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Gut microbiota and vitamin status in persons with obesity: a key interplay.

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Conflict of interest

The authors have no conflict of interest.

Abstract

There are numerous factors involved in obesity progression and maintenance including systemic low-grade inflammation, adipose tissue dysfunction or gut microbiota dysbiosis. Recently, a growing interest has arisen for vitamins' role in obesity and related disorders, both at the host and gut bacterial level. Indeed, vitamins are provided mostly by food but some, from the B and K groups in particular, can be synthesized by the gut bacterial ecosystem and absorbed in the colon. Knowing that vitamin deficiency can alter many important cellular functions and lead to serious health issues, it is important to carefully monitor the vitamin status of patients with obesity and potentially already existing comorbidities as well as dysbiotic gut microbiota and thus potentially altered bacterial metabolism of vitamins. In this review, we examined both murine and human studies, to assess the prevalence of sub-optimal levels of several vitamins in obesity and metabolic alterations. This review also examines the relationship between vitamins and the gut microbiota in terms of vitamin production and the modulation of the gut bacterial ecosystem in conditions of vitamin shortage or supplementation. Furthermore, some strategies to improve vitamin status of patients with severe obesity are proposed within this review.

Key words: biotin, gut microbiota, micronutrients, obesity, vitamins

Introduction

Obesity represents a global health issue with an ever-increasing prevalence over the last 50 years[1,2]. It is expected that over 40% of the world's population will suffer from obesity by 2030[3]. Obesity is associated with several complications such as type 2 diabetes, cardiovascular diseases and cancers[4]. Triggered by multiple environmental factors, the development and progression of obesity are characterized by organ structural and biological alterations and systemic low-grade inflammation. Recently, the gut microbiota (GM) has emerged as a contributive "organ" in the development and maintenance of obesity.

The GM is a complex and abundant ecosystem composed of trillions of microorganisms including bacteria, viruses, archaea, fungi, and phages. The microorganisms present within the gut harbor a myriad of functions, and in particular, the GM is implicated in the fermentation of non-digestible food substrates. This microbial metabolism leads to the production of an important variety of metabolites, which in return are known to have a broad range of bioactivities, including immune modulation and intestinal barrier homeostasis. During obesity, an imbalance in the GM composition, functionality, as well as a decreased bacterial richness and diversity, collectively referred to as GM dysbiosis, have been reported by many studies[5].

Among the numerous GM-derived metabolites (as short chain fatty acids, secondary bile acid molecules, tryptophan derivates to cite only a few), vitamins have been relatively neglected in this context. Yet, gut bacteria are known to produce vitamins from the B and K groups[6]. Vitamins are essential micronutrients, obtained from food and, to some extent, from gut bacterial synthesis. Vitamins serve as coenzymes or cofactors for numerous processes involved in host energy metabolism[7] (Table 1). For example, B vitamins play a key role in maintaining mitochondrial energy metabolism, which is altered by inadequate levels of any of

77 those vitamins[8] (Table 1). Vitamin deficiency, due to an imbalanced diet, increased host
78 physiological requirements or altered drug-micronutrient interactions, affects host health in
79 varying ways and can lead to severe clinical consequences, ranging from fatigue to
80 dermatological, digestive, cardiovascular or neurological and depressive disorders[9] (Table 1).
81 Dietary vitamin absorption occurs mainly in the small intestine for the dietary vitamins but it
82 is now acknowledged that the distal gut may also contribute to vitamin absorption and
83 especially bacterially-produced vitamins[10]. Thus, the alteration of the intestinal environment
84 and absorptive capacities potentially alters vitamins host vitamin status.

85 Despite increasing evidence of deep alterations of gut physiology as well as microbiota
86 composition and functionality observed during obesity and metabolic disorders, the
87 consequences on vitamins biosynthesis and availability have scarcely been studied. Herein,
88 we review vitamin status alterations observed in obesity and metabolic disorders and focus
89 on the production potential of vitamins by the GM as well as its modulation by both vitamin
90 supplementation and deficiency, mostly focusing on B and D vitamins. We also discuss some
91 future strategies for vitamin status management in severe obesity.

