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REVIEW ARTICLE

Practical Recommendations on Micronutrient Deficiencies in Gastrointestinal Diseases

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Abstract

Almost all the micronutrients being absorbed in gastrointestinal tract, patients with gastrointestinal disorders are at highest risk of having multiple nutritional deficiencies including micronutrient deficiencies. Malnutrition and deficiencies can be prevented or treated by optimal medical nutrition therapy, yet limited specific knowledge about micronutrients remains among clinicians. Further knowledge on trace elements remains miniscule as compared to vitamins. Practical recommendations based on available micronutrient guidelines are therefore required regarding procedures for determination of requirements and, especially for gastrointestinal diseases as this is the commonest encountered problem that can impair enzymatic as well as biochemical processes and lead to multiple complications including death. Here we have tried to give consensus based recommendations to help practicing dieticians and clinicians making decision regarding specific micronutrient deficiencies and their implications in gastrointestinal diseases.

Keywords: Practical recommendations on micronutrient deficiencies in gastrointestinal diseases; Malnutrition; IAPEN INDIA consensus statement

Introduction

Micronutrients are required only in micro or milligram quantities for multiple metabolic processes and varied biochemical pathways in human body, whether in health or in diseases, yet they cannot be synthesized in humans and hence they are known as essential dietary factors. Micronutrients (MN) usually include Vitamins and trace elements. Vitamins are further divided into two groups, the fat soluble vitamins (vitamins A, D, E, K) and the water-soluble vitamins.[(1)] These water-soluble vitamins function as coenzymes in metabolic processes and the trace elements function as cofactors for antioxidant enzyme in various biological processes. Adequate intake of micronutrients is crucial for public as well as individual health.

Physiologic and Pathophysiologic Factors Affecting Micronutrient Requirements

The dietary requirements of micronutrients for any individual are affected by a number of physiological and pathological factors such as bioavailability of given micronutrient, amount, age and gender

of an individual as well as any disease or drug that may interfere metabolism of the given micronutrient.

Physiological factors such as aging have specific impact on the requirements of some micronutrients due to the reduced energy requirements, food intake, absorption, metabolism and utilization and that can cause deficiency of certain micronutrients. Atrophic gastritis, is highly prevalent in elderly population and this can lead to impaired absorption of protein bound vitamin B12.[2] As compared to younger adults in RDA, greater requirements are set for Vitamin B6, Calcium and Vitamin D3 to address PEM, anaemia, decreased absorption of calcium, osteoporosis in elderly. Deficiency of Vitamin D3 has been found to have association with multiple diseases like hypertension, dyslipidaemia, insulin resistance, obesity, diabetes, metabolic syndrome[3], Alzheimer's disease[4] and certain cancers.[5]

The ingestion, digestion and absorption of nutrients take place in the gastrointestinal tract. For the transformation of nutrients liver is of prime importance and pancreas is essential to digestion and metabolism. So it is very common that GI, hepatic and pancreatic diseases have significant nutritional impact, and they can cause multiple nutritional deficiencies.

Why micronutrient deficiency in GI diseases?

Lack of availability, reduced intake, malabsorption[6] and maldigestion are the major causes of micronutrient deficiencies globally. Patients having gastrointestinal diseases are significantly predisposed to deficiencies of nutrients be it macro or micronutrients, as they may have multiple factors e.g. reduced food intake, dysphagia, malabsorption, maldigestion, as well as excessive GI losses of fluid and nutrients. And all these can lead to specific deficiencies including micronutrient deficiencies.[7] Reduced intake may be secondary to anorexia, nausea and/or vomiting, severe diarrhoea, dysphagia or odynophagia, abdominal pain, obstruction, iatrogenic factors, restrictive, non-nutritious diets with dietary manipulation. Maldigestion and malabsorption can be the consequent to mucosal disease, decreased absorptive surface area, pancreatic insufficiency, bile salt insufficiency, bacterial overgrowth, drug induced e.g. corticosteroids (calcium), sulfasalazine/methotrexate (folate), cholestyramine (fat and fat soluble vitamins). Gastrointestinal losses involve diarrhoea and bleeding, fistulae, protein-losing enteropathy. There may be increased nutritional requirements during active catabolism, active inflammation, fever, corticosteroid usage.[8]

