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VITAMIN B₁₂ (COBALAMIN) DEFICIENCY IN GASTROENTEROLOGICAL DISEASES - REVIEW

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ABSTRACT:

Introduction: Vitamin B₁₂ is a water-soluble vitamin found primarily in animal-derived products such as red meat, dairy, and eggs. An essential substance for its absorption is the intrinsic factor, produced by the parietal cells of the stomach. After absorption in the distal ileum, cobalamin acts as a coenzyme in DNA synthesis and the metabolism of fatty acids and homocysteine. In addition to its well-known influence on the nervous system, it has been associated with gastrointestinal diseases according to numerous authors.

Objective: The objective of this study is to gather and analyze literature regarding the associations between vitamin B₁₂ deficiency and gastrointestinal diseases, including

gastroesophageal reflux disease (GERD), gastritis, inflammatory bowel disease (IBD), small intestinal bacterial overgrowth (SIBO), and hepatitis C (HCV).

Materials and Methods: A literature review was conducted using the PubMed database with the following search terms: vitamin B₁₂, cobalamin, deficiency, gastrointestinal diseases, GERD, IBD, SIBO, HCV.

Current Knowledge: Vitamin B₁₂ deficiency can be caused by autoimmune factors, dietary insufficiencies, toxin exposure, and malabsorption disorders related to gastrointestinal diseases. Gastrointestinal conditions such as GERD and IBD can both lead to and be exacerbated by cobalamin deficiency. Furthermore, vitamin B₁₂ deficiency may be worsened by prolonged use of proton pump inhibitors (PPIs) and *Helicobacter pylori* infection.

Conclusions: An adequate amount of vitamin B₁₂ is crucial for gastrointestinal health. Deficiency can significantly impact the course and symptoms of many gastrointestinal diseases. Therefore, monitoring and supplementation of vitamin B₁₂ should be an integral part of managing patients with gastrointestinal conditions.

Keywords: Vitamin B₁₂; cobalamin deficiency, gastrointestinal diseases, GERD, IBD, SIBO

INTRODUCTION AND PURPOSE OF THE PAPER

Vitamin B₁₂, scientifically known as cobalamin, is a water-soluble substance found mainly in animal products such as red meat, dairy and eggs.¹

A key factor necessary for the absorption of cobalamin is Castle's factor (intrinsic factor, IF), a glycoprotein produced by the cells lining the stomach. Together, they form a complex that is absorbed in the distal part of the ileum.² Once absorbed, cobalamin acts as a coenzyme essential for DNA and fatty acid synthesis, and plays an important role in the conversion of

homocysteine to methionine, essential for the synthesis of neurotransmitters and phospholipids, a component of myelin.³ Excess vitamin B₁₂ is stored in the liver; however, in situations where it is not absorbed for long periods of time, liver stores become depleted, leading to deficiency.¹

Standards for cobalamin levels are not clearly defined, but it is generally accepted that concentrations below 200 pg/mL constitute deficiency, values of 200-299 pg/mL are the limits, and values above 300 pg/mL are the norm.⁴ In population studies, the prevalence of cobalamin deficiency ranges from 29-35%.⁵

According to the literature, autoimmune factors (e.g., Addison-Biermer anemia,⁶ in which antibodies to IF are present), dietary factors (low vitamin B₁₂ supply, e.g., in a restrictive vegan diet), exposure to toxins (e.g., nitric oxide)¹ and malabsorption due to gastroenterological diseases may contribute to cobalamin deficiency.¹ Although cobalamin is well known for its effects on the hematopoietic (its deficiency can lead to megaloblastic anemia) and nervous systems, according to many authors, it also has links to gastroenterological diseases. On the one hand, diseases of the gastrointestinal tract can cause its deficiency, on the other hand, cobalamin deficiency itself can be the cause of their onset or exacerbate their symptoms, which is the analysis of this publication.

The aim of this study is to collect and publish the current state of knowledge on the association of vitamin B₁₂ deficiency with the occurrence of gastroenterological diseases such as gastroesophageal reflux disease (GERD), gastritis, inflammatory bowel disease (IBD), small intestine bacterial overgrowth syndrome (SIBO) and hepatitis C (hepatitis C).

