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Vitamin D status in Irritable Bowel Syndrome and the impact of supplementation on symptoms: what do we know and what do we need to know?

Claire E. Williams[1], Elizabeth A. Williams[2] & Bernard M. Corfe[1,3,4]

1. Molecular Gastroenterology Research Group, Academic Unit of Surgical Oncology, Department of Oncology & Metabolism, University of Sheffield, Beech Hill Road, Sheffield, S10 2RX
2. Human Nutrition Unit, Department of Oncology & Metabolism, University of Sheffield, Beech Hill Road, Sheffield, S10 2RX
3. Insigneo Institute for In Silico Medicine, The University of Sheffield

Author to whom correspondence should be addressed: Dr BM Corfe, Molecular Gastroenterology Research Group, Academic Unit of Surgical Oncology, Department of Oncology & Metabolism, University of Sheffield, Beech Hill Road, Sheffield, S10 2RX
Tel: 0114 215 9044
Fax: 0114 2713314
Email: b.m.corfe@sheffield.ac.uk

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ABSTRACT

Low vitamin D status is associated with risk of colorectal cancer and has been implicated in inflammatory bowel disease. Irritable Bowel Syndrome (IBS) is a chronic, relapsing, functional bowel disorder. A nascent literature suggests a role for vitamin D in IBS, but this has not been collated or critiqued. To date seven studies have been published: four observational studies and three randomised controlled trials (RCTs). All observational studies reported that a substantial proportion of the IBS population were vitamin D deficient. Two intervention studies reported improvement in IBS symptom severity scores and Quality of Life (QoL) with vitamin D supplementation.

There are limited data around the role of vitamin D in IBS.

The available evidence suggests that low vitamin D status is common among the IBS population and merits assessment and rectification for general health reasons alone. An inverse correlation between serum vitamin D and IBS symptom severity is suggested and vitamin D interventions may benefit symptoms. However, the available RCTs do not provide strong, generalizable evidence; larger and adequately powered interventions are needed to establish a case for therapeutic application of vitamin D in IBS.

194 words

INTRODUCTION

The reported health benefits of vitamin D have recently extended from musculoskeletal health to focus on the potential relationships in systemic diseases, such as Multiple Sclerosis (MS), colorectal cancer (CRC), Inflammatory Bowel Disease (IBD) (1). Vitamin D is a hormone that has two key roles within the body; i) to aid the absorption of calcium and phosphate ii) control the secretion of parathyroid hormone (2). The principal circulating form of vitamin D is 25-hydroxyvitamin D (25(OH)D; calcifediol; ChEBI:17933), which is used clinically to determine vitamin D status (3). There is no universally agreed optimal level of vitamin D, however the National Academy of Medicine (USA and Canada) has asserted that serum 25(OH)D levels need to exceed 50nmol/L (20ng/ml) to be adequate to meet the needs of 97.5% of the population (4) and by extension levels <50nmol/L (<20ng/mL) are considered insufficient (5, 6). Poor vitamin D status is of major public health concern with low vitamin D status affecting 8-24% of children and 20% adults in the UK (7). Consequently SACN guidelines recommend an intake of 10 µg/d for anyone aged 1 year and older (8). Vitamin D has increasingly been implicated in the pathobiology of colorectal diseases. A meta-analysis and systematic review of observational studies in inflammatory bowel disease (IBD) suggested that patients were 64% more likely to be vitamin D deficient compared to controls without IBD (p=0.0001) (9). Similarly, a recent review and a meta-analysis of the potential relationship between vitamin D and colorectal cancer identified an association between vitamin D intake and colorectal cancer prevalence: a significant inverse association between dietary vitamin D intake, 25(OH)D status and colorectal cancer risk was reported (10) (11). The potential for vitamin D as a secondary preventive of adenoma recurrence has also been investigated in several trials both alone and in combination with calcium (12)