92

93 **Evidence of vitamin deficiency in obesity and related metabolic disorders in humans**

94

95 The optimal vitamin reference levels for the general population are reported by
96 national or international expert committees such as the European Food Safety Authority
97 (EFSA)[11] or the US Centers for Disease and Prevention through the National Health and
98 Nutrition Examination Survey (NHANES). Lately, an increasing interest for vitamin status in
99 subjects with obesity has arisen as many studies have revealed that obesity and related

100 metabolic complications are associated with deficiencies or at least sub-optimal blood
101 concentrations of many vitamins, which has been well-reviewed recently[12,13].

102 Briefly, a series of studies exploring different populations with metabolic alterations
103 revealed suboptimal blood level of B vitamins, including vitamin B1 (thiamine), B9 (folate), B6
104 (pyridoxine), B12 (cobalamin). A decrease of vitamin B9 has been observed in pregnant
105 women with overweight in comparison to women with a BMI ranging between 18 and 25
106 kg/m² [14]. Similarly, another study on patients with severe obesity reported an important
107 decrease of vitamin B6 serum concentrations as compared to patients without obesity[15].
108 Moreover, up to 75% patients with type 2 diabetes presented low blood concentration of
109 vitamin B1[16]. Vitamin B12 levels have also been linked with obesity with a significant negative
110 correlation reported between body mass index (BMI) and vitamin B12 blood levels in a cohort
111 of almost 1000 patients with obesity[17]. Moreover, the authors of this study also found a trend
112 toward decreased vitamin B12 blood concentrations in subjects with insulin resistance or
113 metabolic syndrome in comparison to participants without metabolic alterations[17]. In another
114 cohort of participants with overweight or obesity, 13% of participants were found to be
115 deficient in vitamin B12 [18] while in the general US population, the prevalence of vitamin B12
116 was found to be around 5% and increases with age[19]. Interestingly, the serum levels of vitamin
117 B12 are increased after a weight loss induced by a Low Energy Diet (LED)[18]. Another B vitamin,
118 vitamin B7 (biotin) has been shown to be decreased in subjects with moderate obesity[20] and
119 type 2 diabetes[21]. Yet, this vitamin has been neglected in the context of obesity and metabolic
120 disorders; as well as other B vitamins such as vitamins B2 (riboflavin), B3 (niacin).

121 Vitamin deficiency in metabolic disorders extends to vitamin D as well. In Geiker et al.,
122 insufficient levels of vitamin D were observed in 72% of the participants before the LED-
123 induced weight loss, and again, the serum concentration of vitamin D was increased after the

124 nutritional intervention[18]. Unlike B vitamins, the links between vitamin D status and obesity
125 and its complications have been investigated in a larger number of studies and were reported
126 as early as 1985[22]. It has been commonly accepted that vitamin D deficiency can be estimated
127 via the serum concentration of the vitamin D metabolite, 25-hydroxycholecalciferol
128 [25(OH)D], the active form of vitamin D, which integrates both the dietary intake and the
129 endogenous production. For example, analyses in a large population of older individuals
130 revealed a significant inverse association between BMI and more specifically adiposity
131 (especially in the 3rd and 4th quartile when fat percentage was divided in quartiles) and serum
132 25(OH)D concentrations[23]. Moreover, several groups also showed inverse correlations
133 between 25(OH)D serum concentrations and markers of metabolic alterations such as
134 triglycerides[24] or fasting glucose and the HOMA-IR index, a surrogate marker of insulin
135 resistance[25]. An observational transversal study including 73 patients with morbid obesity
136 confirmed the higher prevalence of vitamin D deficiency in comparison to the population
137 without obesity[24]. Here, they found that 50.7% of the participants had vitamin D deficiency.
138 They also reported an increased prevalence of vitamin D deficiency associated with the
139 occurrence of metabolic syndrome in this population. This correlation was confirmed in a large
140 study of over 2 500 Chinese men and women, in which, lower 25(OH)D serum concentration
141 was associated with increased insulin resistance among the participants with overweight or
142 obesity [26]. Finally, a recent meta-analysis of 43 studies confirmed this inverse association
143 between serum concentration of vitamin D and risk of metabolic syndrome in the general
144 adult population[27]. In animals, vitamin D deficiency associates with worsened obesity
145 condition, glucose intolerance and insulin resistance induced by a high-fat diet whereas no
146 such effect for animals experimenting vitamin D deficiency under standard diet were
147 observed[28]. Thus, it seems that inadequate levels of vitamin D in the context of obesity could