CURRENT STATE OF KNOWLEDGE

Vitamin B₁₂ deficiency in gastroesophageal reflux disease (GERD)

Vitamin B₁₂ deficiency may be associated with gastroesophageal reflux disease. The main therapy for GERD is proton pump inhibitors (PPIs), which work by reducing gastric hydrochloric acid production through inhibition of the enzyme H⁺/K⁺ ATP-ase in the lining cells.⁷

Chronic blockade of HCl secretion can lead to impaired B₁₂ absorption through two mechanisms.⁸ First, PPIs can reduce the absorption of cobalamin bound to Castle's factor. In a

study by Marcuar et al,⁹ 10 healthy subjects took omeprazole for 2 weeks, which reduced the percentage of absorbed IF-bound cobalamin from 32% to 0.9% in patients taking 20 mg daily and from 34% to 0.4% in patients receiving 40 mg. It has been suggested that the degree of impairment may be greater in elderly patients.¹⁰ Second, lowering pH may induce proliferation of bacterial flora in the duodenum, which may contribute to increased bacterial consumption of cobalamin.⁸ In a 2022 cohort study conducted by Mumtaz et al,¹¹ among 1225 participants, more than half of the subjects (51%) had low vitamin B₁₂ levels. They observed that cobalamin levels were significantly lower in patients taking omeprazole than in those taking pantoprazole. Vitamin B₁₂ deficiency is 50% more likely in patients taking PPIs. There was a significant difference between early and final vitamin B₁₂ levels indicated by the t-test. Similar findings are published for H₂ receptor antagonists.¹²

According to the authors, not only can GERD and taking PPIs in conjunction with it affect cobalamin levels, but cobalamin itself can alleviate its symptoms by reducing the need to take PPIs and NSAIDs, which exacerbate reflux. A 2006 study by R. Pereira¹³ compared 176 GERD patients supplementing vitamin B₁₂ and folic acid in combination with melatonin, L-tryptophan, methionine and betaine, with 175 GERD patients taking only 20 mg of omeprazole daily. After 40 days, 100% of patients basing their therapy on the above supplements confirmed complete withdrawal of GERD symptoms, compared to 65.7% taking omeprazole. This effect is partly explained by the fact that vitamin B₁₂ has the property of relieving acute pain, and, moreover, enhances the analgesic effect of analgesics such as non-steroidal anti-inflammatory drugs and metamizole.¹⁴ Thus, patients suffering from, for example, neuropathic pain, muscular pain, unspecified ailments, and back pain can reduce the doses of analgesics taken, and thus reduce their harmful effects on GERD [14]. The analgesic effect of vitamin B₁₂ is most often associated with an increased rate of nerve impulse conduction, as well as stimulation of neuronal regeneration by inducing axonal growth and differentiation of Schwann cells.^{15,16} An additional aspect is that cobalamin inhibits nociceptive transduction at the level of the spinal cord,¹⁷ and also stimulates endogenous opioid secretion, activates opioid receptors and GABA metabolism, leading to hyperpolarization of the postsynaptic membrane of neurons in the posterior horns, resulting in reduced pain transmission.¹⁸

Vitamin B₁₂ deficiency in gastritis

Gastritis is strongly associated with vitamin B₁₂ deficiency. In a study by Dholakia et al,¹⁹ the results of gastroscopy and histopathological sections of the stomach were analyzed in

30 patients with newly diagnosed cobalamin deficiency and 16 controls. The endoscopy results showed significant differences in the incidence of gastritis and mucosal atrophy between the groups. Patients without vitamin B₁₂ deficiency were more likely to have superficial gastritis (94% versus 62% in B₁₂-deficient subjects) and less likely to have atrophic gastritis (0% and 28%, respectively). The incidence of intestinal metaplasia was similar in both groups, as were rates of *Helicobacter pylori* infection (40% vs. 31%).¹⁹

Although the mechanism of reduced vitamin B₁₂ absorption is not fully elucidated, studies confirm that absorption of protein-bound cobalamin is reduced in people with atrophic gastritis or hypochlorhydria. This condition can be improved by administering free vitamin B₁₂. In addition, the prevalence of vitamin B₁₂ deficiency is higher with *H. pylori* infection, and eradication of this bacterium can improve vitamin B₁₂ levels.^{20,21}

