

# Adverse Metabolic Sequelae Following Restorative Proctocolectomy with an Ileal Pouch

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## Keywords

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**Abstract:** Ileal pouch–anal anastomosis (IPAA) following total proctocolectomy has become the surgical treatment of choice for ulcerative colitis patients who have medically refractory disease or neoplasia. Unfortunately, various metabolic complications have been reported with this surgical procedure, including anemia, vitamin B<sub>12</sub> deficiency, bile salt and fat malabsorption, vitamin D deficiency, bone loss, and nephrolithiasis. Recognition and early diagnosis of these complications are important when managing IPAA patients.

Ileal pouch–anal anastomosis (IPAA) following total proctocolectomy is the surgical treatment of choice for patients with ulcerative colitis (UC) that is refractory to medical therapy or patients who have neoplasia.<sup>1,2</sup> A significant advantage of this procedure is that it avoids the need for a permanent ostomy by creating a continent fecal reservoir and maintaining bowel continuity. However, inflammatory and noninflammatory complications are common following IPAA. Common inflammatory complications include pouchitis, cuffitis, de novo Crohn's disease (CD), small bowel bacterial overgrowth, and inflammatory polyps. Complications associated with the surgical procedure include anastomotic leaks, sepsis, abscesses, sinus, fistulae, afferent and efferent limb syndromes, infertility, and sexual dysfunction. In addition, systemic and metabolic consequences are increasingly being recognized in patients with healthy or diseased pouches.<sup>1</sup> Table 1 summarizes common metabolic complications of IPAA, including anemia, iron deficiency, vitamin B<sub>12</sub> deficiency, bile salt malabsorption, vitamin D deficiency, bone loss, and nephrolithiasis.

## Anemia and Iron Deficiency

Anemia is common in patients with IPAA, with a reported prevalence of 21%.<sup>3</sup> Clinical and laboratory features of anemia were investigated in 389 patients with pouches for either UC or familial adenomatous polyposis (FAP).<sup>4</sup> In this population, normocytic anemia occurred in 74% of patients, microcytic anemia occurred in

**Table 1.** Summary of Metabolic Sequelae in Patients with Ileal Pouch–Anal Anastomosis

Study	Metabolic parameter	Prevalence	Risk factor(s) or proposed mechanism(s)
Tiainen J, Matikainen M <sup>3</sup>	Anemia	21%	<ul style="list-style-type: none"> <li>• Recurrent pouch bleeding</li> <li>• Chronic pouchitis</li> </ul>
Oikonomou IK, et al <sup>4</sup>	Anemia	17% (2% macrocytic anemia, 24% microcytic anemia, and 74% normocytic anemia)	<ul style="list-style-type: none"> <li>• Malignancy or desmoid tumors</li> <li>• J-pouch configuration</li> </ul>
Pastrana RJ, et al <sup>5</sup>	Iron deficiency	56%	<ul style="list-style-type: none"> <li>• Pouchitis</li> </ul>
Coull DB, et al <sup>11</sup>	Vitamin B <sub>12</sub> deficiency	25%	<ul style="list-style-type: none"> <li>• Possibilities include ileal resection, small bowel bacterial overgrowth, dietary restriction</li> </ul>
Fiorentini MT, et al <sup>23</sup>	Bile salt and fat malabsorption	50%	<ul style="list-style-type: none"> <li>• Bile salt malabsorption from ileal disruption</li> </ul>
Kuisma J, et al <sup>15</sup>	Vitamin D deficiency	10.6%	<ul style="list-style-type: none"> <li>• Possible villous atrophy, according to other studies</li> </ul>
Shen B, et al <sup>34</sup>	Bone loss	32%	<ul style="list-style-type: none"> <li>• Advanced age, low body mass index, absence of calcium supplementation</li> <li>• Possible vitamin D malabsorption</li> </ul>
Mukewar S, et al <sup>43</sup>	Nephrolithiasis	37.2%	<ul style="list-style-type: none"> <li>• Low urine volume, pH value, citrate level, magnesium level</li> <li>• Elevated urine oxalate level</li> </ul>

