Micronutrient Deficiency in Inflammatory Bowel Disease - White Paper

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Introduction

Vitamin and mineral deficiencies are common occurrences in inflammatory bowel disease (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC). These observed deficiencies can be attributed to a combination of gut mucosal inflammation, systemic inflammation, and decreased oral intake.**(1,2)** Mucosal inflammation can result in chronic diarrhea, reduced nutrient absorption and blood loss.**(3)** These deficiencies may be worsened by inadequate dietary intake, which can result from lack of appetite, pain when eating, or by the use of restrictive diets sometimes used to treat IBD. IBD.

Although one or more vitamin(s) or mineral deficiencies may be observed in patients with IBD, there are a group of vitamin and mineral deficiencies that are more commonly seen and may have significant clinical implications. Those micronutrient deficiencies include vitamin D, vitamin B12, folate, iron, calcium, zinc, selenium and magnesium. There are published clinical practice guidelines for use of micronutrient supplementation in IBD; however, these guidelines continue to evolve as physicians and patients become more aware of the importance of the use of micronutrient supplementation as a component of the treatment of IBD.

Vitamin D

Vitamin D has been recognized as essential for the normal development and mineralization of the human skeleton. However, the discovery of vitamin D receptor (VDR) in most tissues and cells in the human body has provided new insights into the importance of this vitamin.

Patients with IBD have an increased incidence of vitamin D deficiency.**(4,5)** Ulitsky et al reported high rates of vitamin D deficiency in a cohort of IBD patients followed in a tertiary referral setting in the north-central United States. Approximately half of tested patients had vitamin D deficiency with 10.9% having severe deficiency. In their report vitamin D deficiency was independently associated with a lower Health Care Quality of Life (HCQOL. Vitamin D deficiency was also associated with increased IBD disease activity.**(6).** Other studies have reported vitamin D deficiency prevalence in IBD patients of 27.3 and 63%.(**7,8)**

Skeletal abnormalities remain a worrisome complication of vitamin D deficiency. Peak bone mass is generally accrued in childhood and adolescence, and so early interventions to optimize skeletal health are critical. The most important interventions in a child with IBD include control of inflammation; increase in weight bearing exercise; and achieving therapeutic levels of vitamin D. The expert panel of the North American Society for Pediatric gastroenterology and nutrition recommended screening for vitamin D levels at least once a year, and keeping a vitamin D level above 32 ng/ml.**(9)**

Low bone mineral density has been reported in 31% to 59% of patients with IBD in cross sectional and prospective study evaluations.**(10)** The prevalence of osteopenia and osteoporosis in patients with IBD has been reported between 17% and 77%.**(11,12)** The relative risk for bone fracture is 40% higher in patients with IBD as compared to those without IBD.**(13)** Vogelsang et al prospectively measured serum vitamin D concentrations during winter and summer in a group of adult European patients with IBD and found decreased bone mineral content in the summer months that correlated with low serum vitamin
D concentrations during the previous winter.**(14)**

Low serum levels of vitamin D have additionally been associated with the increased risk for the development of IBD. Environmental studies have suggested that lower levels of vitamin D associated with reduced solar ultraviolet-B radiation exposure could account for the north-south gradient of IBD, with an increased incidence of IBD among populations at higher latitudes**.(15)** Studies have linked single-nucleotide polymorphisms in the vitamin D receptor (VDR) to increased susceptibility to both CD and UC**.(16)**

A growing body of evidence supports the hypothesis that vitamin D deficiency is an important factor in the stimulation of T-cell–mediated autoimmune diseases such as IBD.**(17)** The result of vitamin D treatment in vivo is a reduction in the autoimmune Th1 response and an amelioration of symptoms of experimental IBD. Vitamin D receptor deficiency and vitamin D ligand deficiency both result in more severe experimental IBD.