A separate issue is autoimmune metaplastic gastritis, which is a chronic inflammatory disease that leads to the destruction of cells lining the gastric body and fundus, which results in vitamin B₁₂ deficiency and can lead to pernicious anemia.^{22,23} In addition, therapy for gastritis, particularly with proton pump inhibitors (PPIs), may contribute to cobalamin deficiency through mechanisms previously described when analyzing GERD.⁸⁻¹¹

Vitamin B12 deficiency in inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis (UC), often leads to impaired nutrient absorption, which can affect the absorption of folic acid and vitamin B₁₂. Vitamin B₁₂ is mainly absorbed in the terminal ileum, and since IBD can involve the small intestine, it has been suggested that cobalamin concentrations may be lower in IBD patients than in healthy individuals.²⁴

A number of studies indicate that serum folate and vitamin B₁₂ concentrations influence the development of IBD.²⁵⁻²⁷ Folic acid is involved in DNA methylation, which may cause epigenetic changes affecting the interaction between the gut microbiota and the body's immune responses,²⁵ having a potential role in the pathogenesis of IBD.^{26,27} Vitamin B₁₂ acts as a coenzyme in various biochemical reactions, including DNA synthesis and folic acid metabolism.²⁸

Although vitamin B₁₂ amount may be lower in patients with Crohn's disease,²⁹⁻³² most studies indicate that they are within the normal range (207-618 pmol/L).^{29,30,33-35} Lambert et

al.³⁶ obtained a mean cobalamin amount of 140 pmol/L in their study, which was significantly below normal; however, the control group had a slightly higher mean level (152 pmol/L). A different result was obtained by Akbulut et al, who showed a mean cobalamin amount among 103 Crohn's disease patients of $161.9 \pm 63.2(73-496)$ pg/m compared to $321.7 \pm 126.3(85-680)$ pg/mL in 114 patients in the control group ($p < 0.001$).³⁷

The prevalence of cobalamin deficiency in Crohn's disease ranges from 5.6% to 38%.^{29,30,35,36,38-41} It is worth noting, however, that the authors refer to different standards, so the definition of cobalamin deficiency varies.⁴² However, additional aspects that are risk factors for vitamin B₁₂ deficiency may contribute to the Crohn's disease picture.

According to Battat et al,⁴² the most important risk factor for cobalamin deficiency in Crohn's disease is resection of the ileum. Depending on the length of the resected intestinal segment, the risk of deficiency varies, which is related to the number of receptors for the cobalamin-Castle factor complex remaining in the intestine.⁴² A resection of more than 30 cm results in cobalamin deficiency due to impaired cobalamin absorption, which reflects an abnormal Schilling test,^{32,39,43-45} and also predisposes to megaloblastic anemia.^{46,47} Resection of a segment smaller than 20 cm usually has no significant effect on cobalamin amount.^{48,49} For a range of 20-30 cm, the results are inconclusive.^{39,47} The location and extent of the disease also affect vitamin B₁₂ absorption; when lesions are within 30-60 cm of the length of the intestine, vitamin B₁₂ absorption is impaired; if inflammation occupies less than 30 cm, the Schilling test result is normal.^{32,50-52}

In ulcerative colitis, cobalamin quantity is comparable to controls.^{29,30} The only predisposing factor for vitamin B₁₂ deficiency is reconstructive proctocolectomy surgery, leading to fecal stasis, adaptive mucosal changes and small bowel bacterial proliferative syndrome.⁵³ According to Coull et al,⁵⁴ cobalamin deficiency occurs in 25% of patients with reconstructive proctocolectomy, but in 94% of cases cobalamin absorption is not impaired (normal Schilling test).⁵⁵

Pan et al. performed a meta-analysis of studies from 1970 to 2016 available on PubMed, Medline, Web of Science, and Google Scholar publishing data on mean differences and standard deviations of vitamin B₁₂ and folic acid values among IBD patients and healthy controls. They concluded that while there are statistically significant differences in folic acid levels, cobalamin deficiency among IBD patients is much less common.²⁴ Moreover, many of

the serum cobalamin deficiencies diagnosed in the study were not confirmed by biomarkers reflecting intracellular amount of the vitamin (i.e., methylmalonic acid levels, homocysteine).⁵⁶ However, this does not change the fact that for symptomatic patients with risk factors for cobalamin deficiency, supplementation is indicated.⁵⁷

Vitamin B₁₂ deficiency in small intestinal bacterial proliferative syndrome (SIBO).