148 worsen the individual metabolic health. Low levels of vitamin D are not only linked with
149 different health conditions such as loss of bone density but also diabetes, high blood pressure,
150 or multiple sclerosis. It also appears that vitamin D deficiency can impede bariatric surgery-
151 induced metabolic improvements. Interestingly, in a mouse model of vertical sleeve
152 gastrectomy, deficient levels of vitamin D were linked with decreased weight loss and glucose
153 homeostasis improvements, as well as intestinal inflammation and permeability [29]. In addition
154 to those metabolic observations regarding vitamin D, many studies also reported strong links
155 of this vitamin with adipose tissue in terms of vitamin D storage but also modulation of
156 adipocyte differentiation or even energy metabolism and inflammation by this vitamin. These
157 aspects have been largely and well-reviewed recently[30].
158
159 **Alteration of vitamin status in the context of bariatric surgery**
160 Vitamin deficiency in obesity has also been investigated in subjects with severe obesity
161 undergoing bariatric surgery. For example, studies showed that the prevalence of vitamin B1
162 deficiency in patients with severe obesity before bariatric surgery is between 15.5% [31] and
163 29% [32]. In the general population, vitamin B1 deficiency is associated with inadequate intake
164 and is more prevalent in underdeveloped countries whereas in industrialized countries,
165 vitamin B1 deficiency is rare and mostly related to alcoholism[33]. Vitamin B9 has also been
166 found to be decreased in patients with severe obesity before the surgery at a rate of 63.2% [34],
167 a much higher percentage in comparison to the general population prevalence of 2% reported
168 by a recent study in the US[35]. Importantly, these studies focused on bariatric surgery
169 candidates who follow weight-loss efforts for several months before the procedures, as
170 recommended by international guidelines[36]. As such, these patients may have reduced
171 vitamin intake due to changes in their diet. Flancbaum and colleagues also revealed a high

proportion (68%) of patients presenting with a vitamin D deficiency before the surgery, which was confirmed in two other cohorts with deficiency rates of 74.35% [37] and 76% [38]. In comparison, a study of vitamin D blood concentrations in elderly people across 11 European countries reported a prevalence of vitamin D deficiency in 36% of men and 42 % of women in the general population[39]. This percentage was even lower in the US population with a prevalence of vitamin D deficiency of 4.0% and 17.4% for inadequacy[40]. To note, vitamin D blood concentration is dependent on the season as well as geographical location, which could explain such discrepancies between prevalence in different populations and studies. The two latter studies investigating vitamin D blood concentrations also reported vitamin B12 deficiency in those patients, reaching 12.3%[37] and 16%[38] respectively.

Moreover, most vitamins are absorbed in the small intestine, a segment bypassed after malabsorptive procedures (e.g., Roux-en-Y Gastric Bypass or biliopancreatic derivation). This purposefully-induced malabsorption further deteriorates vitamin status after the surgical procedure, which may not normalize despite systematic vitamin supplementation. During surgical follow-up, monitoring patients' vitamin status should be reinforced, which is highlighted by studies of micronutrient deficiencies after Roux-en-Y gastric bypass as well as sleeve gastrectomy[41,42]. In fact, despite medical recommendation of micronutrients and especially multivitamins supplementation after the surgery, evidence of decreased compliance has been reported after 10 years of follow-up increasing the risk of vitamin deficiency[43]. It is also possible that the optimization of the pre-operative vitamin status could also contribute to better outcomes of the surgery. It has been suggested that vitamin D could, for example, contribute to improved weight loss following bariatric surgery[44]. A recent review addressed this concern in terms of vitamin status and the physiological, metabolic and also bacterial changes associated with bariatric surgery [45]. More attention should be given to