Irritable bowel syndrome is one of the most common functional bowel disorders seen globally (10-20% of some populations (13) with significant healthcare cost (14). The pathogenesis of the disease remains unclear and is categorised primarily by the symptoms experienced ``z(15-17). Symptoms of IBS include bloating, abdominal pain, diarrhoea and / or constipation; the ROME III criteria incorporate assessment of these symptoms to diagnose the condition (18). There are three recognised sub-types of IBS: diarrhoea-predominant (Type D), constipation-predominant (Type C) and alternating diarrhoea and constipation (Type A) (19). Other common features of this syndrome not covered in the diagnostic criteria are bloating, passing of mucus from the rectum, irregular stool habits and urgency of evacuation (20). These symptoms have a serious impact on the person's every day quality of life and appear to have

strong links to mental health issues such as anxiety and depression (21). A number of reports linking vitamin D and IBS have received significant media attention, this review aims to collate and contextualize this research. The literature was searched systematically (See Supplementary Online Information Section I) to identify the full scope of publications in this area; 7 reports were identified, comprising of 4 observational studies and 3 randomised control trials (RCTs).

SUMMARY OF THE LITERATURE TO DATE

Observational Studies

Four intervention trials were identified that assessed vitamin D status in IBS (see Table 1).

A case study reported that a high dose supplementation (50-75mcg per day throughout the year) of vitamin D significantly improved one woman's IBS symptoms (22), including a return to almost-normal bowel patterns and decreased anxiety and depression. This paper also systematically identified analysed social media (blogs by people with IBS), noting that 70% of 37 individuals' blogs reported that vitamin D supplementation resulted in an improvement of symptoms. This case resided in the UK (hence a Northerly latitude), however blogs were from those living internationally and exact locations were not reported. Deficiency thresholds were not defined and serum 25(OH)D levels were not stated. Although in agreement with some intervention trials (23, 24), case studies are not generalisable or statistically significant.

A case control study reported vitamin D serum concentrations in patients with IBS attending a gastroenterology clinic in Saudi Arabia (International Medical Centre)(5). Cases had a confirmed diagnosis of IBS using ROME III criteria and healthy controls were gender and age matched staff members from the medical centre. This study defined deficient serum 25(OH)D concentrations as <50nmol/L (23, 25); mean serum 25(OH)D concentrations in patients with IBS was 21$\pm$12nmol/L which was significantly different to 31$\pm$16nmol/L reported for the control group. It should be noted that this study only reported serum 25(OH)D concentrations retrospectively from medical records.

A second observational study in Saudi Arabia reported recruitment of subjects (n=498) with both Crohn's Disease (CD) and IBS and compared these to a control group of staff and students (n=442) (26). The study reported insufficiency of serum 25(OH)D concentrations in 67.3% of the patients, however it is difficult to ascertain whether the insufficiency of vitamin D was a result of the IBS, CD, a combination of both or a common issue among this general population. This study neglected to define their threshold of 'vitamin D insufficiency'.

Both studies were conducted in Saudi Arabia known for its year-round sunshine which should have a positive effect on serum 25(OH)D levels. However, for religious reasons the population avoid direct exposure of their skin to sunlight and a recent systematic review (27) of 13 studies (n=24,399) found that 81% of different Saudi Arabian populations (e.g. pregnant/lactating women, children, adults) had serum concentration levels of 25(OH)D <20ng/ml (<50nmol/L).

In a US-based study (Atlanta, Georgia) medical records of 1,000 IBS patients were reviewed (28). The mean serum concentration of 25(OH)D of the population studied was 25.05nmol/L. It was also reported that 72% of women and 3% of men with IBS had a serum concentration

<30 nmol/L. There were no controls used for comparison. Furthermore, this research is only available in abstract form and as such a full analysis is unavailable.

A retrospective case-controlled study (6) analysed the medical records of 55 children and adolescents aged 6-21 diagnosed with IBS living in Massachusetts, USA. This research shows that only 7% of the IBS cohort had sufficient vitamin D levels compared to 25% of BMI-matched healthy controls attending a well-child clinic. This study suggested prevalent vitamin D insufficiency in both the IBS and control populations, albeit with a limited study design.

Intervention studies

Three intervention trials were identified that investigated the possible beneficial effect of vitamin D on IBS symptoms (see Table 2).