Gastrointestinal diseases that affect sites (small intestine, pancreas, and/or hepato-billiary tree) or the mechanisms of nutrient absorption in the GI tract leads to specific nutritional deficiencies. GI diseases such as Inadequate bowel - short gut syndrome, Crohn's disease, Celiac disease, Gastrectomy with Bilroth-II anastomosis, Bariatric surgery, Chronic pancreatitis, Chronic liver disease and cholestatic liver disease may have long term nutritional consequences.[8]

Major micro nutritional deficiencies associated with a variety of GI disorders are nutritional anaemias (iron, folate, B-12), Vitamin deficiencies (A, thiamine, riboflavin, niacin, pyridoxine, D, K) Trace element deficiencies ((iron, copper, selenium, zinc). Trace element toxicity (manganese). Bone disease (decreased bone mineral density and osteomalacia)[8].

Majority of micronutrients including both fat and water-soluble ones except vitamin B12 are predominantly absorbed in proximal small intestine. Therefore, diffuse mucosal diseases affecting proximal small intestine can cause multiple nutritional deficiencies. Even though in the absence of proximal small intestinal diseases, some pathologies such as extensive ileal disease, chronic cholestasis or small intestinal bacterial overgrowth (SIBO) may affect the optimum intraluminal conjugated bile acid concentration leading to impaired absorption of fat soluble vitamins. Conditions like cystic fibrosis or congenital biliary atresia often have overt fat malabsorption, yet having well recognized fat soluble vitamin deficiencies. Conditions like later stages of cholestatic liver disease have subtler fat malabsorption.[23,24], Chronic pancreatic insufficiency cause fat malabsorption leading to maldigestion and fat soluble vitamin deficiencies. Early stages of many micronutrient deficiencies are undetectable and often goes undiagnosed and their progression can sometime lead to increased morbidity and be disastrous as in conditions like irreversible spinocerebellar degeneration due to fat soluble vitamin E deficiency.[23]

Why micronutrient guidelines in GI diseases?

Almost all the micronutrients being absorbed in GI tract, patients with gastrointestinal disorders are at highest risk of having multiple nutritional deficiencies including micronutrient deficiencies. Malnutrition and deficiencies can be prevented or treated by optimal medical nutrition therapy, yet limited specific knowledge about micronutrients remains among clinicians. Further knowledge on trace elements remains miniscule as compared to vitamins. Practical recommendations based on available micronutrient guidelines are therefore required regarding procedures for determination of requirements[9], especially for GI diseases as this is the commonest encountered problem that can impair enzymatic as well as biochemical processes and lead to multiple complications including death.

Methodology

Our present consensus on practical guideline recommendations started with critical evaluation of European Society for Clinical Nutrition and Metabolism (ESPEN) micronutrient guideline[9], Practical considerations on micronutrient sup-

Table 1. Absorption sites and clinical manifestations of deficiency of different micronutrients in gastrointestinal tract

	Micronutrient	Primary site of absorption	Clinical Manifestation of deficiencies
Water-soluble vitamins	B1 (thiamine)	Jejunum/ileum	Apathy, Wernicke-korsakoff encephalopathy, beriberi, congestive cardiac failure, lactic acidosis
	B2 (riboflavin)	Jejunum	Glossitis, Cheilosis, Angular stomatitis
	B3 (niacin)	Jejunum	Pellagra (Diarrhoea, Dermatitis, Dementia)
	B5 (pantothenic acid)	Jejunum	Deficiency very rare, postural hypotension, vertigo
	B6 (pyridoxine)	Jejunum	Glossitis, Cheilosis, Angular stomatitis
	B7 (biotin)	Jejunum	Dermatitis, alopecia, ataxia
	B9 (folate)	Jejunum/ileum	Megaloblastic anemia, pancytopenia, Glossitis, Cheilosis, Angular stomatitis
	B12 (cobolalmin)	Terminal ileum	Glossitis, Cheilosis, Stomatitis, Subacute combined degeneration of spinal cord
	C (ascorbic acid)	Jejunum/ileum	
Fat-soluble vitamins	A	Ileum	Night blindness, Impaired immune response, Poor bone growth
	D	Ileum	Poor bone health, tetany, rickets
	E	Ileum	Peripheral neuropathy, Myopathy, Retinitis pigmentosa
	K	Ileum	Bleeding diasthesis
Trace elements	Iron	Duodenum	Microcytic anemia, Glossitis
	Zinc	Unclear	Bullous dermatitis, Alopecia, Diarrhoea, Increased infections
	Chromium	Proximal small bowel	Alterations of glucose metabolism
	Copper	Duodenum	Microcytic anemia, Hair de pigmentation (symptoms not recognised readily)
	Manganese	unclear	Deficiency exceptional in humans
	Selenium	Ileum	Cardiac and skeletal muscle myopathy