196 vitamin status of patients before and after the bariatric surgery as suggested by recent
197 guidelines published by the British Obesity and Metabolic Surgery Society[46]. The
198 aforementioned studies suggest that acting on the pre-intervention vitamin deficiency might
199 help potentialize metabolic improvement, although more clinical interventions ought to be
200 performed to confirm this hypothesis.
201
202 **Gut microbiota; a source of vitamin production**
203 The composition of the GM has now been meticulously studied over the last decade
204 thanks to major advances in sequencing technologies. Nevertheless, a recent shift towards
205 understanding the functionality of the ecosystem allows for more complete comprehension
206 of how GM modulations are involved in health and diseases. Gut bacteria produce a very large
207 number of metabolites having an impact on the host metabolism[47]. The gut bacteria can
208 produce vitamin K and B vitamins[48]; however the interest for the study of the relationship
209 between GM and vitamin metabolism is only recent and increasing.
210
211 The number of available bacterial genomes increased significantly with the advances
212 in sequencing technologies and metagenomic processing methods, which have allowed for
213 better characterization of GM species and their metabolic capabilities. In 2015, Magnúsdóttir
214 et al., used the PubSEED platform, which provides genome annotations across thousands of
215 genomes, to analyze the ability of human GM organisms to synthesize B vitamins [49]. Thus, they
216 were able to determine that the biosynthesis of B vitamins was common among the species
217 found in the human GM. They also predicted B vitamin synthesis abilities that matched
218 published experimental data. It appears that the synthesis of vitamin B2 and vitamin B3 were
219 most commonly found among all the genomes assessed. Altogether, this study reinforces the

idea that the GM, as an ecosystem, is able to produce vitamins and possibly participates to vitamin homeostasis of the host. Yet, this paper revealed that the production of vitamins by the GM is not sufficient to cover host daily requirements. Moreover, the vitamins synthesized in the gut mostly benefit the neighboring non-producing bacteria through cross-feeding between organisms. To this end, bacterial genome analyses have illustrated that bacterial species can be vitamin prototrophs (capable of *de novo* synthesis) or auxotrophs (dependent on the uptake and salvage of vitamins) highlighting the importance of cross-feeding between GM species[50].

Further evidence of GM mutualism for vitamins comes from co-culture *in vitro* experiments showing that *Anaerobutyricum halii* is able to synthesize and provide *Akkermansia muciniphila* with B12 vitamin, which is used for propionate production[51]. Such cross-feeding mechanisms have also been observed *in vivo,* where non-producing bacteria survive during limitation of vitamin intake suggesting the existence of vitamin sharing between producing and non-producing bacteria[52]. Bacterial mutualism thus contributes to maintaining a relative GM stability thanks to the sharing of micronutrient resources in case of shortage or level modulation due to vitamin intake variability[52]. Noteworthy *Anaerobutyricum halii* and *Akkermansia muciniphila* are both commensal bacteria associated with improved metabolism[53,54].

Together with experimental work, the access to genomic annotation allowed for the identification of specific vitamin producing bacterial strains. It is now known for example, that species from the genera *Lactobacillus* and *Bifidobacterium* can produce vitamin B9. Indeed, both *in vitro* and *in vivo* experiments demonstrated that Bifidobacterial strains are able to increase the vitamin B9 concentration either in the medium or of the host [55,56]. This ability of vitamin B9 production by *Lactobacillus* and *Bifidobacterium* was assessed via the analysis of

genome sequences. The presence of genes and enzymes involved in different steps of the vitamin B9 production pathway allowed to infer theoretical capacity of the studied strains to produce this vitamin at least from a precursor molecule[57]. Nevertheless, it is important to note that the presence of genes involved in the production of a vitamin does not account for its effective production by the bacteria. Thus, experimental validation (*in vitro* and *in vivo)* remains crucial to identify potential vitamin-producing strains that could then be developed as probiotics.