In summary, vitamin D deficiency is common in IBD, resulting in bone mineralization

abnormalities, and reduced bone density, which may in turn predispose the IBD patient to an increased risk of bone fractures.**(18)** In addition, vitamin D has other important disease-related impact including as a causative risk for the development of IBD and, in experimental models, increased disease severity.

Calcium

Calcium plans a significant role in bone mineralization. Calcium is absorbed in the small intestine by two general mechanisms: a transcellular active transport process, located largely in the duodenum and upper jejunum; and a paracellular, passive process that functions throughout the length of the small intestine.**(19)** The amount of calcium absorbed is a function of the journey time of the chyme in a given intestinal segment and is inversely proportional to the rate of intestinal propulsion. In inflammatory disease of the intestines, rapid movement of materials through the digestive system can reduce overall calcium absorption. Calcium absorption from the intestine is also a vitamin D-dependent process; the lower the body vitamin D levels, the less calcium that is absorbed. Calcium deficiency has been reported in 13% of patients with IBD.**(3)** Separately patients with IBD have been found to have deceased calcium intake in 23% to 80% of IBD patients**.(20)**

The recommended dietary allowance for calcium is 1300 mg daily for children aged 9 to 18, and 1000-1200 mg a day for adults.(21)

The diet of IBD patients contains significantly less calcium than healthy controls. Self-reported lactose intolerance, leading to dietary restrictions, is believed to be the single major determinant of low calcium intake. Inadequate calcium intake is present in one third of IBD patients and represents a reversible risk factor for osteoporosis.**(22)** In patients with IBD, total body calcium stores have been shown to be deficient.**(23)** Studies have suggested that increased calcium intake can prevent bone mineralization losses in patients with IBD.**(24)** Inflammatory bowel diseases are chronic, relapsing immune-based diseases affecting the gastrointestinal tract. The immune response associated with experimental IBD is mediated by T cells that produce large amounts of the pro-inflammatory Th1 cytokines; IL-2, IFN-c, and TNF-a. Experimental IBD models suggest that dietary calcium has an independent suppressive effect on IBD severity. Vitamin D and calcium together provide the maximal suppression of experimental IBD.**(25)**

In summary, calcium deficiency is common in IBD and leads to significant bone disease. Experimental models suggest calcium intake has a suppressive effect on IBD.

Iron

Anemia is the most common systemic complication of IBD.**(26)** Almost every anemic patient with IBD demonstrates some degree of iron deficiency.**(27)** One study noted that 30% of patients with IBD have iron deficiency anemia.(**28)** Between 36% and 90% of

adults with IBD ultimately develop iron deficiency.**(29)**
Anemia in IBD has multiple causes.**(30)** Iron deficiency can be as a result of decreased iron absorption in the small intestine or blood loss from mucosal injury. The systemic inflammation seen in Crohn disease increases the levels of pro-inflammatory cytokines such as interleukin-6, which in turn may stimulate the liver to produce hepcidin. Hepcidin blocks iron absorption at the level of the intestinal epithelial cell, and also causes cells of the reticuloendothelial system to retain iron. Thus, inflammation causes anemia by impairing both iron absorption and utilization.

Anemia reduces the ability to perform normal daily activities. Chronic fatigue is a common symptom in IBD patients with anemia.**(31)** Fatigue is associated with significant physical, emotional, psychological, and social consequences, with virtually every aspect of daily life being affected. Successful treatment of anemia in many studies of various disease states has resulted in an improvement in energy, activity level and overall quality of life.**(32)** Oral iron supplementation for the treatment of iron deficiency anemia in IBD has been shown to improve quality of life without negatively impacting the disease course.**(33)**

Guidelines state that treatment should be considered for all IBD patients with a hemoglobin below normal.**(34)** The decision to initiate therapy can depend on patient symptoms and the severity of anemia and associated comorbidities. However, it is important to remember that anemia impairs quality of life even in the absence of specific symptoms and that its treatment often leads to improvement in the quality of life**.(35,36)**

Iron also has been shown to play a significant role in the body's immune response. Iron homeostasis and cellular immunity are closely linked. Iron inhibits Interferon-C activity and thereby has deactivating effects on macrophage function and the Th1 response. Thus, iron therapy and appropriate body iron stores can ease Th1 driven intestinal inflammation in IBD.**(37)**

In summary, iron deficiency and anemia are a common complication of patients with IBD. It is recommended to treat patients with IBD and a hemoglobin below normal. In addition, iron deficiency may have an impact on IBD disease severity.