24% of patients, and macrocytic anemia occurred in 2% of patients.<sup>4</sup> Iron deficiency can be seen in up to 56% of patients with pouches (10/18).<sup>5</sup>

The etiology and pathogenesis of anemia in pouch patients is not clear. Reported risk factors for anemia in patients with IPAA for underlying UC or FAP include concurrent malignancy or desmoid tumors, presence of a J-pouch (as opposed to a S-pouch or Kock pouch), or concurrent pouchitis.<sup>3-5</sup> Finally, anemia of chronic disease, which occurs in patients with chronic mucosal inflammation, may contribute to the anemia seen in pouch patients.<sup>6</sup>

Iron deficiency is common in pouch patients, regardless of the presence of anemia.<sup>5</sup> Postulated mechanisms for iron deficiency include poor oral intake, decreased absorption, intermittent blood loss, and increased nutritional requirements.<sup>7</sup> Attempts have been made to establish a connection between blood loss and anemia. However, extensive work-up consisting of esophagogastroduodenoscopy, pouchoscopy, small bowel histology, capsule endoscopy, and celiac serology revealed the etiology of iron-deficiency anemia in only 29% of patients with ileal pouches.<sup>8</sup> This finding suggests that gastrointestinal losses, including chronic gastrointestinal bleeding, may

not be the main etiology of iron-deficiency anemia. De novo celiac disease following restorative proctocolectomy with IPAA has been described in case reports.<sup>9,10</sup> Although this type of anemia likely represents the underlying diagnosis in only a minority of pouch patients, screening for celiac disease is warranted.

### Vitamin B<sub>12</sub> Deficiency

The physiology of vitamin B<sub>12</sub> absorption is complex. Vitamin B<sub>12</sub> is liberated from dietary sources by acid and pepsin. R factor is released in saliva and binds to free vitamin B<sub>12</sub> to protect it from degradation. In the duodenum, R factor is cleaved by proteases, allowing vitamin B<sub>12</sub> to bind to intrinsic factor produced by the stomach. This complex then moves to the ileum, where it is absorbed by ileal intrinsic factor receptors. Luminal bacteria can bind vitamin B<sub>12</sub> and use it in their metabolic activities, which may interfere with normal transluminal uptake.

Theoretically, patients with pouches have a high risk of vitamin B<sub>12</sub> deficiency, as the ileal pouch created from the distal ileum inherently has fecal stasis, adaptive mucosal changes (colonic metaplasia), and small bowel bacterial overgrowth with subsequent microbial binding and

utilization of luminal vitamin B<sub>12</sub>; these patients also have poor oral intake and dietary restrictions.<sup>7</sup> In one study, 25% of IPAA patients had vitamin B<sub>12</sub> deficiency without evidence of malabsorption, as indicated by normal Schilling tests.<sup>11</sup> Vitamin B<sub>12</sub> deficiency can be corrected with oral supplementation, implicating poor intake as a major mechanism of the condition.<sup>11</sup> However, in another study that examined patients with IPAA, 56% of patients with vitamin B<sub>12</sub> deficiency also had bile salt deconjugation, as determined by <sup>14</sup>C-glycocholic acid breath testing and fecal bile acid secretion.<sup>12</sup> These findings suggest that bacterial overgrowth is the potential causative mechanism.<sup>12</sup> Small bowel bacterial overgrowth is thought to occur due to anatomic and motility changes, particularly loss of the ileocecal valve from the creation of the pouch reservoir.<sup>7</sup> Although small bowel bacterial overgrowth diagnosed via breath testing was not reported to be associated with chronic pouchitis, the suitability of the breath test currently used in patients with intact colons is controversial in the setting of IPAA.<sup>13</sup>

It is unclear whether pouch surgery itself has a positive or negative impact on vitamin B<sub>12</sub> metabolism. In a cross-sectional study, vitamin B<sub>12</sub> deficiency occurred in 13% of UC patients preoperatively and in only 3% of IPAA patients.<sup>14</sup> Although a possible explanation for this finding could be the improved general nutritional status of the patients, this improvement may be secondary to backwash ileitis, which resolves postoperatively. The latter explanation implicates villous changes as having a role in metabolic abnormalities. Villous atrophy is indeed known to occur in patients with IPAA and may be the result of physiologic adaptation (colonic metaplasia of the ileal mucosa) or chronic pouchitis.<sup>15,16</sup> Atrophy may result in abnormal vitamin B<sub>12</sub> absorption and deficiency in this population.