Small intestinal bacterial proliferative syndrome (SIBO) is characterized by an increase in the number of bacteria in the small intestine from 10³ CFU/ml to 10⁵-10⁶ CFU/ml, leading to chronic diarrhea and malabsorption.⁵⁸ Vitamin B₁₂ deficiency in patients with SIBO is common and is the result of increased consumption of cobalamin by anaerobic bacteria in the intestinal lumen, as well as by diarrhea itself, which significantly reduces the absorption of the vitamin into the bloodstream.⁵⁹ A study by Chitti and Cummins⁶⁰ of 62 patients with vitamin B₁₂ deficiency showed a clear diagnosis of SIBO in 26 (42%) of them, and 9 (15%) were suspected of having the syndrome. Wexler et al⁵⁹ demonstrated that bacteria of the genus *Bacteroides* cultured in vitro displace Castle's factor from combinations with cobalamin. A study by Booth and Heat⁶¹ showed that after treatment with metronidazole, tetracycline or linezolid, patients' vitamin B₁₂ absorption returned to normal. In addition, a study by Madigan et al⁶² deduced hydrogen-producing bacteria contribute more to vitamin B₁₂ deficiency than methane-producing bacteria, which are capable of synthesizing cobalamin on their own.

Vitamin B₁₂ deficiency in hepatitis C (Hepatitis C)

Vitamin B₁₂, which is stored in large amounts in the liver, plays a role in regulating the HCV replication cycle responsible for hepatitis C.⁶³ Studies by Lotta et al. have shown that vitamin B₁₂ inhibits the translation initiation site (IRES) of the HCV gene in a dose-dependent manner.⁶³ On the other hand, high serum vitamin B₁₂ quantity is statistically correlated with high HCV viral load,⁶³ which may be due to the fact that HCV uses cobalamin to maximize replication. It is noteworthy that HCV-induced liver diseases, such as hepatitis, cirrhosis, hepatocellular carcinoma and metastasis, can lead to relative vitamin B₁₂ deficiency due to impaired hepatic storage, increased release during hepatic cytolysis and/or reduced clearance by the damaged liver.⁶⁴ Patients with liver dysfunction may have normal or high serum amount of vitamin B₁₂ despite low stores of the vitamin in the body.⁶⁴ Given the role of cobalamin in regulating the HCV replication cycle, it can be inferred that, vitamin B₁₂ supplementation may improve virologic response rates to antiviral therapy in patients with HCV, as confirmed by a

study by Rocco et al. showing that vitamin B₁₂ supplementation significantly improves sustained virologic response in patients undergoing direct-acting antiviral (DAA) drug therapy for HCV.⁶⁵

SUMMARY

A review of the available literature has shown a close association of vitamin B₁₂ deficiency with the occurrence of gastroesophageal reflux disease (GERD), gastritis, small intestinal bacterial overgrowth syndrome (SIBO) and hepatitis C (Hepatitis C). In Crohn's disease and ulcerative colitis, cobalamin amount depends on the degree of intestinal resection. In patients with gastroenterological diseases, diagnosis and correction of possible vitamin B₁₂ deficiencies is therefore crucial. Further research and clinical awareness are needed to address this often overlooked factor in gastroenterology practice.