plementations in Adult Nutrition Therapy by The American Society for Parenteral and Enteral Nutrition (ASPEN)[25], Practice Guidelines for nutrition in Critically ill patients by Indian Society of Critical Care Medicine (ISCCM)[26], Facts on micronutrients by WHO[27], RDA for INDIANS[28] and other relevant literature. Their recommendations and references, on which they were based, underwent several rounds of deliberations by our expert group. Their guidelines were considered within the purview of practicality and feasibility in Indian scenario. Based on these, the first draft of the recommendations was circulated among the experts who provided their inputs based on which these final practical consensus recommendations were arrived at.

General Recommendations

- Micronutrient deficiencies can be suspected and identified firstly based on the dietary recall as well as the NFPE (Nutrion-focused physical examination) followed by screening by laboratory investigations if practical. Assessment of malnutrition and treatment in patients having gastrointestinal diseases is important for positive clinical outcome and to reduce costs.
- Patients may have preexisting malnutrition that can result in further vitamins and trace elements deficiencies when affected by current illness and other treatment related complications.[30]
- Anemia and micronutrient deficiencies should be checked by blood tests in patients with gastrointestinal

Recommendation 1

All patients with GI diseases should be identified with the potential micronutrient deficiencies and screen for the same if practical, as a part of nutritional assessment.[2,29]

Table 2. Different Diseases (not limited to) causing specific micronutrient deficiency or depletion. Modified from [9]

Disease	Deficiency favouring disease development	Inadequacy or deficit worsening the condition	Deficiency as a result of disease	
Alcoholism		B1, Fe	A, D, E, K, B1, B2, B6, B7, B9, B12, C, Zn	[6,10],
Alcoholic hepatitis	B6, Zn	Se, Zn		[11]
Non-alcoholic fatty liver disease	Cu			[12]
Liver diseases		Zn	B12, A, D, E, Se, Zn	[6,13,14]
Chronic atrophic gastritis			B9, B12, C, D, Fe	[15]
Inflammatory bowel disease		Zn	B1, B6, B12, A, D, E, K, Fe, Zn	[6,16,17]
Chronic intestinal failure			B2, B7, B9, B12, A, D, E, K, Cu, Fe, Zn	[18–20],
Obesity preoperative in bariatric surgery	Beta carotene,E, Se, zn	B1, B9, D, Fe, Se, Zn		[21,22]
Obesity post bariatric surgery			A, D, E, K, B1, B9, B12, C, Cu, Fe, Zn	[23,24]

diseases and those with inflammatory bowel disease or malabsorption should be checked for vitamin D deficiency. [31]

Recommendation 2

All Micronutrients will be included in adequate amounts as soon as the medical nutrition therapy is initiated in the patient. Additional supplementation of specific micronutrient will be provided only in the settings of documented deficiencies. [29,32]

- Providing adequate amounts of micronutrients is an integral part of medical nutrition therapy.
- Patients with GI diseases are predisposed to malnutrition with depleted micronutrients due to preexisting illness, reduced intake, increased requirements or due to increased losses. [6]
- Micronutrient deficiencies may lead to serious nutritional consequences. Inadequate intake of micronutrients may initially be compensated by increased absorption from gut, decreased renal excretion or by decreased growth velocity in case of zinc. When there occur progressive depletion intracellular contents may get reduced with resultant impairment in biochemical functions like reduced intracellular enzymatic activity and may also affect gene expression/regulation. Short term effects like cognitive effects fatigue and impaired immune functions, whereas long term effects such as free radical damage to DNA/cell membrane may occur as non-specific functional effects leading to clinical disease or even death. [33] Therefore adequate intake of micronutrients is crucial for public as well as individual health.