Vitamin B12 and Folate
Vitamin B12 (cobalamin) and folic acid (folate) are vitamins and coenzymes involved in a series of complex biochemical reactions, including DNA synthesis.
Vitamin B12 deficiency can result in anemia; it has been reported in approximately 20% of both adult and pediatric IBD patients.**(38)** Other studies have reported a statistically increased prevalence of B12 deficiency in IBD patients as compared to controls.**(39)**
Vitamin B12 deficiency may also result in a peripheral neuropathy that can become

permanent. Optic nerve damage and visual disturbances can also occur. Visible clinical evidence of Vitamin B12 deficiency occurs when body stores are depleted to less than 10% normal. Vitamin B12 is primarily absorbed in the terminal ileum. Chronic ileal inflammation may result in B12 deficiency. More commonly, many patients with Crohn disease undergo surgical removal of the terminal ileum, which greatly increases the risk of a patient developing vitamin B12 deficiency.**(40)**
Folate is absorbed in the duodenum and jejunum and deficiency may be due to inadequate diet, malabsorption, or drug interactions. Clinical manifestation can occur early in the course of folate deficiency as body folate stores last only 1–2 months and include anemia and fatigue. One study noted folate deficiency in 59% of IBD patients.**(41)** Other studies have reported that folate deficiency affects 60% of IBD patients. In addition, treatment with sulfasalazine may exacerbate folate deficiency because it competes with the folic acid present in the intestinal lumen, rendering it unavailable for absorption.**(42)** Methotrexate treatment may also contribute to folate deficiency because methotrexate is an antagonist of folic acid.**(43)** Folate deficiency can cause and worsen anemia in IBD patients.**(44)** Folic acid is an essential co-factor in the metabolic route of homocysteine-methionine. Folate deficiency may result in hyperhomocysteinemia resulting in an increased incidence of thromboembolic events.

In summary, B12 and folate deficiency are common in IBD. A deficiency of B12 and or folate can cause or worsen anemia. A significant peripheral neuropathy and optic nerve damage may develop as a result of vitamin B12 deficiency; this neuropathy may become irreversible. Folate deficiency is associated with increased thromboembolic events.

Selenium, Zinc and Magnesium
Selenium deficiency has been noted in patients with even mild IBD.**(45)** Low levels of serum selenium have been seen in children with IBD as compared to controls.**(46)** Other authors have reported low serum selenium levels in adults with IBD as compared to controls**.(47)**

The serum levels of zinc are lower in children with IBD as compared to controls.**(48)** The exact cause of zinc deficiency in patients with IBD is not clear, but impaired absorption has been implicated.(**49)** Low levels of serum zinc levels have also been reported in adult patients with IBD.**(50)** Low levels of zinc have been linked to increased natural killer cell activity providing a mechanism for increased disease intensity for patients with IBD.**(51)** Zinc plays a pivotal role in wound healing; zinc deficiency may be a co-factor in patients with chronic fistulas that will not heal.**(4,24)**

Magnesium deficiency has been reported in 13-88% of patients with IBD.**(52)** Magnesium losses are accelerated with increased diarrheal output.**(53)** Low magnesium levels in IBD patients have been reported to cause fatigue, tetany, heart arrhythmias and altered gastrointestinal motility.**(54,55)**

Besides reduced ingestion of nutrients in IBD and poor absorption through inflamed mucosal membranes, intraluminal factors may play an additional role in the decreased absorption of some nutrients. The calcineurin inhibitors cyclosporine and tacrolimus, sometimes used to treat severe cases of Crohn disease and ulcerative colitis, may also cause hypomagnesemia by increasing urinary excretion of magnesium. Magnesium, selenium and zinc can form soap complex in the small intestine due to their mixing and reaction with poorly absorbed fats.**(56)** These soap complexes cannot be absorbed.

