

Mistakes in nutrition in IBD and how to avoid them

Joseph Meredith, Konstantinos Gerasimidis and Richard K Russell

The relationship between nutrition and inflammatory bowel disease (IBD) has been an area of substantial interest and research for many decades now. Evidence-based nutritional strategies are being utilised as a key part of the therapeutic armamentarium in Crohn's disease for both induction and maintenance, as primary and adjuvant treatment methods. Exclusive enteral nutrition, for instance, is well established in the treatment of paediatric IBD and adult centres are increasingly incorporating it into treatment models as an effective, drug-free alternative. The role for partial enteral nutrition and Crohn's disease specific diets are also being more clearly elucidated. Used appropriately, and through engagement with dietetic support services, nutritional therapies can not only achieve the IBD treatment 'targets' but serve to optimise other vital aspects of care, such as growth, bone health, body composition and overall patient well-being. Here we discuss some of the mistakes that are frequently made in the area of nutritional management of IBD. The discussion is evidence based, with key references incorporated for further analysis beyond the scope of this article, and combines several decades of leading clinical and research experience in the area of nutrition and IBD from the authors.



Mistake 1 Believing nutritional therapies only work in paediatric patients

Exclusive enteral nutrition (EEN) has been widely utilised as an inherently risk-free and highly effective means of inducing remission in paediatric patients who have active luminal Crohn's disease. European consensus guidelines recommending it as a first-line therapy in this population reflects the weight of evidence in its favour.¹

Clinical response rates to EEN approximating 80% are well supported by the paediatric literature, and for children and adolescents with Crohn's disease nutritional therapies represent a crucial steroid-sparing strategy.² Despite similar efficacy being reported in various large, well-conducted adult studies, the uptake of EEN as part of the therapeutic strategy for adult IBD is limited outside Japan, where EEN (or close to full EEN) is increasingly recommended as a first-line treatment.³ This reluctance has largely been driven by a Cochrane meta-analysis that did not replicate the above results; however, when the analysis was restricted to high-quality studies only, there was no difference between corticosteroids and EEN.⁴ Importantly, several randomised controlled trials (RCTs) show that mucosal healing, one of the key 'targets' when managing IBD, is more likely to be achieved by EEN than corticosteroids.⁵⁻⁷

Poor adherence to EEN by adults generally has also reduced its utility as a key part of the therapeutic strategy. Encouragingly, involving an experienced dietitian and providing appropriate dietetic support, as is often standard practice in

paediatrics, increased compliance rates to >85% in one adult cohort.⁸ Optimal care pathways have been developed to both encourage and support EEN use in adult patients.⁹ We believe EEN should be offered as a standard treatment option for adults with active Crohn's disease both to induce remission or reduce the burden of active disease, particularly as a preoperative strategy for the latter. It is favoured especially as first-line therapy where avoidance of steroids and immunosuppressive medications is desired and where malnutrition is part of the clinical picture.

Bottom line: EEN should be strongly considered as an alternative to systemic corticosteroids for induction therapy in select adults with Crohn's disease, particularly given the increasing accessibility and palatability of polymeric feeds, the multitude of potential benefits beyond disease control and recognising the key role of dietetic support in maximising adherence. This message should be widely communicated especially during the COVID-19 era when alternatives to steroid use are especially relevant.

Mistake 2 Not making exclusive enteral nutrition exclusive during induction

Partial enteral nutrition (PEN) is an attractive alternative to EEN given the restrictive nature of EEN and the subsequent impact on adherence in the absence of appropriate dietetic support. However, PEN is currently not recommended for induction therapy in Crohn's disease.¹

Several studies support the need for exclusivity of enteral nutrition during the induction phase. One prospective study involving 90 children demonstrated that although PEN improved clinical symptoms, EEN was superior in achieving mucosal healing and quality of life (QoL) parameters.¹⁰ An earlier RCT showed threefold higher PCDAI-based remission rates after 6 weeks in children receiving EEN compared with those receiving 50% PEN combined with free diet.¹¹