Tazzyman et al. (2015) conducted a 12 week randomised double-blind three-arm parallel pilot study in people with IBS which compared placebo to either vitamin D supplementation (75µg/d) or combination of vitamin D (75µg/d) plus probiotic (two strains of Lactobacillus acidophilus per capsule). The trial was conducted in the UK in January-April 2015. Analysis of baseline data illustrated that participants with low vitamin D (<50nmol/L) had lower QoL (using the single question in the Total Symptom Severity IBS questionnaire (29) compared to their replete counterparts (p=0.034)). Improvements were reported in all treatment arms, but no significant difference between the treatment arms was observed. The study provides valuable data on which to base power calculations for future randomised control trials.

A RCT conducted in Iran with 85 participants with IBS (23) found significant improvement of IBS symptoms ($p < 0.001$) and quality of life ($p < 0.001$) following very high dose (1250 µg fortnightly for 6 months) vitamin D3 supplementation compared to a placebo over a period of 6 months. Separate tools measured symptom severity (29) and quality of life (30) at baseline and exit of the study.

A second Iranian study (24) used a 2x2 factorial design to conduct a blinded randomised control trial with women aged 18-75 to investigate the effects of vitamin D, soy isoflavones or both on IBS symptoms and quality of life. One hundred participants were randomly assigned to one of four possible arms of the intervention; vitamin D and placebo (D+P), soy isoflavones and placebo (S+P), soy isoflavones and vitamin D (S+D) or both placebo vitamin D and placebo soy isoflavones (P+P). 50 000 IU (1250 µg) of vitamin D was administered fortnightly and 2 x 20mg of soy isoflavones capsules daily. The length of study was a restrictive 6 weeks with a follow-up at 4 weeks post intervention. This study reported significant improvements in IBS symptom severity score and quality of life in participants randomised to either vitamin D

isoflavones. Both S+P and the D+P groups significantly improved IBS total score (p=0.004, p=0.015 respectively). The combination effect of vitamin D and soy on IBS-TS was also significant (p<0.05).

Both the Abbasnezhad and Jalili studies showed extraordinarily low standard deviations of IBS symptom severity scores (around 10% around the mean; our ongoing work suggests that the majority of such studies report the SD of symptom severity in the range of 20-70% of the mean (Corfe, unpublished). This suggests a significantly more homogenous population than comparable publications, the reasons for this are unclear.

All three intervention studies reported low mean baseline vitamin D serum concentrations in the IBS populations studied,, ranging from 14ng/mL-21.23ng/mL (35nmol/L-53nmol/L). Vitamin D deficiency is present in the general populations of both the UK and Iran (31, 32) populations and as such, no causal link with IBS can be inferred without control population data. Two (23, 25) out of the three studies showed an increase in the mean 25(OH)D levels from deficient (<20ng/mL or <50nmol/L) status to replete (>20ng/mL or >50nmol/L) in the active arm. Dosages of vitamin D supplement varied between the studies. The preparations were either in the form of one 50 000IU (1250ug) oral capsule fortnightly or a daily 3000IU (75ug) sublingual spray. Although optimal dosing strategy is not known, research suggests that both larger, less frequent doses and daily preparations are equal in effectiveness in their repletion of 25 (OH)D (33, 34). Despite small losses to follow up, final sample sizes from previous studies appear to be relatively similar.

CONCLUSIONS AND DIRECTIONS

There is a nascent body of literature associating vitamin D status and the pathobiology and management of colorectal conditions including IBD and cancer. Four papers and one abstract report cross-sectional studies. A consistent limitation of these was that vitamin D status of the wider population is not reported. Cause and effect are difficult to determine as it might be argued that individuals with severe IBS may exhibit behaviour changes, for example elevated time indoors consequent to symptoms, that may impact on vitamin D status.

Two of three interventions studies report a positive benefit of vitamin D supplementation in people with IBS, however the low variation in the study populations and unusual dosing regime in these two studies raises questions about the generalisability of the data.. All three RCTs reported a relationship, either at baseline or in response to intervention, between vitamin D and QoL, a symptom domain of particular importance to the patient population.

