine, with bone mineral density (BMD) in CD patients.

Materials and methods. Of the 400 treated adult CD patients invited to participate, 110 responded and met the eligibility criteria for study participation. BMD was measured using dual energy X-ray absorptiometry scanning at the lumbar spine (L1–L4), femoral neck, and total hip sites. Biomarker status of the relevant B-vitamins and homocysteine, and dietary B-vitamin intakes, were measured.

Results. The significant predictors of low BMD were increasing age (B = 0.080, p < 0.001) and decreasing weight (B = 0.072, p = 0.004), whereas no significant relationship with serum 25-hydroxyvitamin D (B = 0.093, p = 0.928) was observed. Following adjustment for these predictors, serum vitamin B12 (but no other B-vitamin biomarker) was found to be a significant determinant of BMD at the femoral neck (β = 0.416, p = 0.011) and total hip (β = 0.327, p = 0.049) in men only. No significant relationships were found between any of the B-vitamin biomarkers investigated and BMD (at any measured site) in women.

Conclusion. These findings add to current evidence suggesting a potential role of vitamin B12 in BMD, particularly in men, and show such a relationship for the first time in CD patients.

Key Words: bone, celiac disease, osteoporosis, vitamin B, vitamin B12

Introduction

Celiac disease (CD) is a common, genetically determined autoimmune multisystem disorder triggered by the ingestion of gluten-related proteins and peptides found in wheat (gliadins and glutenins), barley (hordeins), and rye (secalins). Malabsorption is among the common clinical features of the disease and leads to well-described deficiencies of various micronutrients, including iron, calcium, folate, and vitamin B12 [1,2]. CD patients are also well recognized to be at increased risk of osteoporosis, a serious skeletal disorder characterized by reduced bone mineral density (BMD) and an increased susceptibility to fragility fractures [3,4]. Although the pathology of bone disease in CD is not fully understood, compromised calcium/vitamin D status, related secondary hyperparathyroidism, and failure to acquire peak bone mass in young adulthood are generally considered to be important contributing factors [3]. As recently
reviewed by us, emerging evidence proposes a role of certain B-vitamins in bone health in healthy adults, and it is therefore reasonable to propose that suboptimal B-vitamin status may contribute to the higher risk of osteoporosis in CD patients [5]. Folates, and vitamins B12, B6, and B2 (riboflavin) all play important roles in homocysteine metabolism [6–8]. As a result, plasma homocysteine is invariably elevated with low B-vitamin status and can therefore be used as a functional, although nonspecific, biomarker of folate and related B-vitamin status [9].

Early studies in homocystinuria, a rare autosomal recessive condition characterized by excessively high concentrations of homocysteine in the blood and urine, described premature osteoporosis among the major clinical features of the disease [10]. In generally healthy individuals, mild elevations in homocysteine concentration have been associated with lower BMD [11,12] and up to a fourfold increase in the risk of fracture [15–16]. Consistent with the inverse metabolic relationship between homocysteine and B-vitamin status, large observational studies have also shown associations of low folate, vitamin B12, and vitamin B6 status with an increased fracture risk and/or reduced BMD [15,17,18]. Furthermore, there is strong evidence from genetic studies linking homozygosity for the common 677C→T polymorphism in the gene encoding the folate metabolizing enzyme methylene-tetrahydrofolate reductase (MTHFR) with lower BMD and an increased risk of fracture [19].

Given the emerging evidence to support a role of the B-vitamins in bone health generally and the increased risk of compromised B-vitamin status in CD patients [20], it is possible that low B-vitamin status may be implicated in the development of osteoporosis in this patient group. To date, however, no study investigating this relationship in CD patients has been performed. The present study aimed to explore associations of homocysteine and biomarker status of all four relevant B-vitamins with BMD in patients previously diagnosed with CD.