To explore the contribution of GM's vitamin synthesis, in various diseases including metabolic diseases, *in* vivo experiments are needed. Germ-Free (GF) rodents are an initial model used to determine the general contribution of the GM to metabolic pathways or host physiology. In the absence of GM in GF mice, a systemic deficiency in different vitamins was reported[58,59], suggesting again that those vitamins can be produced by the GM and that microbial vitamin production contributes, at least partially, to vitamin homeostasis of the host. Among those vitamins, earlier studies showed that GF rats developed spontaneously a vitamin K deficiency leading to increased mortality of the animals[58]. The side effects of vitamin K deficiency were corrected by vitamin K1 supplementation and most interestingly with the gut colonization of single strains of bacteria (*Escherichia coli* or *Sarcina-like micrococcus*). Similar results have been found for B vitamins as rats fed a diet deprived of B vitamins stopped growing after 1 to 3 weeks and died prematurely [59]. Yet, in this early study, one rat behaved differently and recovered from the deficiency. When its feces were added to the diet of another group of rats fed the same diet, the symptoms of vitamin B deficiency disappeared in those animals, suggesting that B vitamin-producing bacteria could be present in the feces these rats were given.

Other evidence of B vitamin production by intestinal microorganisms have been reported. The total output of vitamin B7 measured in feces and urine has been shown to be six times greater than the intake in humans, suggesting a production by the GM [60,61] while this needs further exploration. Interestingly, vitamin B7 deficiency induced alopecia only in GF animals and not in conventionally raised animals suggesting that the GM contributes to this vitamin metabolism[62]. A similar phenotype was observed in vitamin B7-deficient mice treated with an antibiotic, vancomycin, again suggesting a contribution of GM to vitamin B7 production. Moreover, those animals presented further reduction in bacterial diversity as well as major increase of *Lactobacillus* genus and in particular *Lactobacillus murinus* in comparison to antibiotic treated animals receiving sufficient levels of vitamin B7. Regarding other B vitamins, GM depletion via antibiotic treatment resulted in a decrease of vitamin B6 levels in colonic content in mice [63].

These observations all identify the GM as a major contributor to the host's vitamin status. Nevertheless, the contribution of the GM's vitamin production to host vitamin circulating levels remains to be experimentally established, in healthy and disease conditions. Indeed, in the context of obesity, alteration in GM richness, diversity and functional anomalies have repeatedly been reported[47,64–66]. Whether these alterations are linked to deficient bacterial vitamin metabolism and production need to be investigated in depth.

Consequence of vitamin deficiencies on GM composition

As raised above, the production of vitamin K by the GM has been known for several decades; but the effect of its deficiency on the GM composition has been studied very recently. Thus, mice fed a vitamin K deficient diet displayed reduced abundance of

290 *Lactobacillus* and enrichment in *Ruminococcus, Anaerostipes* genera as well as
291 *Muribaculaceae* family in comparison to animals supplemented with vitamin K [67].
292
293 A murine study investigating the effect of different micronutrient-deficient (vitamin A,
294 vitamin B9, iron, zinc, or multiple deficiencies) diet on the GM revealed that the vitamin A
295 deficiency had the higher impact[68], although vitamin A is not produced by the GM. The analysis
296 of the GM of mice fed a vitamin A deficient diet revealed an increase of *Bacteroides vulgatus*
297 and an increase of *Bacteroides dorei.* Once the deficiency was corrected via a micronutrient
298 sufficient supplementation of the diet, the initial levels of those bacteria were also restored.
299 In a human study investigating the GM children with vitamin A deficiency, changes in the
300 bacterial community composition were also reported[69]. Increased abundances of *Blautia* and
301 *Faecalibacterium* genera and decreased abundances of *Bifidobacterium, Bacteroides* and
302 *Shigella* were observed in these children. The modulations of *Bifidobacterium* and *Bacteroides*
303 levels were even transmitted via fecal microbiota transfer of the children's feces into germ-
304 free animals. At the phylum level, a decrease of *Bacteroidetes* was observed in mice fed a
305 vitamin A-deficient diet [70]. This decrease is associated with an increase of the
306 *Firmicutes/Bacteroidetes* ratio in those animals, which has been reported associated with
307 obesity and metabolic alterations[71], despite discrepancies in recent studies[72,73]. To be noted,
308 in this study, vitamin A-deficient animals presented characteristics of pre-diabetes with
309 hyperglycemia and delayed response to insulin injection, emphasizing the potential links with
310 metabolic alterations.
311
312 In the last decade, there has been an increasing number of studies investigating the
313 links between vitamin D and the GM. One of them investigated the factors explaining the most