Reactive oxygen species (oxygen free radicals (OFR)) are a causative agent of tissue damage in IBD.**(57)** Abundant production of OFR has been observed in the bowels of IBD patients with active disease. Under normal physiologic conditions, antioxidant defenses protect tissues against the damaging effects of these reactive species. Chronic gut inflammation promotes an imbalance between OFR and antioxidant products resulting in tissue damage. Zinc and selenium are antioxidants and have been found in low levels in patients with IBD.**(46)**

Selenium is a component of glutathione peroxidase, a scavenger of OFR. Selenium deficiency causes a decrease in glutathione peroxidase function, thereby resulting in oxidative damage to many organs.**(58)** Zinc is also a co-factor for superoxide dismutase, an antioxidant; consequently it protects against oxidative cellular damage.**(5)** Selenium has been shown to influence the expression of different genes linked to the activation of stress signal pathways that play an important role in the pathogenesis of inflammation.**(34)**
In summary, zinc, selenium and magnesium deficiency are common in patients with IBD. Both zinc and selenium protect against tissue damage in IBD seen as a result of oxidative stress from OFR. Zinc deficiency results in poor wound healing while selenium deficiency worsens the stress signal pathways that impact the severity of IBD. Magnesium deficiency can result in fatigue, muscle function and gastrointestinal motility.

Conclusion
IBD is a challenging disease with over 1 million people in the United States with the diagnosis, over 30,000 new cases annually, and over 2 million ambulatory care visits yearly.**(59)** There is compelling data within the literature pointing to micronutrient deficiencies in the setting of IBD.

Although any vitamin or mineral may become deficient in IBD patients, Vitamin D, calcium, iron, vitamin B12, folate, zinc, selenium and magnesium are the most common and may have significant clinical consequences. Micronutrient deficiency in IBD has been associated increased risk of prolonged hospitalization, complicated peri-operative courses, and higher mortality.**(60,61)** Clinicians and patients should remain aware of micronutrient deficiencies in order to address the treatable causes of morbidity appropriately and to prevent late and irreversible sequelae.**(59).**

While there is a paucity of randomized, placebo-controlled trial data on micronutrient supplementation in IBD, and for that matter in other complex diseases, patients with IBD should consider using a daily multi-nutrient supplement which is especially fortified with Vitamin D, calcium, iron, vitamin B12, folate, zinc, selenium and magnesium based on published literature and expert opinion. The use of micronutrients in IBD is common, with some studies pointing to supplement use in over 50% of patients.**(62)** The published clinical data underscores the rationale of why patients should be supplemented with micronutrients on a daily basis.

The major medical associations and current society dietary guidelines relevant to IBD acknowledge nutritional deficiency in this patient population and advocate considering nutritional support.**(63)** Special consideration should be given for vitamin D and the other fat soluble vitamins, A, E and K, as well as other nutrients, such as vitamin C, vitamin B12, folate, calcium, magnesium, iron, zinc and copper. IBD patients who are prescribed corticosteroid medications should be informed of the increased risk for osteoporosis and should receive calcium and vitamin D supplementation.