Methods

Participants and study design

This study was conducted as an observational study investigating the relationship between B-vitamin status and bone health in a convenience sample of CD patients recruited from two CD clinics in Northern Ireland. The sample size required for this study was calculated using published data from the Framingham Offspring Osteoporosis Study cohort and was based on a significant improvement of 0.051 g/cm² in BMD at the total hip of men as the plasma vitamin B12 concentration increased from ≤148 pmol/l (lowest quartile) to >259 pmol/l (highest quartile), with a power of 80% and with a significance level (α) of 0.05. Recruitment of potential participants (via a letter of invitation) from CD clinics at Altnagelvin Area and Causeway Hospitals in Northern Ireland was undertaken between August 2011 and May 2012 (Figure 1). Of the 400 potential participants initially approached, 168 patients (40%) responded and were screened for eligibility. Inclusion criteria were: aged >20 years with a confirmed diagnosis of CD based on positive serum endomysial antibody and/or tissue transglutaminase testing, and duodenal biopsy showing villous atrophy with intraepithelial lymphocytosis. Exclusion criteria included a diagnosis of CD <1 year ago, pregnancy, taking B-vitamin supplementation, multivitamins or drugs known to interfere with B-vitamin metabolism (e.g., some antiepileptic drugs and methotrexate), any hepatic, renal or gastrointestinal disease (apart from CD), and the inability to provide consent due to physical or mental impairment. After screening, 110 patients met the criteria and attended study appointments at either the University of Ulster or the Clinical Translational Research Innovation Centre in Altnagelvin Area Hospital, depending on the most convenient location for the patient. Ethical approval for this study was granted by the Office for Research Ethics Committees Northern Ireland (reference 11/NI/0049) in May 2011, and approvals from the two participating hospital trusts (The Northern and Western Health and Social Care Trusts) were received in June 2011. The study was conducted in accordance with the Declaration of Helsinki.

BMD measurement

BMD (gram per square centimeter) was measured at the lumbar spine (L1–L4), femoral neck, and total hip by dual energy X-ray absorptiometry (DXA) scanning (Lunar Prodigy, GE Healthcare, UK). Scans were administered by a qualified radiographer at Altnagelvin Area Hospital or by a trained researcher in the University of Ulster, using the same protocol for patient positioning, and to maintain consistency in analysis all scans were analyzed by a single qualified radiographer. In accordance with the manufacturer’s instructions, both weekly and daily quality control checks were performed using a phantom spine and a standard calibration block, as provided by the manufacturer. The densitometer showed high precision with a percentage coefficient of variation (CV) for phantom spine and calibration block scans of <2% and 0.4%, respectively. If a participant had undergone a DXA scan in <1 year before the study appointment, a copy of this DXA scan was retrieved from hospital
Male and female celiac disease patients over the age of 20 years, and attending celiac disease clinics in two Northern Ireland hospitals, were invited to participate via a recruitment letter ($n = 400$).

No response received from potential participants ($n = 232$).

Screened for eligibility according to study inclusion/exclusion criteria ($n = 168$).

- Excluded from participation ($n = 58$) for reasons of:
  - Diagnosis less than one year ago ($n = 4$)
  - B-vitamin supplementation ($n = 35$)
  - Hepatic, renal or gastrointestinal conditions ($n = 9$)
  - Personal reasons/non-responsive ($n = 9$)
  - Pregnancy ($n = 1$)

Data collection (including bone scans) at the University of Ulster Coleraine or the Clinical Translational Research Innovation Center (CTRIC), Altnagelvin Hospital, in Northern Ireland ($n = 110$).

Figure 1. Flow diagram showing study design and participation.

Records and the BMD data were used for the current study. The World Health Organization criteria were used to classify patients as normal, osteopenic or osteoporotic based on T-scores of $\geq -1.0$ standard deviation (SD), between $-1$ SD and $-2.5$ SD, and $\leq -2.5$ SD, respectively and classification was based on the lowest T-score at any measured site [21].

**Anthropometric and lifestyle data**

Weight (kilogram) and height (meter) were recorded to the nearest 0.1 kg and 0.1 cm, respectively, using a portable scales and stadiometer (Seca; Brosch Direct Ltd, Peterborough, UK), and body mass index (BMI) (kilogram per square meter) was subsequently calculated. A health and lifestyle questionnaire was administered to participants to collect general information relevant to bone health and B-vitamin status including time of CD diagnosis, a history of previous fractures, medication and supplement usage, smoking status, and alcohol consumption.

