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Reviews

Intestinal microbiota as a route for micronutrient bioavailability

Noushin Hadadi^{1,2}, Vincent Berweiler^{1,2}, Haiping Wang^{1,2} and Mirko Trajkovski^{1,2}**Abstract**

The deficiency of micronutrients, including vitamins and minerals, is estimated to affect two billion people worldwide and can have devastating immediate and long-term consequences. Major causes range from inadequate micronutrient consumption mostly owing to a lack of dietary diversity, to poor nutrient absorption in the gastrointestinal tract as a result of clinical or pathological conditions. Recent studies in model organisms and humans demonstrated that intestinal microbiota plays an important role in the *de novo* biosynthesis and bioavailability of several micronutrients and might be a major determinant of human micronutrient status. Here, we address the importance of the gut microbiome for maintaining the balance of host vitamins and minerals and explore its potential therapeutic benefits and implications on human health.

Addresses

¹ Department of Cell Physiology and Metabolism, Centre Médical Universitaire (CMU), Faculty of Medicine, University of Geneva, 1211 Geneva, Switzerland

² Diabetes Centre, Faculty of Medicine, University of Geneva, 1211 Geneva, Switzerland

Corresponding authors: Trajkovski, Mirko (mirko.trajkovski@unige.ch); Hadadi, Noushin (noushin.hadadi@unige.ch)

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Introduction

Vitamins and minerals, collectively termed micronutrients, are crucial for human health. These micronutrients are essential core regulators of fundamental biosynthetic cellular reactions such as immune, and energy functions [1], as well as growth, bone health, fluid balance, and other biological processes [2]. Micronutrient

deficiency is considered a global health issue, as it is associated with severe health problems, particularly in children where it leads to poor physical and mental development and increased susceptibility to pathogen infections, development of allergies, and inflammatory diseases. Deficiency of micronutrients, such as that of vitamin D, may contribute to disordered immune response, both in children and adults, resulting in a higher risk of autoimmune disease development [3,4]. Minerals, particularly zinc, play a critical role in B and T cell-dependent immune activities [5]. Moreover, multiple studies show shreds of evidence that micronutrient deficiency may contribute to the progression of some human cancers [6]. Micronutrients also modulate the abundance and diversity of the gut microbiota resulting in beneficial or detrimental outcomes to the host [7,8].

Humans cannot synthesize all required micronutrients, which therefore need to be acquired exogenously from the three major resources of (i) dietary components, (ii) oral supplements, or (iii) synthesis by commensal gut bacteria. As a large percentage of the population does not meet recommended intakes of micronutrients, oral supplementation of micronutrients and food fortification programs have been implemented worldwide. Despite their effectiveness and positive impacts [9], a considerable number of studies have recently raised serious concerns for the negative health consequences of certain micronutrient supplements. For example, it has been shown that iron supplementation in individuals with an iron overload disease, such as hemochromatosis, iron supplementation/fortification, can lead to iron overload and liver disease, increased abundance of inflammation-associated bacterial species, and markers in the intestine [10], as well as higher risks of intestinal disorders such as colorectal cancer [10,11]. Moreover, folic acid (vitamin B9) supplementation was associated with adverse health outcomes including zinc deficiency caused by impaired absorption in the intestine, neurological damage owing to its role in masking the signs of B12 (cobalamin) deficiency, and increased risk of colorectal cancer [12].

Micronutrient bioavailability is the fraction of a micronutrient that is available for use and storage in the body [13–15]. Micronutrients use various, and in some cases, specific absorption routes and mechanisms that can be both passive and active [16,17]. For example, absorption

of both vitamin C and vitamin B7 (biotin) is mediated by Na⁺-dependent carriers, and vitamin B9 (folate) uses three folate-specific carriers. On the other hand, absorption of vitamins A and D occurs by passive diffusion in the small intestine (Figure 1). However, detailed absorption mechanisms and involved carriers of many micronutrients pend further research [16].