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Bibliography:

1. Ankar A, Kumar A. Vitamin B12 Deficiency. In: StatPearls. Treasure Island (FL): StatPearls Publishing; October 22, 2022.
2. Guéant, Jean-Louis, et al. "Vitamin B12 Absorption and Malabsorption." *Vitamins and Hormones*, vol. 119, 2022, pp. 241–274, pubmed.ncbi.nlm.nih.gov/35337622/, <https://doi.org/10.1016/bs.vh.2022.01.016>.
3. González HF, Visentin S. Micronutrients and neurodevelopment: An update. *Micronutrientes y neurodesarrollo: actualización. Arch Argent Pediatr.* 2016;114(6):570-575. doi:10.5546/aap.2016.eng.570
4. Vargas-Uricoechea H, Nogueira JP, Pinzón-Fernández MV, Agredo-Delgado V, Vargas-Sierra HD. Population Status of Vitamin B12 Values in the General Population and in Individuals with Type 2 Diabetes, in Southwestern Colombia. *Nutrients.* 2023;15(10):2357. doi:<https://doi.org/10.3390/nu15102357>
5. McLean E, de Benoist B, Allen LH. Review of the magnitude of folate and vitamin B12 deficiencies worldwide. *Food Nutr Bull.* 2008;29(2 Suppl):S38-S51. doi:10.1177/15648265080292S107
6. Vaqar S, Shackelford KB. Pernicious Anemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing; May 8, 2023.
7. Ahmed A, Clarke JO. Proton Pump Inhibitors (PPI). In: StatPearls. Treasure Island (FL): StatPearls Publishing; May 1, 2023.
8. RICHTER JE. Q: Should patients receiving long-term gastric acid inhibition therapy be evaluated for vitamin B12 deficiency? *Cleveland Clinic Journal of Medicine.* 2000;67(11):785-787. doi:<https://doi.org/10.3949/ccjm.67.11.785>
9. Marcuard SP. Omeprazole Therapy Causes Malabsorption of Cyanocobalamin (Vitamin B₁₂). *Annals of Internal Medicine.* 1994;120(3):211. doi:<https://doi.org/10.7326/0003-4819-120-3-199402010-00006>
10. Saltzman JR, Kemp JA, Golner BB, Pedrosa MC, Dallal GE, Russell RM. Effect of hypochlorhydria due to omeprazole treatment or atrophic gastritis on protein-bound vitamin

- B12 absorption. *Journal of the American College of Nutrition*. 1994;13(6):584-591. doi:<https://doi.org/10.1080/07315724.1994.10718452>
11. Mumtaz H, Ghafoor B, Saghir H, et al. Association of Vitamin B12 deficiency with long-term PPIs use: A cohort study. *Annals of Medicine and Surgery*. 2022;82:104762. doi:<https://doi.org/10.1016/j.amsu.2022.104762>
 12. News briefs: Heartburn medicine users: Watch vitamin B12 levels. Harvard Health. Published March 1, 2014. <https://www.health.harvard.edu/digestive-health/news-briefs-heartburn-medicine-users-watch-vitamin-b12-levels>
 13. Pereira R de S. Regression of gastroesophageal reflux disease symptoms using dietary supplementation with melatonin, vitamins and aminoacids: comparison with omeprazole. *Journal of Pineal Research*. 2006;41(3):195-200. doi:<https://doi.org/10.1111/j.1600-079x.2006.00359.x>
 14. Jurna I. [Analgesic and analgesia-potentiating action of B vitamins]. *Schmerz (Berlin, Germany)*. 1998;12(2):136-141. doi:<https://doi.org/10.1007/s004829800054>
 15. Suzuki K, Tanaka H, Ebara M, et al. Electrospun nanofiber sheets incorporating methylcobalamin promote nerve regeneration and functional recovery in a rat sciatic nerve crush injury model. *Acta Biomater*. 2017;53:250-259. doi:10.1016/j.actbio.2017.02.004
 16. Okada K, Tanaka H, Temporin K, et al. Methylcobalamin increases Erk1/2 and Akt activities through the methylation cycle and promotes nerve regeneration in a rat sciatic nerve injury model. *Exp Neurol*. 2010;222(2):191-203. doi:10.1016/j.expneurol.2009.12.017
 17. Fu QG, Carstens E, Stelzer B, Markus Bernhard Zimmermann. B vitamins suppress spinal dorsal horn nociceptive neurons in the cat. *Neuroscience Letters*. 1988;95(1-3):192-197. doi:[https://doi.org/10.1016/0304-3940\(88\)90655-6](https://doi.org/10.1016/0304-3940(88)90655-6)
 18. Rahman M, Ferdoush K, Jahan K, et al. ANALGESIC EFFECTS OF VITAMIN B12: A RECENT UPDATE *Journal of Global Biosciences*. *Journal of Global Biosciences*. 2020;9(4):2020-7160. <https://www.mutagens.co.in/jgb/vol.09/04/090416.pdf>
 19. Dholakia K. Vitamin B12 deficiency and gastric histopathology in older patients. *World Journal of Gastroenterology*. 2005;11(45):7078. doi:<https://doi.org/10.3748/wjg.v11.i45.7078>