### Bile Salt Malabsorption

Bile salts are produced in the liver and are excreted in bile, where they play a role in fat and fat-soluble vitamin absorption. Bile salts are chemically modified to enhance solubility and prevent premature absorption. Thus, they traverse the upper small bowel and are preferentially absorbed in the terminal ileum. Bile salt malabsorption occurs when reabsorption is impaired due to ileal disease or resection. Diarrhea may result from fat malabsorption or bile acid actions in the colon of patients without a pouch.

Aqueous-phase fecal bile acids have been detected in patients after IPAA.<sup>17</sup> An alteration in the luminal bile pool may be involved in pouch inflammation.<sup>18</sup> Indirect evidence for this hypothesis was derived from the investigation of patients with primary sclerosing cholangitis (PSC) and known biliary abnormalities. Patients with ileal pouches and PSC have a greater degree of endoscopic

and histologic inflammation in the pouch body and/or distal ileum (ie, PSC-associated pouchitis/enteritis) than pouch patients without PSC.<sup>19</sup>

Inflammatory changes in IPAA patients are postulated to manifest through changes in bile acid conjugation and dehydroxylation rather than changes in bile acid composition.<sup>19,20</sup> Chronic pouchitis and villous atrophy may lead to decreased bile salt absorption. One study found inflammation and villous atrophy in 6 of 14 patients, suggesting that these findings may lead to a decreased absorptive capacity for fat and fat-soluble vitamins.<sup>21,22</sup> The diseased condition of the ileum may impair bile salt and lipid absorption, as evidenced by a study demonstrating abnormal <sup>75</sup>Se homotaurocholate uptake in 7 of 8 patients and by an analysis of abnormal <sup>14</sup>C triolein breath test results in 3 of 8 pouch patients.<sup>23</sup> There have also been reports of fat malabsorption, which appears to be associated with bile acid absorption and was found to be reduced in IPAA patients compared to patients who underwent ileostomy.<sup>24</sup> In patients with clinical pouch dysfunction, presumed fecal stasis with bacterial overload could lead to bile salt deconjugation and decreased absorption, as measured by <sup>75</sup>Se homotaurocholate, compared to patients with healthy pouches.<sup>24</sup> Clinically, decreased serum levels of total low-density lipoprotein cholesterol and triglycerides were reported in patients with ileoanal anastomosis.<sup>25</sup>

### Vitamin D Deficiency

Vitamin D is a fat-soluble vitamin that is primarily absorbed in the duodenum and jejunum. This vitamin is hydroxylated in the liver to form 25-OH vitamin D and hydroxylated in the kidney to form 1, 25-OH vitamin D. The association between vitamin D metabolism and inflammatory bowel disease (IBD) is reciprocal: Chronic gut inflammation may interfere with vitamin D metabolism, while deficiency in vitamin D (an anti-inflammatory substance) may predispose patients to development of inflammation. The vitamin D receptor (VDR) is involved in maintaining mucosal integrity, and its abnormality has been implicated in the pathogenesis of IBD.<sup>26,27</sup> In one study, VDR-positive mice were less likely to develop inflammation secondary to colonic insult with dextran sulfate sodium, while VDR-knockout mice were prone to developing severe colitis. Histologic inflammation with ulceration was noted in VDR-knockout mice.<sup>26</sup> In other murine models, inflammation of the gastrointestinal tract developed in VDR-knockout animals.<sup>27</sup>

Clinically, vitamin D deficiency is common in patients with IBD, with the lowest levels of vitamin D occurring in patients with severe disease.<sup>28-30</sup> This deficiency independently lowers quality of life (QOL) in IBD patients.<sup>30</sup>