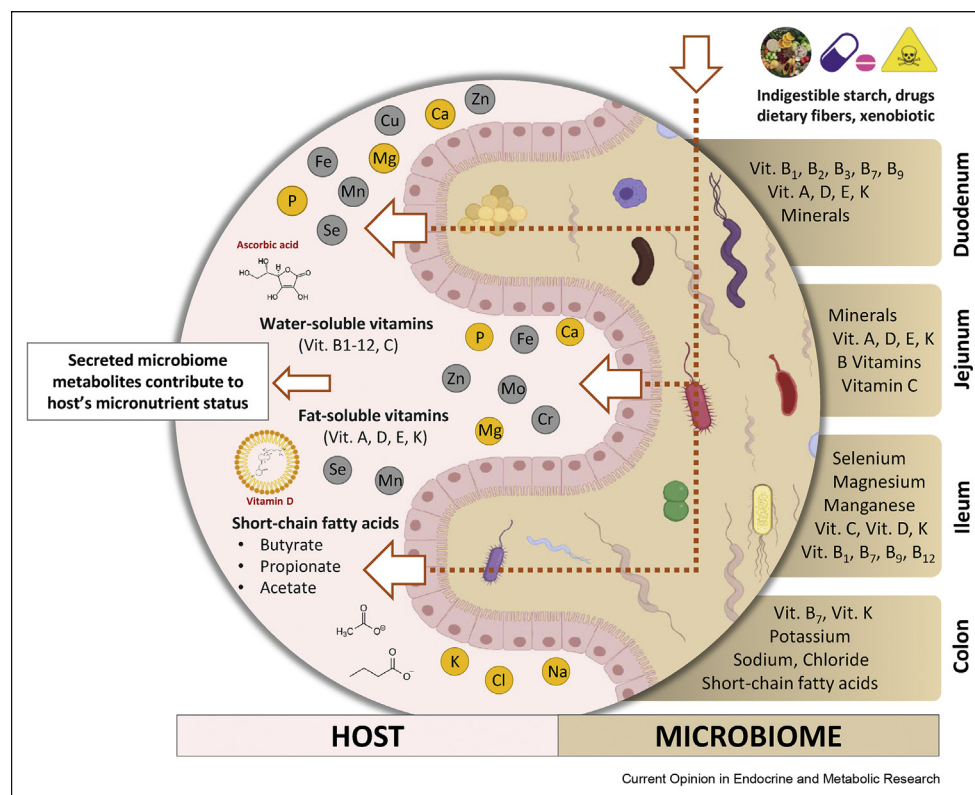
Commensal gut bacteria supply their host with essential nutrients and are the least explored resource for acquiring micronutrients. Gut microbiota is considered an effective bioreactor in the human intestinal tract, transforming various compounds into beneficial or harmful metabolites, thus having a crucial role in their bioavailability [18]. Although many efforts in microbiome research have been directed toward discovering effective means for modulating the microbiome to improve health, the contribution of gut microbes in the biosynthesis, uptake, absorption, and bioavailability of micronutrients remains less well studied. With the advances of metagenomics technologies in microbiome research, there has been an increasing interest in understanding the contribution of different bacteria to human micronutrient status. In this review, we primarily focus on the *in vivo*

studies and clinical trials addressing the association between bacterial classes/families with the host micronutrient balance, the microbiota role in biosynthesis and bioavailability of a given micronutrient, and the potential therapeutic benefits and implications of this interplay on human health.

Gut microbiota and micronutrients

The micronutrient–microbiome axis is bidirectional. On one hand, microbes in the gut are consumers of micronutrients for their growth and functioning. The host nutrition and micronutrient supplementation largely impact the gut microbiota composition and function (Figure 1). In particular, supplementation of vitamin A [19], vitamin C [20], vitamin B12 [21], and vitamin D [22] contribute to changes in the composition of the gut microbiota by promoting colonization of several beneficial species from the *Bifidobacterium*, *Lactobacillus*, and *Roseburia* genera. Assessing the effect of mineral deficiency or supplementation on the gut microbiota is an emerging field [23], and it has been shown that iron [24], calcium [25], zinc [26], and magnesium [27] supplementation modulate the gut microbiome (reviewed in the study by Yang et al. [8]).

Figure 1



Micronutrient interchange between the gut microbiota and host. Differences in the physicochemical properties of various sections of the gastrointestinal tract, together with the presence of site-specific receptors, enable absorption of different vitamins and minerals along the tract. The colonization of each different section by different microorganisms can impact the local environment and thereby positively or negatively influence the bioavailability of micronutrients.