Recently 50% PEN in combination with a Crohn's disease exclusion diet (CDED) — a whole food diet that excludes postulated pro-inflammatory dietary components in a phased manner — has been shown to induce remission in mild–moderate luminal disease in children and young adults.¹² Corticosteroid-free remission was achieved in 75% of patients after 12 weeks, and the PEN plus CDED combination had superior tolerance rates to EEN but no difference in efficacy. This indicates that exclusion of elements of the 'free diet' that are part of a PEN strategy alone might be important in achieving substantive remission rates at induction. While small deviations from EEN may be OK for pragmatic reasons, at present it is best to emphasise exclusivity until 'allowed' deviations that don't impact on efficacy are better understood.¹³

Specifically developed diets including CD-Treat and CDED are gaining an increasing evidence base as safe, effective and sustainable dietary therapies for induction, maintenance and rescue therapies for Crohn's disease in adults and children in research studies.¹⁴ CD-Treat, like

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the CDED, is a whole food diet that mimics the nutritional components of EEN as far as possible, but offers diverse food and drink options and as such offers a far more palatable and acceptable therapy for patients.¹⁴ PEN strategies may be used as a step-down therapy following completion of EEN and the specific whole food diets mentioned offer a potential option for long-term maintenance therapy, especially where avoidance of immunosuppressant medications is desired and/or malnutrition is a concern. Further research on the extended utility of such dietary therapies is underway.

Bottom line: Unless tailored expertise in the provision of whole food diets is available, it is important to achieve maximum efficacy by emphasising the initial E in EEN!

Mistake 3 Confining EEN to initial induction therapy for mild-moderate luminal small-bowel Crohn's disease

Historical practice has limited EEN use to active small-bowel disease, but it has proven efficacy regardless of the intestinal site of luminal involvement. As such, the use of EEN should be considered for all disease locations. There is also growing evidence for its use in perianal disease as an adjunct therapy.^{4,15} Furthermore, there is increasing evidence of efficacy for EEN in the management of exacerbations of Crohn's disease distinct from its use at diagnosis, with repeat courses as effective as initial courses.^{16,17}

There is growing support for the use of perioperative EEN in Crohn's disease; however, large RCTs are currently lacking.^{18,19} The pooled, mainly retrospective, data available indicates that 2–6 weeks of preoperative EEN markedly reduces postoperative complications versus standard nutritional care, particularly for those who have more severe disease.

One of the best illustrations of the benefit of preoperative EEN is a case-control study of 114 adult Crohn's disease patients with stricturing or penetrating complications.²⁰ Those who were given a mean duration of 6 weeks of preoperative oral EEN therapy had significantly reduced CRP values and intraoperative times, and a ninefold reduction in the incidence of postoperative abscess and/or anastomotic leak. Furthermore, 25% of the EEN group avoided surgery and were bridged to medical therapy. However, no statistically significant differences were seen in readmission or recurrence rates at 12 months in those who underwent surgery.

A large but unmatched retrospective study (498 patients; 219 treated with EEN for 4 weeks) showed a significant reduction of postoperative complications, rates of stoma creation, and need for urgent operations for patients given preoperative EEN.²¹ Clearly, more robust data is sought after but it is likely that by improving

nutritional status and reducing the inflammatory burden preoperative EEN improves surgical outcomes in Crohn's disease patients.

Bottom line: EEN is effective for all disease locations, in complicated disease, as a preoperative preparation and can be used for both induction and subsequent treatment courses in Crohn's disease.

Mistake 4 Assuming dietary therapies improve short-term outcomes and patient well-being only but not other key IBD targets including markers of remission and mucosal healing

EEN therapy is associated with benefits over and above QoL measures and 'hits' many contemporary Crohn's disease treatment targets. Marked improvements in biomarkers of disease activity, including CRP, ESR and albumin, are well established. More importantly, significant rates of mucosal healing have been demonstrated with EEN induction therapy. A prospective paediatric cohort study from Australia reported an early endoscopic response in 58% of patients, and 1/3 had complete transmural healing on small-bowel imaging after 8 weeks of treatment. Similarly designed European studies have shown that EEN confers superior mucosal healing rates to steroids when compared in RCTs.^{5,6} Concordantly, faecal calprotectin levels have been shown to decline by approximately 50% following completion of an EEN course.²²