Collectively the studies reviewed, although restricted, offer enough justification for further work in this subject area. In particular, future research may benefit from adequate powering (Tazzyman et al. suggests 74 subjects / arm), now that effect size data are in the public domain, to assure generalisability and conclusiveness. Future studies should include a broader spread of participant, or multiple studies should address the potential benefits in defined populations and limit claims to these populations.

Less equivocally, the body of evidence accrued across multiple populations already suggests that vitamin D status assessment should be incorporated as a routine assessment alongside IBS diagnosis in routine practice to identify individuals at risk and likely to benefit from vitamin D intervention for general health as much as for IBS symptoms.

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CONFLICT OF INTEREST

The authors authored two of the systematically reviewed papers. BetterYou markets vitamin D supplements.

AUTHORSHIP

CEW undertook the searches, collated literature and wrote the first draft. EAW co-conceived the study, reviewed and edited all drafts. BMC co-conceived the study, undertook the searches, collated the literature and edited all drafts. All authors agreed the final version of the manuscript.

REFERENCES

1. Kulie T, Groff A, Redmer J, Hounshell J, Schrager S. Vitamin D: an evidence- based review. Journal of the American Board of Family Medicine : JABFM. 2009;22(6):698.
2. Fraser DR. Vitamin D. The Lancet. 1995;345(8942):104-7.
3. Holick MF, Holick MF. Vitamin D [electronic resource] : physiology, molecular biology, and clinical applications. 2nd ed. ed. Totowa, N.J.: Totowa, N.J. : Humana, 2010; 2010.
4. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D From the Institute of Medicine: What Clinicians Need to Know. Obstetrical & Gynecological Survey. 2011;66(6):356-7.
5. Khayyat Y, Attar S. Vitamin D Deficiency in Patients with Irritable Bowel Syndrome: Does it Exist? Oman medical journal. 2015;30(2):115.
6. Nwosu BU, Maranda L, Candela N. Vitamin D status in pediatric irritable bowel syndrome. PLoS ONE. 2017;12(2):<xocs:firstpage xmlns:xocs="&#/>.
7. NICE. Vitamin D: increasing supplement use in at-risk groups https://www.nice.org.uk/guidance/ph56: NICE; 2014 [
8. Buttriss JL. Vitamin D: Sunshine vs. diet vs. pills. Nutrition Bulletin. 2015;40(4):279-85.
9. Del Pinto R, Pietropaoli D, Chandar A, Ferri C, Cominelli F. Association between inflammatory bowel disease and vitamin D deficiency: A systematic review and meta-analysis. Digestive And Liver Disease. 2016;48:E161-E.
10. Zhang X, Giovannucci E. Calcium, vitamin D and colorectal cancer chemoprevention. Best Practice & Research Clinical Gastroenterology. 2011;25(4):485-94.
11. Touvier M, Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, et al. Meta-analyses of vitamin D intake, 25-hydroxyvitamin D status, vitamin D receptor polymorphisms, and colorectal cancer risk. 2011.
12. Dulai PS, Singh S, Marquez E, Khera R, Prokop LJ, Limburg PJ, et al. Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia: systematic review and network meta-analysis. BMJ. 2016;355.
13. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional Bowel Disorders. Gastroenterology. 2006;130(5):1480-91.
14. Soubieres A, Wilson P, Poullis A, Wilkins J, Rance M. Burden of irritable bowel syndrome in an increasingly cost-aware National Health Service. Frontline Gastroenterol. 2015;6(4):246.
15. Lee B, Bak Y. Irritable Bowel Syndrome, Gut Microbiota and Probiotics. J Neurogastroenterol Motil2011. p. 252-66.
16. Boersma K, Ljótsson B, Edebol-Carlman H, Schrooten M, Linton SJ, Brummer RJ. Exposure-based cognitive behavioral therapy for irritable bowel syndrome. A single-case experimental design across 13 subjects. Cogn Behav Ther. 2016;45(6):415-30.
17. Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome. Aliment Pharmacology Therapy Journal. 2014;40(9):1023-34.
18. Wilkins T, Pepitone C, Alex B, Schade RR. Diagnosis and management of IBS in adults. American family physician. 2012;86(5):419.
19. Drossman DA. The Functional Gastrointestinal Disorders and the Rome III Process. Gastroenterology. 2006;130(5):1377-90.
20. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. Br Med J. 1978;2(6138):653.
21. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health- related quality of life. Gastroenterology. 2000;119(3):654-60.
22. Sprake EF, Grant VA, Corfe BM. Vitamin D3 as a novel treatment for irritable bowel syndrome: single case leads to critical analysis of patient-centred data. BMJ case reports. 2012;2012.