the variance in alpha-diversity of the human GM, and found that the serum concentration of $1,25(OH)_2D$ was the most contributing variable, explaining 5% of the variance of the alpha-diversity[74]. In terms of specific compositional changes associated with vitamin D deficiency, it seems that vitamin D deficiency (in models of knock-out mice for the vitamin D receptor (VDR), not able to produce $1,25(OH)_2D$) appeared to be associated with a decrease of the abundance of the phylum *Firmicutes*[75] and the associated families *Ruminococcaceae, Lachnospiraceae, Lactobacillaceae* and *Streptococcaceae*. Interestingly, in another study on VDR KO mice, a significant decrease of the abundance of the genus *Lactobacillus* was observed in comparison to wild-type animals [76]. In a human trial on older men, a positive association was also found between serum $1,25(OH)_2D$ levels and the abundance of the genus *Ruminococcus* [74]. On the contrary, vitamin D deficiency seems to be associated with an increase in *Bacteroidetes* and *Proteobacteria* phyla, and more precisely *Bacteroidaceae* and *Desulfovibrionaceae* families [75]. This increase was again confirmed in the study from Jin and colleagues, in which an increase in the genus *Bacteroides* was noticed in VDR KO animals[76]. In the murine study by Zhang *et al*., investigating the effect of vitamin D deficiency on the metabolic improvements after vertical sleeve gastrectomy, they also analyzed the effects on the GM composition. The authors revealed that, despite known beneficial effects induced by the surgery itself, deficient levels of vitamin D were associated with limited improvements of the gut dysbiosis induced by the high-fat diet feeding. Indeed, the effects of the surgery, a decrease of *Firmicutes* and an increase of *Bacteroidetes* phyla abundance, were weaker in the group of vitamin-D-deficient animals post-surgery in comparison to the group with normal levels of vitamin D[29].

The effect of B vitamins deficiency on the GM has also been recently studied in the context of metabolic diseases. In a recent study, the effects of low B6 vitamin levels on host phenotype and GM of weaning rats was explored[77]. The animals receiving a standard chow

diet with low levels of vitamin B6 displayed a decreased body weight and circulating triglycerides levels compared to control animals as well as changes in the GM composition. Indeed, an increase in *Lachnospiraceae* and a decrease of *Bacteroides* were observed in both male and female rats.

In patients with obesity, an association was found between low niacin (vitamin B3) intake and reduced alpha-diversity as well as levels of Bacteroidetes. These findings were particularly significant in subjects with obesity and insulin-resistance but not with overt type 2 diabetes[78]. The authors suggested that in patients with type 2 diabetes, medications such as metformin known to modulate the GM[79,80] should be taken into account to explain those differences.

These collective findings illustrate the need to investigate the interplay between GM, vitamin and host metabolism. Yet, few studies investigated the effects of vitamin deprivation on the GM composition in the context of obesity and metabolic disorders. Considering the links between obesity, GM dysbiosis and alteration of vitamin status as presented above, it is important to study these factors to decipher the mechanisms involved.