There is growing evidence that EEN achieves such results through modulation of the pro-inflammatory state, plus improved epithelial barrier function and gut dysbiosis, which are potential key components in the pathogenesis of IBD.²³ Clinical studies show there is a return to a more 'normal' inflammasome with EEN, based on microRNA expression indices and down regulation of inflammatory cytokine signalling, including from IL-1 β , IL-1ra, IL-6, IL-8 and TNF- α .²⁴ It is clear that the microbiome is significantly altered within days of commencing EEN and how these changes impact the pro-inflammatory state are being studied in detail.²⁵

Bottom line: Being aware of the many 'gains' associated with EEN at both the patient and mucosal level is essential for the treating team and for patients and families alike to improve understanding, uptake, adherence and ultimately patient outcomes.

Mistake 5 Recommending dietary restrictions based on limited evidence – exaggerating the role of food additives and emulsifiers

Epidemiological and preclinical investigations have implicated certain food additives, especially emulsifiers, in the aetiology of IBD. Work in animal

models and in vitro suggests food additives may impair gut health through alterations in the microbiome, barrier function and gut-based immune signalling.^{26,27}

Carrageenan, a polysaccharide commonly used as a food additive, induced an inflammatory response in experimental models.^{28,29} Others have also implicated emulsifiers in producing colitis in mice.³⁰ As such, dietary recommendations and exclusions have migrated into real-world practice. However, few convincing studies have established a causative or exacerbating role for such food additives in IBD in humans. Rather, recent in-depth compositional analysis of EEN, in view of its well-established efficacy in the treatment of IBD, suggests that such ingredients, at the levels present in formula, are unlikely to have a significant role at least as triggers for exacerbation of IBD.³¹

Food additives implicated in Crohn's disease aetiology are present in EEN formulas to varying degrees, and include modified starches (in 100% of formulas tested), carrageenan (in 22%), carboxymethyl cellulose (in 13%) and polysorbate 80 (in 5%).³¹ Remission rates did not differ between patients given EEN formulas with and without those food additives. While such evidence is clearly not definitive, this research, along with other work in the area, emphasises the need for well-conducted in vivo human studies before wide-ranging dietary interventions are recommended in clinical practice.

Bottom line: Unnecessary dietary restrictions negatively impact on a patient's food-related quality of life. Any restrictions must be based on validation in IBD patients and not simply on the translation of epidemiological or laboratory-based work.

Mistake 6 Assuming diets linked to IBD in epidemiological studies match up with those that should be used for dietary treatment

There is increasing evidence around the role of diet in the pathogenesis of IBD and the development of specific exclusion diets as therapeutic tools. However, there is danger in prescribing dietary restrictions based on evidence that is not derived from well-controlled, interventional, human studies.^{32,33} Macronutrients including fibre, polyunsaturated fatty acids (PUFAs) and meat protein have been implicated in IBD, but dietary interventions based around these elements have not proven successful in mitigating the disease.³⁴

For instance, a recent systematic review of 23 RCTs involving dietary interventions with fibre failed to show any significant efficacy in improving disease outcomes.³⁵ Also, 80% of formulas investigated in the EEN composition study contained essentially no fibre.³¹ Fish consumption and dietary intake of omega-3 fatty