Guidelines pertinent to IBD nutrition reviewed are: The American Dietetic Association; The American College of Gastroenterology; World Gastroenterology Practice Guidelines; The American Society of Parenteral and Enteral Nutrition; the European Society for Clinical Nutrition & Metabolism; The Japanese Society for Pediatric Gastroenterology, hepatology and Nutrition; the Crohn's & Colitis Foundation of America, The National Digestive Diseases Information Clearinghouse and Medline Plus. The following are relevant statements:

ESPEN (European Society for Parenteral and Enteral Nutrition) Guidelines: Clinical Nutrition in Inflammatory Bowel Disease:
- Patients with IBD should be checked for micronutrient deficiencies on a regular basis and specific deficits should be appropriately corrected.
- Treatment of iron deficiency anemia in IBD is valuable
- Selected IBD patients, e.g. those treated with sulphasalazine and methotrexate, should be supplemented with vitamin B9/folic acid
- In IBD patients (adults and children) with active disease and those who are steroid-treated, serum calcium and 25(OH) vitamin D should be monitored and supplemented if required to help prevent low bone mineral density
- Interesting new data suggest that a diet rich in vitamin D and zinc may also protect against IBD.

American Dietetic Association guidelines for IBD:
- “Use of a multivitamin in IBD is important.”

ACG Ulcerative Colitis and Crohn's Disease Guidelines (2009 and 2010):
- "Owing to a significantly increased risk of osteoporosis in the setting of CD when conventional glucocorticosteroid therapy is used, a baseline DEXA scan, supplementation of calcium and vitamin D… [is] warranted once corticosteroid therapy is initiated"

IBD Section of the British Society of Gastroenterology, 2004:
- "Malnutrition is common and multifactorial in origin…Specific attention should be paid to vitamin B12 status, especially after ileal resection."

Gut, 2002
- "…it seems reasonable to recommend correction of vitamin D insufficiency with an oral daily dose of 800 IU of vitamin D3…"

References

1. Sanhu BK, Fell JM, Beattie RM, et al. Guidelines for the management of inflammatory bowel disease. J Pediatr Gastro Nutr 2010;50:S1-S13.

2. Hartman C, Eliakim R, Shamir R. Nutritional status and nutritional therapy in inflammatory bowel disease. W J Gastro 2009;15:2570-2578.

3. Massironi S, Rossi RE, Cavalcoli FA, et al. Nutritional deficiencies in inflammatory bowel disease: therapeutic approaches. Clin Nutr 2013;32:904-910

4. Siffledeen JS, Siminoski K, Steinhart H, et al. The frequency of vitamin D deficiency in adults with Crohn's disease. Can J Gastroenterol. 2003;17:473-478.

5. Tajika M, Matsuura A, Nakamura T, et al. Risk factors for vitamin D deficiency in patients with Crohn's disease. J Gastroenterol.2004;39:527-533.

6. Ulitsky A, Ananthakrishnan A N, Naik A, et al. Vitamin D deficiency in patients with inflammatory bowel disease. Association with disease activity and quality of life. J Parent Ent Nutr 2011;35:308-316.

7. Tajika M, Matssura A, Nakamura T. Risk factors for vitamin D deficiency in patients with Crohn's disease. J Gastro 2004;39:527-533**.**

8. Suibhne TN, Cox G, Healey M, et al. Vitamin D deficiency in Crohn's disease prevalence, risk factors and supplementation. J Crohn's Colitis 2012; 6:182-188

9. Pappa H, Thayu M, Leonard M, et al. Bone health in IBD: a clincial report on skeletal health in children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2011 ; 53(1): 11–25.

10. Abitbol A, Roux C, Chaussade S, et al. Metabolic bone assessment in patients with inflammatory bowel disease. Gastro 1995:108:417-422

11. Bjarnason I, Macpherson A, Mackintosh C, et al. Reduced bone density in patients with inflammatory bowel disease. Gut 1997;40(2):228–233.

12. Pollak RD, Karmeli F, Eliakim R, et al. Femoral neck osteopenia in patients with inflammatory bowel disease. Am J Gastroenterol 1998;93(9):1483–1490

13. Compston JE, Judd D, Crawley EO, et al. Osteoporosis in patients with inflammatory bowel disease. Gut 1987;28(4):410–415.

