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SUPPLEMENT ARTICLE

# Iron and vitamin D deficiency in inflammatory bowel disease

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Nutrient deficiencies are common in inflammatory bowel disease. This is most marked during periods of prolonged disease activity, extensive small bowel involvement or recurrent surgical resections. Iron stores and vitamin D are frequently found to be deficient and carry significant health consequences.

Iron deficiency is the most common cause of anemia in inflammatory bowel disease, although it frequently coexists with anemia of chronic disease. Anemia is associated with a decreased quality of life, reduced ability to work, greater need for hospitalization and overall increased healthcare utilization.

Current European consensus guidelines recommend intravenous iron as first line treatment in patients with clinically active inflammatory bowel disease (IBD), with previous intolerance to oral iron or with hemoglobin below 10 g $dL^{-1}$. Compared with oral iron, intravenous iron results in a faster rise in serum ferritin and is better tolerated but has not been consistently shown to be superior at improving hemoglobin levels.[1] New formulations of oral iron (such as ferric maltol) have completed phase 3 trials and are well tolerated even in those with IBD and previous intolerance to ferrous sulfate [2]. If treating with intravenous iron, proactive monitoring and repeat iron infusion when the ferritin drops below 100, is proven to prevent anemia recurrence.[3]

In Australia, intravenous formulations containing iron polymaltose and more recently ferric carboxymaltose (FCM) are approved by the pharmaceutical benefits scheme (PBS) for the treatment of iron deficiency anemia where oral therapy is contraindicated, not tolerated or enteric absorption is defective. Iron sucrose is another formulation, but is only PBS approved in the setting of chronic hemodialysis. FCM can be rapidly infused (over 15 min) in large single doses (up to 100 mg; 20 mg $kg^{-1}$). Large total-dose infusions of iron polymaltose (commonly 1000–2500 mg for an adult) require approximately 5 h. There have not been any head-to-head comparative studies of FCM and iron polymaltose. These formulations of intravenous iron are safer than earlier iron dextran preparations where hypersensitivity reactions were more frequent. Anaphylactic or anaphylactoid reactions occur in 0.1% of FCM infusions, which is similar to iron polymaltose and iron sucrose.

Hypophosphatemia is an under recognized complication of treatment with FCM and iron polymaltose but not iron sucrose. The reported incidence is between 2.1% and 86%.[4] While most are transient and not clinically significant, there are case reports of serious hypophosphatemia resulting in osteomalacia and low impact fractures. Vitamin D deficiency and malnutrition are reported risk factors. This may be particularly relevant in the sick IBD patient requiring multiple iron infusions.

Vitamin D deficiency is common in IBD but varies between 16% and 95% of patients.[5] This is potentially due to different study methodologies, small patient cohorts, different sunlight exposures or daylight hours, inconsistent inclusion of appropriate control groups and contrasting definitions of sufficiency, insufficiency and deficiency. The Institute of Medicine in 2010 defined vitamin D sufficiency as ≥50 nmol $L^{-1}$, insufficiency as 25–50 nmol $L^{-1}$ and deficiency as <25 nmol $L^{-1}$. These are in contrast to those published by the Endocrine Society where sufficiency is ≥75 nmol $L^{-1}$, insufficiency 50–75 nmol $L^{-1}$ and deficiency <50 nmol $L^{-1}$.

The impact of vitamin D deficiency on bone and muscle health is well recognized but over the last decade it is clear that there is a role for vitamin D as a regulator of both the innate and adaptive immune responses. To date, vitamin D deficiency has been associated with numerous aspects of IBD including, its onset, activity, the need for hospitalization and surgery, as well as the risk of malignant transformation.[6] Vitamin D supplementation has also been suggested as a potential adjunctive therapy in Crohn's disease.

Oral cholecalciferol remains the mainstay of vitamin D replacement in IBD. For most patients with vitamin D insufficiency or mild deficiency, supplementing with cholecalciferol 1000–2000 international units (IU) daily for 3 months will be adequate. For those with extensive small bowel disease, severe vitamin D deficiency or poor compliance, high dose oral therapy, or intramuscular cholecalciferol may be considered. Current approved formulations in Australia are limited to capsules with 1000 IU or liquid formulation with 1000 IU 0.5 $mL^{-1}$. High dose capsules (50,000 IU), can be imported but require prescriber approval by the Therapeutic Goods Association (TGA) or alternatively can be prepared by compounding chemists at low cost. Intramuscular cholecalciferol may be appropriate for those with extensive small bowel disease, non-compliance or severe deficiency (<10 nmol $L^{-1}$). These can only be prescribed by TGA-approved prescribers. Individual patient response to vitamin D replacement is variable, but high dose replacement is more effective at raising the serum 25(OH)D level. It is not clear if daily dosing is equivalent to intermittent high-dose replacement. Emerging data suggests that the parent vitamin D3 compound as acquired from supplements or sunlight may have important physiological functions, but due to its short half-life, circulating concentrations can only be maintained with daily dosing.[7] The optimal serum 25 (OH)D level is also a subject of debate with most experts, including the Institute of Medicine, agreeing that a level >50 nmol $L^{-1}$ is ideal for bone health but whether higher levels are needed for immune modulatory properties remains controversial.[8]

In summary, iron and vitamin D deficiency are common in IBD, particularly during periods of prolonged disease activity and are associated with adverse clinical outcomes and reduced quality of life. Proactive monitoring to identify and correct these deficiencies is an important part of managing IBD.

## References


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