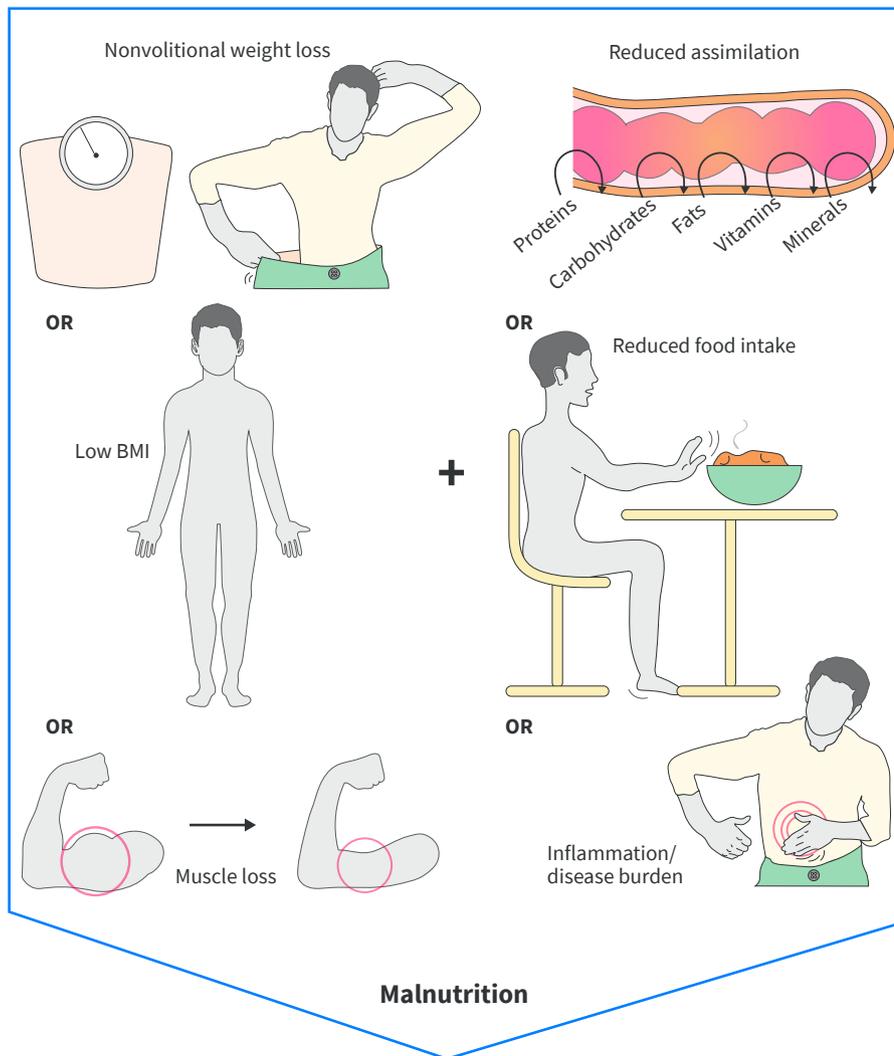


Figure 1 | Diagnosis of malnutrition. The ESPEN global consensus for diagnosis of malnutrition (GLIM) has identified several key features that contribute to the diagnosis of malnutrition.^{67,68} The role of muscle loss/sarcopenia must not be forgotten.

acids has epidemiological links with IBD and has been regarded as having therapeutic potential—eliciting anti-inflammatory properties and ameliorating gut inflammation in mouse models.³⁶ Currently, however, evidence for clinical benefit in both Crohn’s disease and ulcerative colitis is lacking.^{37,38}

Red meat consumption has for some time been regarded as a contributing dietary factor for relapse in Crohn’s disease.³⁹ In a study from Japan, a semi-vegetarian diet was shown to dramatically improve remission rates at 2 years versus a regular omnivorous diet.⁴⁰ By contrast, a well-conducted RCT from 2019 in patients with Crohn’s disease in remission showed there were no significant differences in relapse rates between participants on a high versus low red meat diet.⁴¹

Bottom line: Evidence from animal and epidemiological studies does not necessarily equate to efficacy of dietary interventions in IBD practice. Don’t make the mistake of prescribing or supporting restrictive diets in the absence

of good clinical data and that are potentially harmful.

Mistake 7 Missing malnutrition in patients with IBD

Malnutrition, both undernutrition and over-nutrition, should be considered as a systemic and serious complication of IBD and should not be overlooked (figure 1).⁴² It may be present in approximately 2 out of every 3 patients with IBD, but is more common in those with new-onset disease.⁴³ In hospitalised patients, malnutrition is a risk factor for multiple comorbidities, including; infection, thromboembolism, emergency surgery, prolonged length of stay and mortality, although this may be related to its association with disease severity.⁴⁴

For children, the effects of malnutrition on puberty and growth velocity are well described and may have translational effects that persist into adulthood. Growth failure is present in 15–40% of paediatric IBD patients.⁴⁵ Specific attention

must be paid to the consideration, diagnosis and optimisation of nutritional status wherever possible. A 2019 study reported that just over half of adult patients at high risk for malnutrition in dedicated IBD treatment centres in the UK and Greece had nutrition discussed at routine outpatient visits.⁴⁶