Effect of vitamin supplementation on GM

Recent interest regarding the effect of vitamin supplementation on the composition of the GM has led to an increase of publications on this topic. A recent review extensively summarized the effects of vitamins and other dietary micronutrients such as polyphenols and minerals on the composition of the GM[81]. Although no clear patterns of GM modulation can be identified from this review due to a relatively low number of studies for some vitamins and

a great variability in experimental designs, it seems that vitamin supplementation can induce significant changes in GM composition.

In the context of obesity, the establishment of multiple large cohorts in the last decade has allowed the collection of important data sets of microbiome analysis, clinical and lifestyle information. Data from the American Gut Project were used to assess the impact of vitamin B and/or D supplementation on the GM in groups of people with normal weight (NW) or overweight (OW) [82]. Despite no significant impact on alpha-diversity indexes in all groups, the vitamin supplementation alone had almost no effect in NW group but had beneficial impact in OW. Noteworthy, vitamin B supplementation induced a significant decrease in *Tenericutes* at the phylum level and several groups at the family level (*Mogibacteriaceae, Porphyromonadaceae, Coriobacteriaceae* and *Comamonadaceae*). All these bacterial families have been associated with infections, inflammation and even obesity in the literature, suggesting that vitamin B supplementation in the context of obesity could help decrease the abundance of pathogens in the GM[83–86]. Regarding vitamin D supplementation, effects on the GM composition were observed both in the NW and OW groups. In NW group, it induced a decrease of several families *Erysipelotrichaceae*, *Turicibacteraceae* and *Bifidobacteriaceae*. The same effect on this last beneficial family was observed among OW participants, as well as a decrease of pathogens (*Actinomycetaceae*) for this group. The effects of a combined vitamin B and D supplementation was also investigated and showed a decrease of *Lachnospiraceae* and *Enterobacteriaceae*, which have been shown to be associated with obesity and production of endotoxins respectively[87,88].

Vitamin supplements, and in particular vitamin D, also had an important impact on the functionality of the GM[82]. In NW groups, there was a decrease in genes implicated in amino-acids biosynthesis and an increase of vitamin biosynthesis (related to vitamin B1 and B5) in

385 the GM of people supplemented with vitamin D. Those pathways were not impacted by
386 vitamin D in the OW group. Here again, the association of the two vitamins had specific effect
387 regarding the functional machinery of bacteria. The authors observed a decrease in the
388 potential of amino acid consumption by GM and of the degradation of polysaccharides in the
389 OW group. This paper supports the beneficial effects of vitamin D (alone or combined with
390 vitamin B) on microbial communities in a context of overweight or obesity, although effects
391 vary according to the severity of obesity.

392 Another recent trial of vitamin D supplementation over 16 weeks in overweight and
393 patients with obesity showed modulation of the GM composition[89]. Despite no effect on
394 alpha-diversity, vitamin D supplementation was associated with an increase of *Lachnospira*
395 genus and a decrease of the abundance of *Blautia* genus in comparison to the group receiving
396 placebo. Moreover, the authors observed a significant correlation between serum levels of
397 25(OH)D and the abundance of *Coprococcus* genus. Yet, these studies remain quite small in
398 size as only 17 people received vitamin D supplementation and 15 received the placebo in the
399 Naderpoor study[89]. In the study from Jiang and colleagues, the groups of people with
400 overweight supplemented with only vitamin D, or only vitamin B, or both vitamins comprised
401 respectively 88, 16 and 214 individuals, and supplementation was based on dietary
402 supplement intakes self-reported by patients [82].

403 In a murine study of weaning male C57BL/6J, the effect of vitamin A supplementation
404 in condition of standard chow diet (CD) or high fat high sugar diet (HFSD) was studied [90].
405 Vitamin A was administered in the form of retinol, directly incorporated to the diet. After 9
406 weeks of follow-up, the supplementation with vitamin A (+VitA) limited HFSD-induced fat
407 mass gain but was not able to reverse metabolic alterations induced by the diet. At the GM
408 level, this study revealed that retinol supplementation prevented most of the compositional

changes induced by HFSD. First, vitamin A supplementation protected against the decrease of alpha-diversity induced by HFSD, as HFSD+VitA animals had alpha-diversity values to the level of the CD group. In CD groups, a decrease of alpha-diversity was observed in the vitamin A supplemented group, to the surprise of the authors. Second, HFSD-feeding led to a decrease of *Porphyromonadaceae* and *Mycoplasmataceae* and an increase of *Family XIII* in comparison to CD group. All these changes were prevented by administration of vitamin A, which in addition increased the abundance of *Lachnospiraceae*.