20. de Groot CPGM, van Staveren WA. OLDER PEOPLE | Nutrition-Related Problems. Encyclopedia of Human Nutrition. Published online 2005:444-449. doi:<https://doi.org/10.1016/b0-12-226694-3/00242-8>
21. Cabrera de León A, Almeida González D, Almeida AA, et al. Factors associated with parietal cell autoantibodies in the general population. *Immunol Lett.* 2012;147(1-2):63-66. doi:10.1016/j.imlet.2012.06.004
22. Kulnigg-Dabsch S. Autoimmune gastritis. *Wiener Medizinische Wochenschrift.* 2016;166(13-14):424-430. doi:<https://doi.org/10.1007/s10354-016-0515-5>
23. Hershko C, Ronson A, Souroujon M, Maschler I, Heyd J, Patz J. Variable hematologic presentation of autoimmune gastritis: age-related progression from iron deficiency to cobalamin depletion. *Blood.* 2006;107(4):1673-1679. doi:<https://doi.org/10.1182/blood-2005-09-3534>
24. Pan Y, Liu Y, Guo H, et al. Associations between Folate and Vitamin B12 Levels and Inflammatory Bowel Disease: A Meta-Analysis. *Nutrients.* 2017;9(4):382. doi:<https://doi.org/10.3390/nu9040382>
25. Leddin D, Tamim H, Levy AR. Is folate involved in the pathogenesis of inflammatory bowel disease? *Medical Hypotheses.* 2013;81(5):940-941. doi:<https://doi.org/10.1016/j.mehy.2013.08.025>
26. Shanahan F. The microbiota in inflammatory bowel disease: friend, bystander, and sometime-villain. *Nutrition Reviews.* 2012;70:S31-S37. doi:<https://doi.org/10.1111/j.1753-4887.2012.00502.x>
27. Kellermayer R. Epigenetics and the Developmental Origins of Inflammatory Bowel Diseases. *Canadian Journal of Gastroenterology.* 2012;26(12):909-915. doi:<https://doi.org/10.1155/2012/526408>
28. Bermejo F, Algaba A, Guerra I, et al. Should we monitor vitamin B12 and folate levels in Crohn's disease patients? *Scandinavian Journal of Gastroenterology.* 2013;48(11):1272-1277. doi:<https://doi.org/10.3109/00365521.2013.836752>