Recommendation 3

If possible, provision of micronutrient supplements should be done orally or enterally considering the safety and effectiveness of the same. [16]

- The current recommendations are for both hospitalized as well as outpatients with gastrointestinal diseases. Majority guidelines on micronutrient provision are primarily for hospitalized or critical patients receiving medical nutrition support. However, the clinician should not forget that some patients especially out patients may be benefited from specific single or multiple oral micronutrient supplements. [9]
- Ideal way to provide micronutrients is through gut as absorption of micronutrients by the gut can be adapted to the requirements [25]. During the critical illness nutrient absorption can be compromised due to bowel ischemia, edema or ileus, yet even in haemodynamically unstable patients hypo caloric enteral feeding have been found to be unaffected regarding nutrient absorption [34] and micronutrient supplementations are required in very small quantity. However levels can be achieved more confidently with the intravenous administration of micronutrient supplementation. [25]

Recommendation 4

While determining the blood levels of micronutrients in the patients with Gastrointestinal diseases-reactive protein as well as Albumin should be determined in the settings of inflammation. [16]

- -Blood levels of micronutrient determined are found to be low as an effect of redistribution of micronutrients from circulation to other organs due to inflammation in the cases like surgery, infection, acute or chronic diseases. [32]
- It has been found in healthy individuals undergoing elective surgeries that without any change in whole body micronutrient status, within one day of surgery their plasma concentration of multiple micronutrients were significantly decreased. [35]
- Except vitamin B12 micronutrient levels in blood are impacted by inflammation usually when CRP levels exceeds 20mg/dl. Albumin is a negative acute phase protein and affected by dilution during inflammation. Being career for many micronutrients it should be determined too in the settings of inflammation. [9,35]

Recommendation 5

If patient is on standard, balanced and complete formula feeds, with provision of formula as a soul source of nutrition providing 2000kcal/day, there is no requirement of additional micronutrient supplementation. [34,36]

- To comply with the directives regarding formulation of food for medical nutrition therapy, the complete formula should contain the 100% RDA for micronutrients if it is providing 1500 kcal(35), therefore those who are on complete nutritionally balanced formula feeds may not require supplementation of micronutrients. [26]
- Minimum intake suggested for an individual with complete formula feeding is kept 2000kcal/day, which is higher than the energy requirements of normal population to address increased requirements of an individual on enteral feeding. [29,37]

Recommendation 6

Patients who are on parenteral nutrition or on blenderized feeding additional micronutrient should be considered. [32]

- Commercially available PN solutions contain only lipids, glucose, amino acids and some electrolytes but trace elements and vitamins are excluded in PN solutions because of the stability reasons.so should be prescribed separately, [38] however Unfortunately Micronutrients are not added in majority of the patients on parenteral nutrition. [39]
- It is a practice to add multivitamin preparation (including vitamin) and a multiple trace element admixture (containing Zn, Se, Cu, Cr, and Mn) to be added to (PN) formulations. [25] The recommendations for vitamins and trace elements of interest for enteral and parenteral formula in practice and their suggested composition are there. [25]
- Blenderised feeds lack in uniform and optimal nutritional composition that is recommended to meet the requirements, as compared to commercial feeds. [40], there for with relation to meet daily micronutrients requirements additional supplementation should be considered.

Disease specific recommendations for major Gastrointestinal Diseases

Inflammatory Bowel diseases

Recommendation 7

7A Being at higher risk of malnutrition including micronutrient deficiency, regular assessment and optimal correction of micronutrient deficiencies in IBD patients should be done. Routine monitoring (at least annually) is advised in well-nourished IBD patients too, even during remission period. [41]

- Malnutrition is highly prevalent in IBD patients and CD patients have higher occurrences (25%-69%) of deficiencies as compared to UC patients (1%-32%) as majority of micronutrients are absorbed in small intestine. To prevent loss of visceral protein mass, impairment of cellular healing leading to poor wound healing, nutritional therapy is essential. [36,42]
- The mechanism of malnutrition in IBD patients are multifactorial significantly reduced intake in relation to increased requirements, malabsorption, increased losses as well as a consequences of medical and surgical treatment modalities. [36]