Nowadays, obesity has become the number one nutritional issue in patients with established Crohn’s disease.⁴⁴ Obesity, and sarcopenic obesity in particular, are independent risk factors for osteopenia, more rapid disease progression, metabolic syndrome and cardiovascular disease.⁴⁷ The cumulative effects of obesity and systemic inflammation heighten the cardiovascular risks in IBD patients, who already have a significantly increased cardiovascular risk based on disease status alone.⁴⁸

Covert deficits in fat free mass (FFM) and increased abdominal adiposity are common in both Crohn’s disease and ulcerative colitis and may persist despite remission.⁴⁹ These important measures may be missed using common anthropometrics, such as BMI. Incorporating measures of lean tissue mass—through simply modifying protocols of frequently utilised cross-sectional imaging modalities, using DXA or other surrogate markers—into nutritional assessment may improve the detection and management of malnutrition in IBD.

Bottom line: Obesity is now the overwhelming nutritional problem in patients with IBD. Sarcopenic obesity especially should be considered a key comorbidity that needs to be managed. Regular dietetic multidisciplinary team involvement is key and measures of lean tissue mass may be targeted to improve nutritional and overall outcomes.

Mistake 8 Not taking the inflammatory state into account when assessing micronutrient deficiency

Vitamin and trace element (VTE) deficits are often only clinically apparent when stores are already significantly depleted. Interpretation of clinical signs and laboratory biomarkers can be challenging and misleading. Interpretation of serum levels is complicated by the frequent co-existence of a systemic inflammatory response, which may lead to the erroneous diagnosis of VTE deficiencies.⁵⁰ The variations can be extreme (figure 2).⁵¹ Aside from ferritin and ceruloplasmin, VTE levels are often grossly underestimated, particularly for selenium, zinc, vitamins A, B6, C and D. Levels for selenium, B6 and C may be significantly depressed, with CRP levels as low as 5–10mg/L. Results must be interpreted in parallel with CRP and albumin levels and the current clinical state. Unless the specific context dictates, avoid the temptation to give megadoses acutely to replace low levels and ideally assess