14. Vogelsang H, Ferenci P, Woloszczuk W, et al. Bone disease in vitamin D-deficient patients with Crohn's disease. Dig Dis Sci 1989;34:1094–1099

15. Lim WC, Hanauer SB, Li YC. Mechanisms of disease: vitamin D and inflammatory bowel disease. Nat Clin Pract Gastroenterol Hepatol 2005;2:308–315

16. Martin K, Radlmayr M, Borchers R, et al. Candidate genes co-localized to linkage regions in inflammatory bowel disease. Digestion 2002;66:121–126

17. Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Biol 2004;229:1136-1142

18. Reference: Vazquez MA, Lopez E, Montoya MJ, et al. Vertebral fractures in patients with inflammatory bowel disease COMPARED with a healthy population: a prospective, case-controlled study. BMC Gastro 2012;12:47-53.

19. Bronner F. Mechanisms of calcium absorption. J Cell Bio 2003;88:387-393

20. Ref: https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/

21. Vagianoski K, Bector S, McConnel J, et al. Nutrition assessment of patients with inflammatory bowel disease. J Parent Ent Nutr 2007;31:185-191

22Vernia P, Loizos P, Di Giuseppatonio I, et al. Dietary calcium intake in patients with inflammatory bowel disease. J Crohn's Colitis 2014;8:312-317

23. Bernstein CN, Ament M, Artinian L, et al. Milk tolerance in adults with ulcerative colitis. Am J Gastroenterol 1994; 89: 872-872-879.

24. Lindsay R. Prevention and treatment of osteoporosis. Lancet 1993; 341: 801-805.

25. Zhu Y, Mahon BD, Froicu M, et al. Calcium and 1a,25-dihydroxyvitamin D3 target the TNF-a pathway to suppress experimental inflammatory bowel disease. Eur J Immunol 2005;35:217-234

26. Schreiber S, Wedel S. Diagnosis and treatment of anemia in inflammatory bowel disease. Inflamm Bowel Dis 1997;3:204 –216

27. Horina JH, Petritsch W, Schmid CR, et al. Treatment of anemia in inflammatory bowel disease with recombinant human erythropoietin: results in three patients. Gastroenterology 1993;104:1828 –1831

28. Thomson ABR, Brust R, Ali MAM, et al. Iron deficiency anemia in inflammatory bowel

disease, Am J Dig Dis 1978;23:705-709.

29. Gomollón F, Gisbert JP. Anemia and inflammatory bowel diseases. World J Gastroenterol 2009;15:4659-4665.

30. Gasche C. Anemia in IBD: the overlooked villain. Inflamm Bowel Dis 2000;6:142–150.

31. Mitchell A, Guyatt G, Singer J, et al. Quality of life in patients with inflammatory bowel disease. J Clin Gastroenterol 1988;10:306–310

32. Demetri GD, Kris M, Wade J, et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. J Clin Oncol 1998;16:3412–25

33. Gomollón F, Gisbert JP. Anemia and inflammatory bowel diseases. World J Gastroenterol 2009;15:4659-4665

34. Gasche C, Berstad A, Benfrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel disease. Inflamm Bowel Disease 2007;13:1545-1553

35. Wells CW, Lewis S, Barton JR, et al. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflamm Bowel Disease 2006;12:123–130.

36. Gasche C, Dejaco C, Waldhoer T, et al. Intravenous iron and erythropoietin for anemia associated with Crohn disease. A randomized, controlled trial. Ann Intern Med 1997;126:782–787.

37. Gasche C, Lomer MCE, Cavill I, et al. Iron, anemia, and inflammatory bowel diseases. Gut 2004;53:1190-1197

38. Yakut M, Ustün Y, Kabaçam G, et al. Serum vitamin B12 and folate status in patients with inflammatory bowel diseases. Eur J Intern Med 2010;21:320-323

39. Erzin Y, Uzun H, Celik AF. Hyperhomocysteinemia in inflammatory bowel disease without intestinal resections: correlation with cobalamin, pyridoxine acute phase reactant activity and prior thromboembolic complications. J Clin Gastroenterol 2008;42:481-486.

