Micronutrient deficiencies in Inflammatory Bowel Disease (IBD)

Overview:
Inflammatory bowel disease (IBD) is an idiopathic disease characterized by dysregulated immune response to commensal intestinal microflora.¹ Two types of IBD are ulcerative colitis, inflammation of colon, and Crohn’s disease, inflammation of one or more sections of the gastrointestinal tract.² Malnutrition in IBD patients can be divided into protein-energy malnutrition and micronutrient deficiency.³ Although micronutrient deficiencies are caused by multiple mechanisms the four key causes are:

a) Reduced food intake: A study of IBD patients in remission found avoidance of major food groups - ½ avoided grains, ½ avoided dairy, 18% avoided vegetables and 11% avoided fruits.⁴ IBD cohorts have been reported to have inadequate intake of iron, Vitamin D, Vitamin C and calcium, folate, Vitamin B1 and B6, beta-carotene, Vitamin K, and Vitamin E.⁵,⁶

b) Enteric loss of nutrients: Chronic diarrhea and fistula leads to wasting of zinc, potassium and calcium while gastrointestinal bleeding might cause iron deficiency.⁷,⁸

c) Malabsorption: Inflammation and resection of the small bowel >40-60 cm can lead to Vitamin B₁₂ deficiency and bile-salt wasting leading to impaired fat soluble vitamin absorption.⁹

d) Drug interaction: Medications used by IBD patients can interfere with nutrient absorption. For example, sulfasalazine is a folate antagonists, cholestyramine impairs absorption of fat soluble vitamins, and glucocorticoids might impair absorption of calcium, phosphorus and zinc and alter metabolism of calcium and Vitamin D. While parenteral nutrition can also lead to deficiencies of micronutrients not included in sufficient quantity.¹⁰

e) Other causes include - anorexia secondary to inflammation, steatorrhea which leads to malabsorption of fat soluble vitamins and divalent cations and hypermetabolic state which alters the resting energy expenditure.¹¹

---

² http://www.crohnscolitisfoundation.org/assets/pdfs/updatedibdfactbook.pdf accessed February 27, 2017
Here is a summary of common micronutrient deficiencies in IBD patients:

<table>
<thead>
<tr>
<th>Micronutrients</th>
<th>Site of Absorption</th>
<th>Prevalence of deficiencies based on serum levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water Soluble Vitamins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamine (B₁)</td>
<td>Jejunum/ileum</td>
<td>32%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Niacin (B₃)</td>
<td>Jejunum</td>
<td>77%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Folate</td>
<td>Jejunum/ileum</td>
<td>19%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>B₆</td>
<td>Jejunum</td>
<td>29%&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>B₁₂</td>
<td>Terminal ileum</td>
<td>18.4%&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>C</td>
<td>Jejunum/ileum</td>
<td>84%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Fat Soluble Vitamins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Ileum</td>
<td>23.4%&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>D</td>
<td>Ileum</td>
<td>17.6%&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>E</td>
<td>Ileum</td>
<td>16%&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Macrominerals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>Duodenum/ Jejunum</td>
<td>80-86%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Iron</td>
<td>Duodenum</td>
<td>39.2%&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Microminerals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>Jejunum</td>
<td>15.2%&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Copper</td>
<td>Duodenum</td>
<td>84%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Selenium</td>
<td>Ileum</td>
<td>82%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Anemia:**
The most common complication of IBD is anemia which is associated with impaired quality of life. Although there is guidelines on how to care for anemia in patients with IBD, there are gaps in clinical

---

The leading cause of anemia in IBD patients is iron deficiency. Iron deficiency is caused predominantly by impaired metabolism. There is increased retention of iron in enterocytes, macrophages and monocytes due to pro-inflammatory cytokines stimulated upregulation of hepcidin, a regulator of iron homeostasis. Reduced circulating iron levels decreases plasma ferritin levels, an indicator of iron status. However, ferritin is an acute phase reactant, whose levels are elevated in inflammation, making the diagnosis of iron deficiency in IBD patients challenging. Per the guidelines for diagnosis and treatment of iron deficiency anemia in IBD patients, C-reactive protein (CRP) levels should also be considered. The guidelines state that the goal of iron supplementation should be achieve ferritin >100 mcg/L, hemoglobin (12g/dL in women and 13 g/dL in men) and transferrin saturation (16-50%).