**Biomarker and dietary status of B-vitamins**

All participants provided a 29 ml non-fasting blood sample. Sample preparation and fractionation were performed within 4 h of blood collection, and blood aliquots were stored at $-80^\circ$C until batch analysis. Samples were analyzed for plasma homocysteine by fluorescence polarization immunoassay [22], and serum and red cell folate [23], and serum vitamin B12 [24], by microbiological assays. Determination of vitamin B2 (riboflavin) status was by erythrocyte glutathione reductase activation coefficient (EGRac), calculated as the ratio of flavin-dependent glutathione reductase activity before and after in vitro reactivation with its prosthetic group flavin adenine dinucleotide [25]. Higher EGRac values were indicative of lower riboflavin status, and suboptimal riboflavin status was defined as a coefficient $>1.3$ [26]. Plasma pyridoxal 5-phosphate (PLP) (vitamin B6) was determined using high-performance, reverse phase, liquid chromatographic separation with detection by fluorescence [27]. Additionally, serum 25-hydroxyvitamin D was determined by liquid chromatography-mass spectrometry using the Mass Spec Api 4000 system (Applied Biosystems, CA, USA). For all assays, samples were analyzed blind, within 1 year of collection, and quality controls were provided by the repeated analysis of stored batches of pooled samples that covered a wide range of values.

Dietary data were collected using a food frequency questionnaire in combination with a 4-day food diary, a method previously validated for B-vitamin intakes against biomarker status of specific B-vitamins at this center [28]. The food composition database Weighed...
Intake Software Package (WISP; version 3; Tinuviel Software, Anglesey, UK) was used to determine nutrient intakes and, as we previously described, was customized by our group to update micronutrient values to reflect any recent changes in manufacturer’s fortification practices [28]. Specifically for the current project, we further customized the WISP database to add a range of currently available gluten-free food products on the local retail market and/or accessible through pharmacies (for prescribed food products).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 20, SPSS UK Ltd, Chertsey Road, Surrey, UK). Before statistical analysis, tests for normality were performed and variables were log-transformed where appropriate. Data were analyzed using independent sample t-tests and chi-square analysis for categorical variables. Established predictors of bone health, age, sex, weight, vitamin D status, smoking status, and alcohol consumption were examined using linear regression. Bivariate correlation analysis was performed to examine associations of B-vitamin biomarker status with B-vitamin intakes. Linear regression was used to investigate B-vitamin biomarkers as determinants of BMD at the hip sites in men, whereas plasma homocysteine was higher in men than women. There was a high prevalence of low BMD (osteopenia or osteoporosis) in both sexes (Figure 2). Patients with low BMD were significantly older, weighed less, and were more likely to be prescribed a calcium and/or vitamin D supplement and bisphosphonate medication than those with normal bone status (data not shown).

In general, B-vitamin intakes of men and women compared favorably to the current reference nutrient intake values [30]. Women had lower riboflavin status than men, whereas plasma homocysteine was higher among men, but none of the other B-vitamin biomarkers showed gender differences (Table II). Overall, a high proportion of patients (49%) were found to have suboptimal riboflavin status (i.e. EGRac >1.3) [30]. Similarly, a high prevalence (75%) of elevated homocysteine concentration (≥10 μmol/l) was observed among patients [31].

B-vitamin status and bone

The main determinants of low BMD in the total cohort (unstandardized coefficient values) were increasing age (B = 0.080, p < 0.001) and decreasing...
weight ($B = 0.072, p = 0.004$), but not female sex ($B = -1.220, p = 0.169$), serum 25-hydroxyvitamin D ($B = 0.093, p = 0.928$), smoking ($B = -0.034, p = 0.946$), or alcohol consumption ($B = 0.188, p = 0.773$) (data not shown). After adjustment for age, weight, and serum 25-hydroxyvitamin D, it was found that serum vitamin B12 (but no other B-vitamin biomarker) was a significant predictor of BMD at the femoral neck ($b = 0.416, p = 0.011$) and total hip ($b = 0.327, p = 0.049$) in men (Table III). Similar analysis in the women alone (Table III), and the total group (data not shown), showed no

Table II. B-vitamin intakes and biomarker status in celiac disease patients.