23. Abbasnezhad A, Amani R, Hajiani E, Alavinejad P, Cheraghian B, Ghadiri A. Effect of vitamin D on gastrointestinal symptoms and health-related quality of life in irritable bowel syndrome patients: a randomized double-blind clinical trial. Neurogastroenterology and Motility. 2016;28(10):1533-44.
24. Jalili M, Hekmatdoost A, Vahedi H, Poustchi H, Khademi B, Saadi M, et al. Co-Administration of Soy Isoflavones and Vitamin D in Management of Irritable Bowel Disease. PLoS ONE. 2016;11(8).
25. Tazzyman S, Richards N, Trueman AR, Evans AL, Grant VA, Garaiova I, et al. Vitamin D associates with improved quality of life in participants with irritable bowel syndrome: outcomes from a pilot trial. BMJ Open Gastroenterology. 2015
2(1):e000052.
26. Al-Ajlan AS. Screening of coeliac disease in undetected adults and patients diagnosed with irritable bowel syndrome in Riyadh, Saudi Arabia. Saudi Journal of Biological Sciences. 2016;23(4):462-6.
27. Al-Daghri NM. Vitamin D in Saudi Arabia: Prevalence, distribution and disease associations. Journal of Steroid Biochemistry and Molecular Biology. 2016.
28. Yarandi S, Christie J. The Prevalence of Vitamin D Deficiency in Patients with Irritable Bowel Syndrome. American Journal Of Gastroenterology. 2013;108:S565-S.
29. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Alimentary Pharmacology & Therapeutics. 1997;11(2):395-402.
30. Bengtsson M, Hammar O, Ohlsson B, Mandl T. Evaluation of gastrointestinal symptoms in different patient groups using the visual analogue scale for irritable bowel syndrome (VAS-IBS). BMC Gastroenterology. 2011;11.
31. Rahnavard Z, Eybpoosh S, Rezaei Homami M, Aghaei Meybodi HR, Azemati B, Heshmat R, et al. Vitamin D deficiency in healthy male population: Results of the Iranian multi- center osteoporosis study. Iranian Journal of Public Health. 2010;39(3):45-52.
32. Kazemi A, Sharifi F, Jafari N, Mousavinasab N. High prevalence of vitamin D deficiency among pregnant women and their newborns in an iranian population. Journal of Women's Health. 2009;18(6):835-9.
33. Ahmad S, Mohammad Hassan L, Zahra N, Sedighe Akhavan K, Malihe G, Mehrdad S. Study to Evaluate Two Dosage Regimens of Vitamin D Through an Academic Year in Middle School Girls: A Randomized Trial. Acta Medica Iranica. 2011;49(12):780-3.
34. Meybodi H, Bagheri A, Soltani A, Tehrani MM, Khashayar P, Heshmat R, et al. Effect of high dose versus conventional vitamin D supplement on serum 25(OH)D levels in women with low bone mass. Osteoporosis International. 2010;21:S744-S.

LEGENDS

Table 1. Observational studies identified linking IBS symptoms and vitamin D status. Papers are in order of publication, showing populations used in the study

Table 2. Intervention Studies identified testing the effect of vitamin D supplementation on IBS symptoms. Papers are in order of publication, the study size, population and principle outcomes are shown. Abbreviations: IBS-SSS = Irritable Bowel Symptom Severity Score, TSS = Total Severity Score, QoL = Quality of Life, D = vitamin D, S=soy isoflavones, P=placebo.