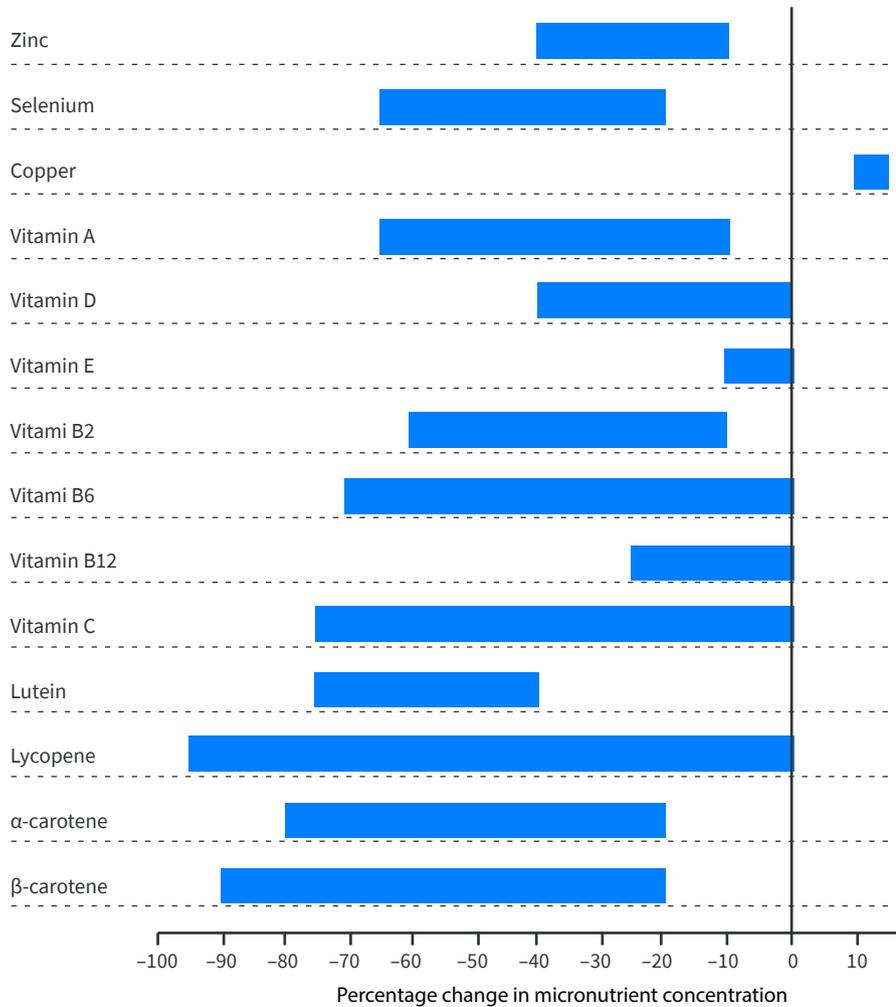


Figure 2 | Magnitude of effect (percentage change) of the systemic inflammatory response effect on the concentration of plasma vitamin and trace elements (data from Gerasimidis et al.⁵⁰).

levels when no significant systemic inflammatory response is present (figure 3).

Although generally not readily available, red blood cell levels of various VTEs are far more representative than the highly fluctuant plasma levels, and some, including selenium and B2/B6, remain very accurate in the face of acute inflammation.⁵⁰

Bottom line: Testing for VTE deficiency should ideally be avoided in the setting of a systemic inflammatory response unless necessitated by the specific clinical context. Significantly low VTE levels may accompany systemic inflammation and it is prudent to reassess if relevant in a more quiescent state before replacing them. Use dietary assessment to compliment the results from biomarkers.

Mistake 9 Failing to recognise and treat nutritional deficiencies

A systematic approach to the diagnosis and management of some nutritional deficiencies (e.g. iron, vitamin D and B12) is essential given

their high frequency. Iron deficiency, for example, has a reported prevalence of 36–90% in patients with IBD, up to a third of patients may have vitamin D deficits with similar rates of B12 deficiency in those specifically with ileal resections. These deficits have considerable implications for patient outcomes.^{44,52}

Evidence-based guidelines provide a useful framework for day-to-day clinical practice.^{44,53} IBD patients with anaemia have equivalent QoL impairments as those with anaemia in the setting of advanced malignancy.⁵⁴ As a major contributor to anaemia, iron deficiency must be treated accordingly, but it is important to distinguish iron deficiency anaemia from anaemia of chronic disease. No longer is expectant management of iron deficiency anaemia sufficient—expeditious use of intravenous preparations when active disease is present and treating to normalise haemoglobin and iron stores is now recommended.^{55,56}

It is important, particularly for paediatric gastroenterologists, to be aware that reference ranges for nutritional deficiencies may be based on data that is not entirely relevant for all patients.

Indeed, reference ranges are often based on adult cohorts or small samples, at times from populations in which deficiencies are more of a public health concern, and do not reflect the biological variations with age.⁵⁰ Interpretation in both adult and paediatric patients must consider the specific metabolic and nutritional context, including highly malabsorptive states and treatment with medications such as methotrexate that antagonises folate metabolism. Anatomic variants of disease, such as ileal inflammation or resection, that may necessitate lifelong B12 therapy must also be considered, as should sodium loss in protracted diarrhoea.

Consequently, treatment must be individualised and patients may require significantly higher doses than typically prescribed to maintain homeostasis.

Bottom line: Have a systematic approach to testing and treating deficiencies of iron, vitamin D and B12 given their very high prevalence in IBD patients. For less common deficiencies individualise testing and treatment regimes where they are indicated.

Mistake 10 Neglecting exercise as a key part of the nutritional management of IBD

It can be a mistake to ignore exercise as a therapeutic strategy when looking to optimise the nutritional and overall well-being of patients with IBD. Gastroenterologists may learn from oncology colleagues who have recently formalised ‘prescriptions’ of exercise as ‘medicine’ and published guidelines on overcoming barriers to exercise referrals.^{57,58} This includes prescribing structured, supervised or highly supported exercise regimes. Several large clinical trials show significant benefits in morbidity, mortality and QoL metrics for patients—cancers of the gastrointestinal tract being some of the most heavily studied.^{59–61} Barriers to exercise that are often also seen in IBD patients (e.g. nausea, diarrhoea, anorexia, stomas, fatigue) were overcome.