7B While offering medical nutrition therapy in IBD patients, multivitamin and micronutrient supplementations should be ensured. A Daily multivitamin supplement may be helpful, however Iron, Zinc and Vitamin D deficiencies should be anticipated over longer period requiring specific correction therapy. [43]

- Micronutrient status even during the remission phase is depleted in IBD patients and daily supplementation with a multivitamin may be used for correction. However adequacy remains uncertain even over long term, therefore Iron, Zinc and Vitamin D3 should be supplemented to avoid anemia, poor linear growth and compromised bone health.[44] keeping in mind that Ileal disease can result in poorly absorbed fat-soluble vitamins due to decrease in bile acid absorption.

7C All IBD patients require iron supplements if found anemic. Oral iron should be considered first in mild anemia, inactive IBD and patient has no oral iron intolerance, but in those who are intolerant to oral iron supplements, with active disease, serum hemoglobin level< 10gm/dl and who require erythropoiesis stimulating agents Intravenous iron should be considered as a first line of treatment. Pregnant IBD patients should be regularly monitored for iron and folate deficiency and supplemented accordingly.[45]

- Patients most frequently have anemia as manifestation of IBD other than intestinal symptoms. Anemia is prevalent in 6%-74% patients due to both iron deficiency as well as GI blood loss. B12 and folate deficiency and certain medications in IBD can also cause anemia, especially in UC as compared to CD.[46]

7D Patients with active IBD, on treatment with Steroids should be monitored for calcium and Vitamin D deficiency and adequate supplementations to correct deficiency should be offered to prevent bone loss.[45]

- Vitamin D can be deficient in IBD patients due to malabsorption leading to reduced bone density especially in patients on corticosteroid treatment.[47]

7E Resection of More than 20 cm with or without ileo cecal valve, distal ileum in CD patients, warrants vitamin B12 administration.[45]

- In CD patient if ileum is involved or ileal resection is more than 30cm of distal ileum, this puts the CD patient at high risk of B12 deficiency.[41]

7F IBD patients with anticipated folate deficiency e. g. on Sulfasalazine or Methotrexate should receive folic acid supplementations.

- Folate deficiency is prevalent in IBD due to poor intake, malabsorption, higher utilization for inflammation and due to medication such as Sulfasalazine, methotrexate.[48]

Liver Diseases

Recommendation 8

In patients with severe Alcoholic Steatohepatitis micronutrient deficiencies should be foreseen and replaced, especially vitamin B, zinc and Vitamin D. In the absence of expensive laboratory measurements for deficiencies, empirical oral micronutrient supplementation of multivitamin and Zinc may be reasonable. Routine supplementation of Thiamin is advised to avoid Wernicke's encephalopathy and korsakoff psychosis.[49]

- Alcoholic liver disease make patient vulnerable to multiple micronutrient deficiencies due to poor intake and based on evidences they have depleted stores of B vitamin, Zinc and Vitamin D, their empiric oral supplementation is less expensive and justified[43]

Recommendation 9

9A Vitamin E supplementation with 800 IU/day in an adult non diabetic histopathologically confirmed NASH patient is beneficial to improve liver enzymes levels as well as liver histology.

- Vitamin E supplementation in NASH patients improve liver enzymes, inflammation and steatosis in NASH patients.[45]

9B Vitamin C supplementation as an antioxidant for treatment of NASH cannot be recommended at present.[49]

- Vitamin C deficiency has been linked with NASH/NAFALD, yet supplementation with vitamin C lack adequate data to be recommended for its antioxidant properties to treat NASH/NAFALD.[43]

9C I n obese NASH patients undergoing bariatric surgeries, preoperative vitamin and mineral testing as well as post operatively at regular interval as surgical weight loss patients are at high risk of micronutrient deficiencies either due to primary or secondary malabsorption or inadequate dietary intake.[50,51]

- Obese NASH patients may have both preoperative micronutrient deficiencies due to obesity, (see Table 3) as well as due to primary or secondary malabsorption and reduced intake attributed to bariatric surgery[21,22]. Therefore, baseline along with follow-up lab assessment in surgical weight loss patients are of prime importance.[52]