On the other hand, the gut microbiota produces significant quantities of a wide range of vitamins, notably vitamin K and B group vitamins, and facilitates uptake and absorption of minerals such as iron and calcium. The Human Microbiome Project [28] provided high-resolution portrayal of the human gut microbiota, which enabled a wealth of *in vitro* studies evaluating the bacterial metabolic capabilities, including micronutrient biosynthesis, uptake, absorption, and secretion capabilities of some of the representative strains. Engevik et al. [29] assessed the folate (vitamin B9) biosynthesis capabilities of 512 gastrointestinal strains from six key phyla of the human microbiome (Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, Fusobacteria, and Verrucomicrobia) and found that only 13% of the investigated strains, all belonging to *Proteobacteria*, encompass the required genes for a complete *de novo* folate biosynthesis. Another 39% of the strains (mostly from *Firmicutes*, *Actinobacteria*, and *Verrucomicrobia*) had the partial genetic capacity to synthesize folates. This group of bacteria required pABA, a biosynthesis pathway intermediate that can be obtained from the diet or other intestinal microbes, to completely generate folate *de novo*. These findings suggest a close cooperation amongst intestinal microbes to provide the required folate for both the host and the microbiome metabolic activities. Another *in vitro* study by González et al. [30] addressed the mechanisms by which probiotic bacteria increase iron absorption in the host. Fe(III) must be reduced to Fe(II) to be properly absorbed in the gastrointestinal tract. The authors demonstrated that *Lactobacillus fermentum*, one of the main probiotics of the microbiota, exhibits a remarkably high ferric-reducing activity. They also found that excretion of p-hydroxyphenyllactic acid by *L. fermentum* results in increasing Fe(II) bioavailability and its uptake by enterocytes. These *in vitro* studies advance our understanding of the gut microbiota contributions to the overall host micronutrient status. Nevertheless, considering the complexity of the human gut microbiota and its metabolic interactions with the host, *in vivo* studies are essential for probiotics-based nutritional counseling aiming to improve the host micronutrient states. The *in vivo* studies investigating the microbiome–micronutrient axis are reviewed in the following sections.

Vitamins

Human gut commensals such as *Bacteroides*, *Enterococcus*, and *Bifidobacterium* can synthesize vitamin K and most water-soluble B-vitamins *de novo*. Magnúsdóttir et al. [31] systematically assessed the *in silico* biosynthetic capability of common human gut bacteria for the production of eight B-vitamins and showed that 40–65% of each of those vitamins was produced by the studied gut microbes. To be available to the host, however, the bacterial *de novo* synthesis of micronutrients must take place upstream of their dedicated intestinal absorption

zone. For example, because cobalamin is only absorbed in the ileum, B12-producing colonic bacteria will unlikely contribute to increasing the bioavailability of this vitamin for the host, except in the case of coprophagy seen in rodents and nonhuman primates [32]. Recent *in vivo* studies and clinical trials shed light on the role of microbiota in the host vitamin balance (Table 1). Using *C. elegans*, Maynard et al. [12] found that *Escherichia coli* assists the metabolism of vitamin B9 (folic acid) by increasing its bioavailability, through uptake of the breakdown product (PABA-glu), and via *de novo* synthesis of tetrahydrofolate, demonstrating that bacteria play an important role in the effective metabolism of micronutrients. In addition, *E. coli* acts as an indispensable conduit of vitamin B12 for the host, by scavenging exogenous vitamin B12 (cobalamine) through the tonB siderophore [12]. Several members of the Firmicutes phylum identified using 16S ribosomal RNA sequencing of human stool samples, such as Clostridia class, Clostridia order, and part of the *Ruminococcaceae*, *Coprococcus*, *Mogibacterium*, *Blautia* genera, were positively associated with the vitamin D levels in serum [33] (Table 1). Butyrate-producing bacteria were linked to an increased vitamin D receptor protein expression in a human cohort. This is in line with an earlier study in mice [34], which demonstrated a relationship between the vitamin D receptor and gut microbiota, important for maintaining intestinal homeostasis and for the pathophysiology of inflammatory bowel disease.

Microbiota can also be negatively associated with vitamin bioavailability. A recent mouse study [35] suggested an increased bioavailability of vitamin E after an antibiotic treatment, likely owing to increased absorption of vitamin E, or its decreased degradation by gut microbes after microbiota depletion. In contrast, Subramanian et al. [36] have shown that an increase in the circulating lipopolysaccharide, which is produced by the microbiota, inhibits sodium-dependent transport of ascorbic acid within the intestine, and in some cases, could lead to vitamin C deficiency by reducing its absorption.

Minerals

The gut microbiota affects the mineral metabolism by (i) directly influencing mineral absorption in the gastrointestinal (GI) tract during digestion and by (ii) producing an array of enzymes, which are exclusive for the colonic microbes and that help releasing minerals from foods [37]. Such are the bacterial phytases, which catalyze hydrolysis of the phytic acid found in many plant tissues, releasing useable forms of minerals such as calcium, magnesium, and phosphate [38].