<table>
<thead>
<tr>
<th>Males (n = 31)</th>
<th>Females (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dietary Intakes</strong></td>
<td>% Outside reference range</td>
</tr>
<tr>
<td><strong>Cut-off/range</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Energy (MJ/day)</strong></td>
<td>53.0 (12.3)</td>
</tr>
<tr>
<td><strong>Total folate (µg/day)</strong></td>
<td>83.7 (10.9)</td>
</tr>
<tr>
<td><strong>Vitamin B12 (µg/day)</strong></td>
<td>9.758 (2.067)</td>
</tr>
<tr>
<td><strong>Vitamin B6 (mg/day)</strong></td>
<td>200</td>
</tr>
<tr>
<td><strong>Riboflavin (mg/day)</strong></td>
<td>5.6 (2.2)</td>
</tr>
<tr>
<td><strong>Serum folate (nmol/l)</strong></td>
<td>2.4 (0.5)</td>
</tr>
<tr>
<td><strong>Serum vitamin B12 (pmol/l)</strong></td>
<td>1.1 (F)/1.3 (M)</td>
</tr>
<tr>
<td><strong>Plasma pyridoxal 5-phosphate (nmol/l)</strong></td>
<td>1.9 (0.6)</td>
</tr>
<tr>
<td><strong>EGRac</strong></td>
<td>11.5</td>
</tr>
<tr>
<td><strong>Plasma homocysteine (µmol/l)</strong></td>
<td>3.2</td>
</tr>
<tr>
<td>*<em>Values are presented as mean (SD). Differences between groups were assessed using an independent sample t-test on log-transformed data where appropriate; <em>p &lt; 0.05 was considered significant.</em></em></td>
<td></td>
</tr>
</tbody>
</table>

1 Percentage outside of reference range indicates dietary intakes below the RNI values [30]. For biomarker values, reference ranges were as per the laboratory of analysis, or EGRac and homocysteine cut-offs as described elsewhere [26,31].

2 Dietary data are available for 24 male and 53 female participants.

3 Total folate intake was expressed as natural food folate plus folic acid from fortified foods. The DFE, to account for the higher bioavailability of synthetic folic acid added to food than of natural food folate, was 291 (156) µg/day in men and 270 (119) µg/day; DFEs were calculated as microgram natural folate plus 1.7 × µg added folic acid [56].

4 EGRac for riboflavin status. Higher values indicate lower riboflavin status, with values >1.3 generally indicative of suboptimal status [26]. Abbreviations: DFE = Dietary folate equivalent; EGRac = Erythrocyte glutathione reductase activation coefficient; F = Female; M = Male; RNI = Reference nutrient intake.

Figure 2. Bone health status among celiac disease patients is shown.
relationships between BMD (at either hip site) and any of the B-vitamin biomarkers investigated.

In males, serum B12, but none of the other B-vitamin biomarkers, was significantly correlated with BMD at the femoral neck and total hip after adjustment for age, weight, and serum 25-hydroxyvitamin D (Figure 3). Additional adjustments for height and dietary protein intake did not affect these relationships. Following exclusion of patients who were prescribed proton pump inhibitors (n = 6), the results remained largely unchanged (data not shown). There were no significant correlations between B-vitamin biomarkers and BMD at any site, in the total group (data not shown) or women alone (Figure 3).

Retrospective power calculations were used to examine the hierarchical multiple regression relationships between serum B12 and BMD at the femoral neck and total hip sites in both males and females. Using a type one error rate of 5% and the observed effect size as defined by Cohen [32], the power was very favorable (90–99%) within the adjusted regression models. However within the unadjusted regression models, with the exception of the relationship between the serum B12 and the femoral neck site (69% power) among men, reduced power was observed (12–44%).

Dietary intakes

Strict adherence with a gluten-free diet was self-reported by 95% of participants (data not shown). B-vitamin intakes of folate and vitamins B12, B6, and B2, were each significantly correlated with the corresponding biomarker concentrations of these micronutrients in blood (Figure 4).

Discussion

This study examined the relationship of B-vitamin biomarkers with BMD in CD patients and showed a significant association of serum vitamin B12, but no other B-vitamin, with BMD at the hip among men. No significant association of serum vitamin B12 (or any other B-vitamin biomarker investigated) with BMD was observed in women. Although, vitamin B12 and/or folate have previously been linked with BMD (and fracture risk) in healthy cohorts, this is the first report to have investigated their potential roles in CD patients.