While large-scale RCTs are lacking in the field of IBD, there is a growing body of evidence supporting exercise as feasible, safe and beneficial particularly for osteopenia, sarcopenia and quality of life in this population.^{62,63} However, a 2020 Cochrane review assessing interventions for fatigue in IBD did not find sufficient evidence to support a specific recommendation for exercise.⁶⁴ A 2015 prospective study of almost 2,000 patients in remission who had increased exercise levels as part of the study were significantly less likely to flare at 6 months [adjusted RR 0.72, 95% CI 0.55–0.94, p=0.02].⁶⁵ A 2010 systematic review and other more recent studies similarly report reduced disease activity secondary to increased physical activity in patients with IBD.⁶⁶ ESPEN

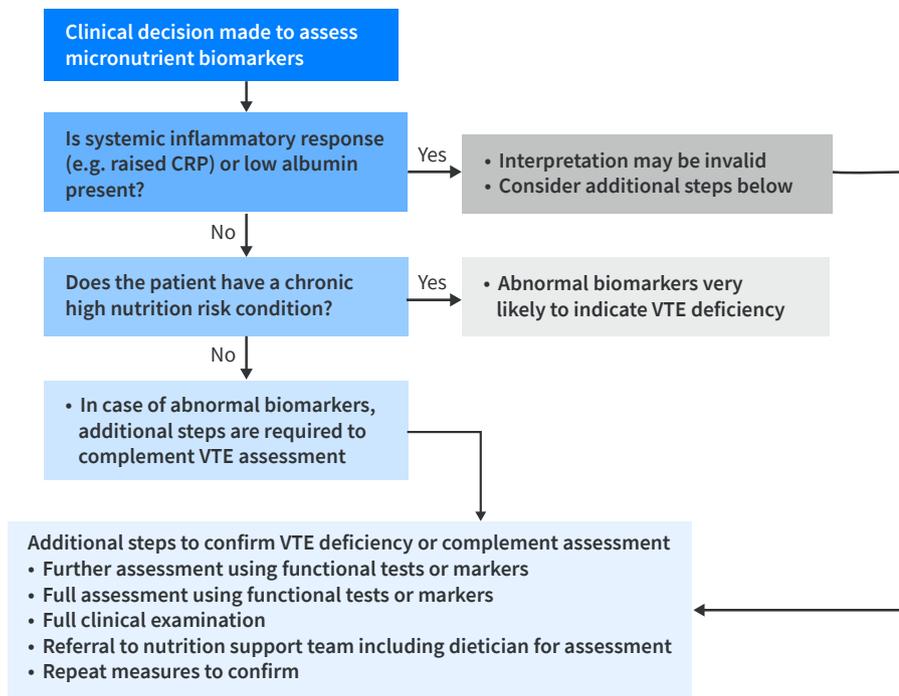


Figure 3 | A decision tree for the evaluation of vitamin and trace element (VTE) status with laboratory biomarkers. Reproduced from Gerasimidis K, et al. *J Pediatr Gastroenterol Nutr* 2020; 70: 873–881 © 2020 by ESPGHAN and NASPGHAN, with permission from Wolters Kluwer.

guidelines recommend prescribed endurance exercise for all patients with IBD, as well as weight-bearing exercises for those with, or at risk of, sarcopenia.⁴⁴

Bottom line: Exercise is safe and probably beneficial for patients with IBD in several key areas. Gastroenterologists should utilise and promote the philosophy that “exercise is medicine” to complement other nutritional strategies in place for IBD patients.

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Online courses

- Epidemiology and Aetiology of Inflammatory Bowel Disease [<https://ueg.eu/p/179>].

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- Intestinal failure in Crohn disease: A challenge for artificial nutrition and medical therapies [<https://ueg.eu/library/webinar-intestinal-failure-in-crohn-disease-a-challenge-for-artificial-nutrition-and-medical-therapies/236836>].

UEG Week

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Standards and Guidelines

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