In iron-deficient women, the gut microbiome is relatively depleted of genus *Lactobacilli* compared with

<i>In vivo</i> and clinical studies demonstrating association between the gut microbiota and host micronutrients.			
Vitamins	Studied in	Commensal bacteria	References
Vitamin B9 (folic acid) and vitamin B12 (cobalamin)	<i>C. elegans</i>	<i>Escherichia coli</i>	C. Maynard et al. (2020) [12]
Vitamin D	Humans	<i>Ruminococcus</i> genus <i>Coprococcus</i> genus <i>Mogibacterium</i> genus <i>Blautia</i> genus	R.L. Thomas et al. (2020) [33]
	Humans	<i>Lactobacillus reuteri</i>	M.L. Jones et al. (2013) [49]
	Mice	Colonic butyrate producers	S. Wu et al. (2015) [34]
Vitamin E	Mice	Antibiotic-mediated microbiota depletion	L. Ran et al. (2019) [35]
Vitamin C	Mice	Gram-negative bacteria overgrowth	V.S. Subramanian et al. (2018) [36]
Minerals			
Iron	Humans	<i>Lactobacillus plantarum</i>	N. Scheers et al. (2016) [40]
	Humans	<i>Lactobacilli</i> genus	R. Balamurugan et al. (2010) [39]
	<i>C. elegans</i>	<i>Escherichia coli</i>	B. Qi et al. (2018) [42] A K. Sewell (2018) [41]
Calcium	Rats	<i>Bacteroides</i> genus <i>Butyricoccus</i> genus <i>Oscillibacter</i> genus <i>Dialister</i> genus	C.M. Weaver (2015) [44]
	Humans	<i>Bifidobacterium lactis</i> <i>Lactobacillus acidophilus</i>	Z. Asemi et al. (2013) [46]
Phosphate	Broilers	<i>Enterococcus faecium</i> <i>Eubacterium</i> genera <i>Ruminococcaceae</i> genera	W. Wang et al. (2020) [47]

controls [39]. Although it is not clear whether less abundant *Lactobacilli* contribute to iron deficiency, or the iron deficiency instead results in reduction of the *Lactobacilli* genus, further studies in humans demonstrated that *Lactobacillus plantarum* increases the amount of hydrated ferric iron Fe(III) via lactic fermentation, which leads to enhanced iron absorption [40]. Moreover, two studies conducted in *C. elegans* showed that secretion of the bacterially produced siderophore enterobactin facilitates host uptake of iron by promoting mitochondrial iron uptake [41,42]. This finding introduced an unexpected benefit from commensal bacteria to the host by uncovering a distinct beneficial role of a bacteria-generated molecule in promoting the host's iron homeostasis.

The dynamic relationship between the gut microbiota and mineral bioavailability is well illustrated in the bone field. Increased vitamin D intake can enhance the calcium active absorption, in part mediated by vitamin D-regulated calcium-binding proteins, calbindin D9k [43]. However, under conditions of low calcium intake, microbiota plays an important role in calcium bioavailability. Weaver et al. [44] showed that prebiotics, which alter the gut microbiome in genera known to enhance short-chain fatty acid production (such as *Bifidobacteria*, *Lactobacilli*, *Eubacterium*, and others), correlated with increased calcium absorption (in humans and animal

models) and bone density and strength (animal models) (Table 1). Mineo et al. [45] showed an increase in the production of short-chain fatty acids and organic acids by dietary fiber fermenters, resulting in a decrease of the cecal pH. This in turn led to solubilization of calcium and increase in its passive absorption in the large intestine of rats. Similarly, Asemi et al. [46] found that consumption of probiotic yogurt containing *Bifidobacterium lactis* and *Lactobacillus acidophilus* in pregnant women resulted in maintaining serum calcium levels compared with subjects consuming conventional yogurt. Wang et al. [47] also showed that *Enterococcus faecium* treatment increases the mRNA expression of the IIb sodium-dependent phosphate cotransporter (NaP-IIb) and enhances bone's phosphate content. *E. faecium* supplementation also induced changes in the microbiota by promoting development of butyrate producers from the genus *Eubacterium* and family *Ruminococcaceae*. Although this is in line with several other studies demonstrating the microbiota importance in preventing bone loss [23,48], it further demonstrates that microbiota may regulate bone via various mechanisms, including micronutrient bioavailability.

Gut microbiota as sustainable therapeutic targets for improving host micronutrient status

The composition of the human gut microbiome largely contributes to the host's micronutrient status. The

forementioned studies demonstrate that several micronutrient deficiencies could be positively or negatively associated with gut microbiota. Therefore, an alternative solution for increasing the micronutrient bioavailability could be applied by correcting the microbiome (in the case of the pathologic role of gut microbiota) or by promoting a specific microbiome (in the case of the positive contribution of gut microbiota), thereby addressing the underlying cause of the problem rather than its symptoms. Further research should explore the actions of specific bacterial species and their effects on improving or preventing micronutrient deficiency.

Similarly, a better understanding of the underlying mechanisms by which intestinal microbiota impacts host micronutrient uptake and absorption would enable postbiotic approaches for tailoring the micronutrient availability relative to the host demands. In this light, it would be interesting to assess how endogenous bacterially derived micronutrients contribute to the host micronutrient status compared to exogenous micronutrients provided by the diet and supplementations. Such studies would help in developing physiological and effective interventions against micronutrient deficiency.

Conflict of interest statement

Nothing declared.

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