The current findings add to the emerging evidence from large US cohort studies suggesting that vitamin B12 may have a protective role in maintaining BMD, particularly at the hip, in adults generally [18,33,34]. In strong support of the current findings, a recent study in Turkish men (n = 269) reported a positive correlation of serum vitamin B12 (r = 0.362; p < 0.001), but not folate, with BMD at the femoral neck [35]. In general agreement with a role for vitamin B12 in bone health, one large study (n = 9,506) of pernicious anemia patients from the General Practice Research Database in the UK showed a significantly higher risk of fracture in patients (1 year post-diagnosis) compared with healthy age- and sex-matched controls [36].

The current study found no association between homocysteine and BMD at any site, which is in agreement with results of a number of other studies in generally healthy cohorts [14,37], although evidence that elevated homocysteine is linked with higher fracture risk in such cohorts exists [13,14]. Additionally, no significant relationship with BMD was

Table III. Associations between B-vitamin biomarker concentrations and bone mineral density.

<table>
<thead>
<tr>
<th>Femoral neck</th>
<th>Total hip</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males (n = 31)</strong></td>
<td></td>
</tr>
<tr>
<td>Red cell folate (nmol/L)</td>
<td>0.042</td>
</tr>
<tr>
<td>Serum B12 (pmol/L)</td>
<td>0.469</td>
</tr>
<tr>
<td>Plasma PLP (nmol/L)</td>
<td>−0.281</td>
</tr>
<tr>
<td>EGRac</td>
<td>0.081</td>
</tr>
<tr>
<td>Plasma homocysteine (μmol/L)</td>
<td>−0.099</td>
</tr>
</tbody>
</table>

| Females (n = 79) | | |
| Red cell folate (nmol/L) | −0.015 | 0.896 | −0.059 | 0.569 | 0.042 | 0.723 | −0.017 | 0.863 |
| Serum B12 (pmol/L) | −0.077 | 0.519 | 0.006 | 0.953 | −0.064 | 0.593 | 0.039 | 0.682 |
| Plasma PLP (nmol/L) | 0.083 | 0.483 | 0.123 | 0.222 | 0.135 | 0.256 | 0.176 | 0.058 |
| EGRac | 0.130 | 0.256 | 0.119 | 0.230 | 0.099 | 0.593 | 0.080 | 0.387 |
| Plasma homocysteine (μmol/L) | −0.197 | 0.088 | −0.081 | 0.438 | −0.237 | 0.040 | −0.137 | 0.155 |

1 Adjustments for age, weight, and serum 25-hydroxyvitamin D. Age and weight were found to significantly predict bone mineral density by multiple regression. Standardized β values are reported; p < 0.05 was considered significant.

Abbreviations: EGRac = Erythrocyte glutathione reductase; PLP = Pyridoxal 5-phosphate.
demonstrated for vitamin B6 or riboflavin. Although a previous study has shown a relationship between vitamin B6 deficiency and bone loss [17], and evidence to support a role of riboflavin in BMD has been limited to an interactive effect of riboflavin with the common C677T polymorphism in MTHFR [38,39].

In contrast to certain previous reports from healthy cohorts of associations between vitamin B12 and BMD in both sexes [18,33], this study like others [40,41] found no significant relationship of vitamin B12, or any B-vitamin biomarker, with BMD in female CD patients. Interestingly, in the latter studies, the women investigated more closely matched the age profile of the female CD patients in the current study, and it is possible that a substantial number of women were perimenopausal, a stage of life when profound hormonal effects on bone health are well documented to occur [42], potentially superseding any effect of B-vitamins on BMD in these female CD patients.

The dietary intakes of all four measured B-vitamins correlated well with corresponding biomarker concentrations in our patient group, and such relationships were comparable to those observed in healthy cohorts examined previously at this center [28], suggesting that nutrient malabsorption was not a significant issue, and indicating generally good compliance with the gluten-free diet, among these treated CD patients. Additionally, the biomarker status of the B-vitamins in this patient group was generally adequate.