29. Headstrom PD, Rulyak SJ, Lee SD. Prevalence of and risk factors for vitamin B(12) deficiency in patients with Crohn's disease. *Inflamm Bowel Dis.* 2008;14(2):217-223. doi:10.1002/ibd.20282
30. Yakut M, Ustün Y, Kabaçam G, Soykan I. Serum vitamin B12 and folate status in patients with inflammatory bowel diseases. *Eur J Intern Med.* 2010;21(4):320-323. doi:10.1016/j.ejim.2010.05.007
31. Erzin Y, Uzun H, Celik AF, Aydin S, Dirican A, Uzunismail H. Hyperhomocysteinemia in inflammatory bowel disease patients without past intestinal resections: correlations with cobalamin, pyridoxine, folate concentrations, acute phase reactants, disease activity, and prior thromboembolic complications. *J Clin Gastroenterol.* 2008;42(5):481-486. doi:10.1097/MCG.0b013e318046eab0
32. Filipsson S, Hultén L, Lindstedt G. Malabsorption of fat and vitamin B12 before and after intestinal resection for Crohn's disease. *Scand J Gastroenterol.* 1978;13(5):529-536. doi:10.3109/00365527809181760
33. Vagianos K, Bernstein CN. Homocysteinemia and B vitamin status among adult patients with inflammatory bowel disease: a one-year prospective follow-up study. *Inflamm Bowel Dis.* 2012;18(4):718-724. doi:10.1002/ibd.21785
34. Kuroki F, Iida M, Tominaga M, et al. Multiple vitamin status in Crohn's disease. Correlation with disease activity. *Dig Dis Sci.* 1993;38(9):1614-1618. doi:10.1007/BF01303168
35. Jayaprakash A, Creed T, Stewart L, et al. Should we monitor vitamin B12 levels in patients who have had end-ileostomy for inflammatory bowel disease?. *Int J Colorectal Dis.* 2004;19(4):316-318. doi:10.1007/s00384-003-0556-2
36. Lambert D, Benhayoun S, Adjalla C, et al. Crohn's disease and vitamin B12 metabolism. *Dig Dis Sci.* 1996;41(7):1417-1422. doi:10.1007/BF02088567
37. Akbulut S. An assessment of serum vitamin B12 and folate in patients with Crohn's disease. *Medicine.* 2022;101(50):e31892. doi:https://doi.org/10.1097/md.00000000000031892
38. Oostenbrug LE, van Dullemen HM, te Meerman GJ, Jansen PL, Kleibeuker JH. Clinical outcome of Crohn's disease according to the Vienna classification: disease location is a useful

- predictor of disease course. *Eur J Gastroenterol Hepatol.* 2006;18(3):255-261. doi:10.1097/00042737-200603000-00005
39. Dyer NH, Dawson AM. Malnutrition and malabsorption in Crohn's disease with reference to the effect of surgery. *Br J Surg.* 1973;60(2):134-140. doi:10.1002/bjs.1800600211
 40. Roblin X, Phelip JM, Genevois M, Ducros V, Bonaz B. Hyperhomocysteinaemia is associated with osteoporosis in patients with Crohn's disease. *Aliment Pharmacol Ther.* 2007;25(7):797-804. doi:10.1111/j.1365-2036.2007.03260.x
 41. Vasilopoulos S, Saiean K, Emmons J, et al. Terminal ileum resection is associated with higher plasma homocysteine levels in Crohn's disease. *J Clin Gastroenterol.* 2001;33(2):132-136. doi:10.1097/00004836-200108000-00008
 42. Battat R, Kopylov U, Byer J, et al. Vitamin B12 deficiency in inflammatory bowel disease. *European Journal of Gastroenterology & Hepatology.* 2017;29(12):1361-1367. doi:https://doi.org/10.1097/meg.0000000000000970
 43. Duerksen DR, Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with limited ileal resection. *Nutrition.* 2006;22(11-12):1210-1213. doi:10.1016/j.nut.2006.08.017
 44. Fromm H, Thomas PJ, Hofmann AF. Sensitivity and specificity in tests of distal ileal function: prospective comparison of bile acid and vitamin B 12 absorption in ileal resection patients. *Gastroenterology.* 1973;64(6):1077-1090.
 45. Behrend C, Jeppesen PB, Mortensen PB. Vitamin B12 absorption after ileorectal anastomosis for Crohn's disease: effect of ileal resection and time span after surgery. *Eur J Gastroenterol Hepatol.* 1995;7(5):397-400.
 46. BOOTH CC, MOLLIN DL. The site of absorption of vitamin B12 in man. *Lancet.* 1959;1(7062):18-21. doi:10.1016/s0140-6736(59)90979-1
 47. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis.* 2007;13(12):1545-1553. doi:10.1002/ibd.20285
 48. Roblin X, Phelip JM, Genevois M, Ducros V, Bonaz B. Hyperhomocysteinaemia is associated with osteoporosis in patients with Crohn's disease. *Aliment Pharmacol Ther.* 2007;25(7):797-804. doi:10.1111/j.1365-2036.2007.03260.x