Recommendation 10

10A In patients with chronic Cholestatic liver diseases, deficiencies of fat soluble vitamins are expected. Vitamin D, at least 800 IU/day should be considered to prevent bone loss.[53]

- Patients with chronic cholestatic liver diseases are predisposed to osteoporosis with double the risk as compared to healthy individuals, because fat soluble vitamin deficiencies[54] mainly Vitamin D are common in them that may lead to hepatic osteodystrophies. With a view of preventing bone loss, vitamin D at least 800 IU/day is advised.[55]

10B Patient with PBC should have their vitamin A levels checked, but in patients having vitamin A deficiency only those who have impaired dark adaptation should be advised vitamin A supplements in water soluble form along with zinc to increase absorption.[49]

- Vitamin A being hepatotoxic it's intake is advised to be decreased, however patients with advanced cholestic liver diseases suffering from night blindness, e.g. PBC patients on treatment with cholestyramine impairing vitamin A absorption may be considered for vitamin A supplementation with zinc and in its water-soluble form.[50,56]

Recommendation 11

11A In patients with cirrhosis micronutrient supplementations e. g. Water soluble vitamins particularly thiamine, fat soluble vitamins especially vitamin D and Trace elements mainly Zinc and Selenium should be treated in case of documented deficiency or when suspected clinically.[49]

- Cirrhotic patients have deficiencies of water-soluble and fat-soluble vitamins as well as trace elements. Thiamine deficiency is most common among water-soluble vitamins, Vitamin D, Zinc and selenium deficiencies in cirrhosis should be treated.[51]

11B Cirrhotic patients often have severe malnutrition which makes them vulnerable to refeeding syndrome as well as thiamine deficiency.[49]

- Prevalence of malnutrition including thiamine deficiency in cirrhosis is very high predisposing them to refeeding syndrome[43].
- Almost all patients had vitamin D deficiency who were on transplant list.[53] 25% patients on waitlist for liver transplant were having osteoporosis with approximately 12% having bone fractures. Post liver transplant impaired bone health is significant and multifactorial. Therefore to minimize bone loss both pre and post-transplant.[57]

Recommendation 12

Among patients on wait list for liver transplant, with decompensated cirrhosis, micronutri ent deficiencies particularly vitamin D deficiency is highly prevalent. Pre-transplant minimum 800 IU /day vitamin D should be advised to improve post-transplant outcome, while post-transplant at least 400 IU/day vitamin D is recommended.[53]

Pancreatic diseases

Acute and chronic pancreatitis impairs physiological digestive and absorptive functions through exocrine and endocrine insufficiency. Therefore, in both acute and chronic pancreatitis nutritional deficiencies prevalent, and they are multifactorial. As compared to acute pancreatitis, micronutrient deficiencies are higher due to malabsorption, diabetes and alcoholism. Micronutrient deficiencies increase with the increase in severity of steatorrhoea in chronic pancreatitis patient and this can lead to bone loss, debility and ophthalmic disorders.[49]

Table 3. Common deficiencies of micronutrients found in CP.[49]

Micronutrient	Mechanism
VitaminA, D, E, K	Exocrine insufficiency in lipid malabsorption (E>A, D, K) Due to Alcohol Anorexia
Vitamin B1, B2, B6, B12	Due to alcohol R-binder inability impairing B12 absorption
Zinc	Due to alcohol, decreased pancreatic exocrine stores

Recommendation 13

Micronutrient deficiencies should be anticipated in chronic pancreatitis patients. Management and adequate correction of micronutrient deficiencies especially fat-soluble vitamins and minerals are advised to prevent problems arising due to these deficiencies. Appropriate diet recommendations and pancreatic enzyme supplementations are equally important.

Conclusion

A micronutrient deficiency in gastrointestinal diseases is a huge topic beyond the scope of this chapter. Here we have tried to give general guidelines to help clinician make decision regarding specific micronutrient deficiencies and their implications in gastrointestinal diseases. This chapter has its aim of helping clinician to understand the role of micronutrients in GI diseases. However, it would be interesting to explore therapeutic aspects, toxicity of higher doses, interaction and absorption as well as limitations of micronutrient supplementation treatment. We hope that clinician will invariably include micronutrients in nutrition therapy.

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