Although there is no clear mechanism to explain the link between low vitamin B12 and decreased BMD demonstrated here, previous in vivo and in vitro studies support a causative relationship. A trial by Carmel et al. found reduced concentrations of the bone formation markers alkaline phosphatase and osteocalcin among vitamin B12-deficient patients compared to non-deficient and iron-deficient controls, and demonstrated that vitamin B12 therapy led to an increase in skeletal alkaline phosphatase in vitamin B12-deficient patients but not in controls [43]. Additionally, cell and animal studies support a stimulatory effect of vitamin B12, and an inhibitory effect of B12 deficiency, on bone

Figure 3. Association is shown between serum B12 and BMD at the femoral neck (A) and total hip (B) in male celiac disease patients, and at the femoral neck (C) and total hip (D) in female celiac disease patients, controlling for age, weight, and serum 25-hydroxyvitamin D. Correlations were carried out on log-transformed data where appropriate and calculated using partial correlation coefficients (r). (A) One outlier was removed; p < 0.05 was considered significant.
formation [44,45]. This further strengthens the case for a role of vitamin B12 in the metabolism of bone and has led to a call for further research in at-risk populations [46]. It is also possible that the role of the relevant B-vitamins in bone health is via their integral roles in one carbon metabolism, required for the methylation of DNA, proteins, and other molecules via S-adenosylmethionine, a universal methyl donor. Up to four B-vitamins are required for efficient one carbon metabolism; thus, low folate or vitamin B12 may emerge as a risk factor, depending on the prevailing B-vitamin status of the population under examination and the limiting nutrient involved [47,48].

The current findings will have greatest relevance to CD patients who are at an increased risk of osteoporotic fracture compared to healthy controls [49] and 38–72% of whom are reported to have low BMD at presentation [3]. Additionally, the current findings may be relevant in other gastrointestinal conditions such as Crohn’s disease and ulcerative colitis, also associated with an increased risk of both osteoporosis [50] and nutrient deficiencies [51,52]. Furthermore, these results may also be applicable in the general population, particularly in groups at risk of suboptimal B-vitamin status, such as non-consumers of fortified foods [28]. Specifically in relation to vitamin B12 deficiency, those at risk include users of proton pump inhibitors [53], and older people generally, with atrophic gastritis and the resultant hypochlorhydria which was reported to affect up to 30% of the population over the age of 60 years [54].

A number of factors contribute to the strength of this study. This is the first study to relate homocysteine and all four relevant B-vitamins, measured using well-established biomarkers of nutrient status, to bone health in a well-characterized cohort of treated CD patients. Dietary intakes were assessed using a method previously validated against B-vitamin biomarkers at this centre [28], and customized for the current study to include gluten-free foods. BMD was assessed using DXA scanning, the gold standard in the diagnosis of osteoporosis [55]. This study, however, also has limitations. Primarily, its observational nature means that a causal relationship between B-vitamins and BMD could not be investigated.

In conclusion, this study investigated B-vitamin status and bone disease in CD patients for the first time and found that serum B12 was a significant predictor of BMD at the hip in male patients with CD. These findings add to the current evidence

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Figure 4. Relationship is shown between intake of (A) folate (B) vitamin B12 (C) vitamin B6, and (D) riboflavin, with the corresponding biomarker status of the B-vitamin in celiac disease patients. Correlations were carried out on log-transformed data where appropriate and calculated using Pearson’s correlation coefficients (r). Erythrocyte glutathione reductase activation coefficient (EGRac), a functional indicator of riboflavin status, higher values indicate lower riboflavin status, with values >1.3 generally indicative of suboptimal status; p < 0.05 was considered significant. ¹Total folate intake was expressed as dietary folate equivalents (DFEs) calculated as microgram natural folate plus 1.7 × µg added folic acid [56].
showing that B-vitamins may play potential protective roles in bone health. These results could potentially be applicable in the general population, specifically in groups at risk of suboptimal B-vitamin status, such as users of proton pump inhibitors and older individuals generally at high risk of lower B12 status due to atrophic gastritis – a common problem in aging. There is a need for a well-designed intervention trial of B-vitamin supplementation in CD patients to establish if a causal relationship exists.

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