49. Chowers Y, Sela BA, Holland R, Fidler H, Simoni FB, Bar-Meir S. Increased levels of homocysteine in patients with Crohn's disease are related to folate levels. *Am J Gastroenterol*. 2000;95(12):3498-3502. doi:10.1111/j.1572-0241.2000.03367.x
50. Beeken WL. Absorptive defects in young people with regional enteritis. *Pediatrics*. 1973;52(1):69-74.
51. Kennedy HJ, Callender ST, Truelove SC, Warner GT. Haematological aspects of life with an ileostomy. *Br J Haematol*. 1982;52(3):445-454. doi:10.1111/j.1365-2141.1982.tb03914.x
52. Fernandez-Banares F, Abad-Lacruz A, Xiol X, et al. Vitamin status in patients with inflammatory bowel disease. *Am J Gastroenterol*. 1989;84(7):744-748.
53. Khanna R, Shen B. Adverse metabolic sequelae following restorative proctocolectomy with an ileal pouch. *Gastroenterol Hepatol (N Y)*. 2012 May;8(5):322-6. PMID: 22933864; PMCID: PMC3424428.
54. Coull DB, Tait RC, Anderson JH, McKee RF, Finlay IG. Vitamin B12 deficiency following restorative proctocolectomy. *Colorectal Dis*. 2007;9(6):562-566. doi:10.1111/j.1463-1318.2007.01117.x
55. Battat R, Kopylov U, Szilagyi A, et al. Vitamin B12 Deficiency in Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. Published online April 2014:1. doi:<https://doi.org/10.1097/mib.0000000000000024>
56. Carmel R. Biomarkers of cobalamin (vitamin B-12) status in the epidemiologic setting: a critical overview of context, applications, and performance characteristics of cobalamin, methylmalonic acid, and holotranscobalamin II. *Am J Clin Nutr*. 2011;94(1):348S-358S. doi:10.3945/ajcn.111.013441
57. Carmel R. How I treat cobalamin (vitamin B12) deficiency. *Blood*. 2008;112(6):2214-2221. doi:10.1182/blood-2008-03-040253
58. Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. *Gastroenterol Hepatol (N Y)*. 2007;3(2):112-122.
59. Wexler AG, Schofield WB, Degnan PH, Folta-Stogniew E, Barry NA, Goodman AL. Human gut *Bacteroides* capture vitamin B12 via cell surface-exposed lipoproteins. *Elife*. 2018;7:e37138. Published 2018 Sep 18. doi:10.7554/eLife.37138

60. Chitti L, Cummins A. COBALAMIN DEFICIENCY and SMALL BOWEL BACTERIAL OVERGROWTH: A COMMON ASSOCIATION. *Journal of Gastroenterology and Hepatology*. 2001;16:22-22. doi:<https://doi.org/10.1111/j.1440-1746.2001.ca01-22.x>
61. BOOTH CC, HEATH J. The effect of E. coli on the absorption of vitamin B12. *Gut*. 1962;3(1):70-73. doi:10.1136/gut.3.1.70
62. Madigan KE, Bundy R, Weinberg RB. Distinctive Clinical Correlates of Small Intestinal Bacterial Overgrowth with Methanogens. *Clinical Gastroenterology and Hepatology*. 2022;20(7):1598-1605.e2. doi:<https://doi.org/10.1016/j.cgh.2021.09.035>
63. Lott WB, Takyar SS, Tuppen J, et al. Vitamin B12 and hepatitis C: Molecular biology and human pathology. *Proceedings of the National Academy of Sciences*. 2001;98(9):4916-4921. doi:<https://doi.org/10.1073/pnas.081072798>
64. Partearroyo T, Úbeda N, Montero A, Achón M, Varela-Moreiras G. Vitamin B(12) and folic acid imbalance modifies NK cytotoxicity, lymphocytes B and lymphoproliferation in aged rats. *Nutrients*. 2013 Nov 26;5(12):4836-48. doi: 10.3390/nu5124836. PMID: 24288024; PMCID: PMC3875921.
65. Rocco A, Compare D, Coccoli P, et al. Vitamin B12 supplementation improves rates of sustained viral response in patients chronically infected with hepatitis C virus. *Gut*. 2013;62(5):766-773. doi:10.1136/gutjnl-2012-302344