Vitamin D deficiency has been reported in 10.6% of patients with pouches (n=107).<sup>15</sup> However, in our recent cohort study of 157 patients, the prevalence of low serum vitamin D levels was 69%.<sup>31</sup> In this analysis, anemia was associated with low vitamin D levels, but the geographic location of the patients, season of measurement (ie, spring, summer, fall, or winter), and medication use were not significant.<sup>31</sup> Pouch inflammation was not associated with low vitamin D levels, suggesting that the pouch exerts independent metabolic consequences.<sup>31</sup> Similarly, a recent letter to the editor reported low vitamin D levels in 80% of patients with IPAA.<sup>32</sup> However, a longitudinal study evaluating serum vitamin D levels both preoperatively and postoperatively is needed to examine this hypothesis.

## Bone Loss

Bone loss is common in patients with IPAA. In a study of 53 patients from St. Mark's Hospital in London, United Kingdom, the prevalences of osteopenia and osteoporosis were 43% and 13%, respectively.<sup>33</sup> In a separate study of 327 patients from The Cleveland Clinic, 32% (n=105) had low bone mineral density (BMD) values.<sup>34</sup> Factors associated with low BMD values included advanced age, low body mass index, and absence of calcium supplementation. Factors related to the condition of the pouch itself—such as the presence of chronic pouchitis or CD of the pouch—were not significantly associated with bone loss in this study.<sup>34</sup>

It is not clear whether inflammatory complications following construction of an ileal pouch have a beneficial or detrimental impact on bone metabolism. It is well known that patients with UC are at risk for bone loss.<sup>35</sup> However, there have been conflicting reports regarding the impact of colectomy on BMD values. When a group of 267 UC patients with IPAA was compared to a group of 119 UC patients without IPAA in a cross-sectional study, 83 patients (31.1%) and 18 patients (15.1%), respectively, had low BMD values. Interestingly, 64 patients with IPAA (24.0%) were using steroids postoperatively compared to 93 patients in the non-IPAA group (78.2%). In this analysis, the presence of IPAA was an independent risk factor for low BMD values (odds ratio, 6.02; 95% confidence interval, 2.46–14.70).<sup>36</sup> In contrast, another study showed that BMD values increased over time following IPAA.<sup>37</sup> There is a need for longitudinal studies with longer follow-up periods that examine BMD values before and after IPAA, as well as before and after development of inflammatory pouch conditions.

The etiology and pathogenesis of bone loss in IPAA patients remain unclear. Reported risk factors include advanced age, low body mass index, and lack of calcium supplementation.<sup>16,34,36</sup> Moreover, 37% of IPAA patients

with villous atrophy had osteopenia, compared to 0% with normal villous structure.<sup>16</sup> The lowest BMD scores were found in patients who had inflammation in the afferent limb of their IPAA.<sup>16</sup> Supplementation of calcium and vitamin D were shown to increase BMD scores in patients with IBD.<sup>38</sup> Although increased inflammatory activity of the pouch has been associated with lower BMD scores, a clear connection between pouchitis and vitamin D remains to be determined.

## Nephrolithiasis

Although overall QOL often improves following IPAA, nephrolithiasis can impact this parameter.<sup>39,40</sup> The prevalence of nephrolithiasis has been estimated to be 5% in the general population and 7% in patients with IBD.<sup>41,42</sup> Possible explanations include elevated levels of urine oxalate and/or low urine volumes, pH values, or levels of citrate or magnesium.<sup>43</sup> A recent abstract that reviewed patients with IPAA determined that the prevalence of nephrolithiasis was 37.2% in this population. The majority of these patients had symptomatic stones. IPAA patients with extraintestinal manifestations, no use of antibiotics, and lower serum bicarbonate levels had a higher risk of developing kidney stones.<sup>43</sup>

## Summary

Although patients' QOL often improves following IPAA, long-term metabolic complications include anemia, iron deficiency, vitamin B<sub>12</sub> deficiency, bile salt malabsorption, vitamin D deficiency, bone loss, and nephrolithiasis. Clinicians should be aware of these complications and facilitate appropriate screening and counseling.

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