Folate deficiency causes macrocytic megaloblastic anemia. Without folate intake of 400-1000 mcg/day, folic acid stores are readily depleted. In IBD patients, there are no clear guidelines for screening for folate deficiency, although measuring serum and RBC folate levels is indicated. Vitamin B₁₂ deficiency is also associated with megaloblastic anemia. Evaluating Vitamin B₁₂ status is indicated for patients with macrocytic anemia or anemia not corrected by iron. If serum Vitamin B₁₂ levels are normal then levels of Vitamin B₁₂ metabolites, methylmalonic acid and homocysteine, should be checked as these metabolites are more sensitive markers of B₁₂ deficiency than serum B₁₂ levels.

**Bone Metabolism:**

Bone disease, osteopenia and osteoporosis, occur in 22-77% and 17-41% of IBD patients, respectively. Although malnutrition and malabsorption plays an important in pathogenesis of bone disease, other risk factors include inflammation, corticosteroid use, and reduced physical activity. Calcium supplementation at doses of 1000–1500 mg/day (1000 mg for women age 25 until menopause and men <65 years old; 1300 mg for women between 18–25 years; 1500 mg for postmenopausal women, and men >65 years old), is recommended in IBD patients. In bone metabolism, calcium works in concert with Vitamin D thus, Vitamin D status should be measured and monitored in all IBD patients. If a patient is Vitamin D deficient (<15 ng/mL) various regimens can be employed. Supplementation with 6000 IU/day till serum 25-OHD levels of >30 ng/mL are achieved followed by a maintenance dose of 1500-2000 IU/day is recommended. However, for obese patients or patients on glucocorticosteroids, Vitamin D dose should be two-thrice times greater than the recommended amount for their age group.

---

Hyperhomocysteinemia:
The prevalence of hyperhomocysteinemia is higher in patients with IBD.\textsuperscript{21} Hyperhomocysteinemia is a risk factor for venous thrombosis and other atherosclerotic cardiovascular diseases. Folate status is the strongest determinant of homocysteine levels along with Vitamin B\textsubscript{6} and Vitamin B\textsubscript{12}. Once folate and Vitamin B\textsubscript{12} deficiencies are addressed, serum pyridoxal phosphate levels should be evaluated to ascertain Vitamin B\textsubscript{6} deficiency. Homocysteine levels can be lowered by 7.6 - 51.7\% with folic acid, Vitamin B\textsubscript{12} and Vitamin B\textsubscript{6} supplementation in healthy subjects. The effect of Vitamin B supplementation has not been studied in IBD patients.\textsuperscript{22}

Wound healing:
Wound healing is important for IBD patients. Micronutrients - Vitamin A, Vitamin C, and zinc play an important role in wound healing. To support wound healing in patients on corticosteroids 10,000-15,000 IU/day of Vitamin A is recommended.\textsuperscript{23} For patients with Vitamin C deficiency, supplementation at 100-200 mg/d is recommended for acute wound healing. Also, 40 mg of elemental zinc (176 mg of zinc sulfate) for 10 days is recommended to enhance wound healing for patients with zinc deficiency.\textsuperscript{24}

Conclusion:
Micronutrient deficiencies are common in IBD and its' mechanism is multifactorial. There are no guidelines for micronutrient deficiencies assessment in patients with IBD. Micronutrient deficiencies are associated with complications. Anemia in IBD patients is precipitated due to iron deficiency caused by inadequate intake, impaired absorption and utilization, and chronic gastrointestinal bleeding; folate deficiency due to medication interaction, inadequate intake, and malabsorption; and Vitamin B12 deficiency due to ileal resection or ileocolonic resection. Altered bone metabolism due to calcium deficiency caused by inadequate intake, diarrhea, and malabsorption and Vitamin D deficiency due to insufficient intake, small bowel resection or steatorrhea. IBD patients have hyperhomocysteinemia due to Vitamin B12, Vitamin B6 and folic acid deficiencies. It is highly recommended to determine micronutrient status in IBD patients on certain medications, long term total parenteral nutrition, diarrhea, and fistula or non-healing wounds and provide them with adequate micronutrient supplementation for repletion and maintenance of their micronutrient and overall health status.

\textsuperscript{24} Dorner, Becky, Mary Ellen Posthauer, and David Thomas. The role of nutrition in pressure ulcer prevention and treatment: National Pressure Ulcer Advisory Panel white paper. \textit{Advances in skin & wound care} 22.5 (2009): 212-221.