40. Gerson CD, Cohen N, Janowitz HD. Small intestine absorptive function in regional enteritis. Gastroenterology 1973;64:907-912

41. Elsborg L, Larsen L. Folate deficiency in chronic inflammatory bowel disease. Scan J Gastro 1979;14:1019-1024.

42. Lucendo AJ, De Rezende LC. Importance of nutrition in inflammatory bowel disease. World J Gastroenterol 2009;15:2081-2088

43. Yakut M, Ustün Y, Kabaçam G, et al. Serum vitamin B12 and folate status in patients

with inflammatory bowel diseases. Eur J Intern Med 2010;21:320-323

44. Goh J, O'Morain A. Review article: nutrition and adult inflammatory bowel disease. Aliment Pharmacol Ther 2003;7:307-320

45. Hinks LJ, Inwards KD, Lloyd B, et al. Reduced concentrations of selenium in mild Crohn's disease. J Clin Pathol1988;41:198-201

46. Ojuawo A, Keith l. Serum concentrations of zinc, copper and selenium in children with inflammatory bowel disease. Centr Afr J Med 2002;48:116-119

47. Ringstat J, Kildebo S, Thomassen Y. Serum zinc, copper and zinc concentrations in Crohn's disease and ulcerative colitis. Scan J Gastroenterol 1993;28:605-608

48. Ojuawo A, Keith l. Serum concentrations of zinc, copper and selenium in children with inflammatory bowel disease. Centr Afr J Med 2002;48:116-119

49. Griffin IJ, Kim SC, Hicks, PD, et al. Zinc metabolism in adolescents with Crohn's disease. Pediatr Res. 2004 56:235-9.

50. Hendricks KM, Walker WA. Zinc deficiency in inflammatory bowel disease. Nutr Rev 1988;46: 401-408

51. Egawa S, Hiwatachi N. Natural killer cell activity in patients with inflammatory bowel disease. J Clin Lab Immunol 1986;20:187-192

52. Galland L. Magnesium and inflammatory bowel disease. Magnesium 1988;7:78-83

53. Nylin H, Dyckner T, Ek B, et al. Magnesium in Crohn's disease. Acta Med Scan Suppl 1982;661:21-25.

54. Hessov I, Hasselblad C, Fasth S, et al. Magnesium deficiency after ileal resection for Crohn's disease. Scan J Gastroenterol 1983;18:643-649

55. Galland L. Magnesium and inflammatory bowel disease. Magnesium 1988;7:78-83.

56. Andersson H, Bosaeus I, Brummer R-J, et al. Nutritional and metabolic consequences of extensive bowel resection. Dig Dis 1986;4:193–202

57. Geerling BJ, Bandart-Smook A, Stockbrugger RJ, et al. Comprehensive nutritional status in patients with long-standing Crohn's disease currently in remission. Am J Clin Nutr 1998;67:919-926

58. Rotruck JT, Pope AL, Ganther HE, et al. Selenium: biochemical role as a component of glutathione peroxidase. Science 1973;179:588-590

59. Weisshof R, Chermesh I. Micronutrient deficiencies in inflammatory bowel disease. Curr Opin Clin Nutr Metab Care. 20;18:576–581

60. Loftus, EV. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence and environmental factors. Gastroenterology 2004;126:1504-1507

61. O'Sullivan M. Symposium on 'The challenge of translating nutrition research into

public health nutrition'. Session 3: Joint Nutrition Society and Irish Nutrition and Dietetic Institute Symposium on 'Nutrition and autoimmune disease' Nutrition in Crohn's disease. Proc Nutr Soc 2009;68:127–134

62. Kong S, Hurlston D, Pocock CY, et al. The incidence of self-prescribed oral and complimentary medicine used by patents with gastrointestinal diseases. J Clin Gastroenterol 2005;39:138-141

63. Brown AC, Rampertab SD, Mullin GE, et al. Existing Dietary Guidelines for Crohn's Disease and Ulcerative Colitis. Exp Rev Gastroenterol Hepatol. 2011;5:411-425