These studies reinforce the links between vitamins and GM as oral vitamin supplementation is reported to induce modifications of the GM composition.

Future strategies of vitamin status management in obesity

Knowing the alteration of vitamin status in some patients with obesity, the obesity-associated dysbiosis and relationships observed between GM and vitamin metabolism, several strategies can be considered to optimize vitamin levels subjects with obesity.

Whereas obesity is often considered as a disease characterized by over-nutrition, it is also well recognized that there are issues of malnutrition, explaining at least partially inadequate vitamin intakes observed during obesity. Thus, a well-balanced and micronutrient-sufficient diet could help prevent deficiencies in some cases. In case of deficiency or sub-optimal levels, the oral vitamin supplementation also seems rational to rescue the host's vitamin status. However, most vitamins are absorbed in the small intestine and only small amounts of dietary intake reach the colonic bacterial ecosystem. Yet, as summarized in this review, many studies showed that vitamins can modulate the distal GM composition and have even been included in the definition of prebiotics by the International Scientific Association

433 for Probiotics and Prebiotics (ISAPP) in 2016. Thus, delivery tools allowing for oral vitamin
434 supplementation specifically targeting the colon might be useful. A recent control trial
435 investigated such systems to administer several vitamins (vitamin C, B2, E, D and A) in 96
436 healthy volunteers and revealed modifications of the microbial composition and metabolic
437 activity such as an increased of bacterial diversity and fecal short-chain fatty acids[91]. At the
438 species level, the authors observed an increase in *Bifidobacterium longum* and
439 *Anaerobutyricum hallii,* both studied for their beneficial effects in several health conditions[91].
440 Similar studies in patients with severe obesity would be helpful to further investigate the
441 effects of vitamin supplementation in this context, also taking into account the potential risk
442 of over-dosing vitamin supplementation.

443 Probiotic supplementation of strains known to produce vitamins can also be a strategy
444 to rescue vitamin bacterial metabolism, altered in obesity. As reviewed by LeBlanc and
445 colleagues, it has been demonstrated that specific bacterial strains are able to produce
446 vitamins. For example, *Lactobacillus rhamnosus* GG can produce three B vitamins in culture
447 medium which are vitamin B1, B2 and B9 [92]. *Bifidobacterium adolescentis* DSM 1835O [93] has
448 been shown to increase vitamin B9 fecal levels in humans. For such a strategy, it is important
449 to identify strains capable of complete *de novo* synthesis. As proposed by Engevik and
450 colleagues, an alternative could be to rely on cross-feeding, mentioned above, and construct
451 probiotic combinations of strains depending on one another for the production of
452 intermediates involved in the vitamin synthesis[94]. It would be thus of interest to investigate
453 how the host can benefit from these bacterial cross-talks. Yet, the long-term engraftment of
454 probiotics remains a challenge for long-term therapeutic perspectives.

455 Prebiotics can influence the growth and metabolism of specific gut bacteria, thus, their
456 use to promote bacterial vitamin production could also be envisaged. A recent *in silico* study

457 reported that inulin and short-chain fructo-oligosaccharides supplementation could increase
458 the production of an intermediate of the vitamin D biosynthesis pathway[95] . This effect seems
459 to be mediated by the secretion of short-chain fatty acids induced by the prebiotic
460 supplementation. The authors thus suggest that prebiotic supplementation could help
461 decrease vitamin D deficiency linked to insufficiency of this intermediate in this study.
462 Appropriate *in vivo* and clinical studies should be designed to confirm the potential use
463 of these strategies in vitamin status management in severe obesity.
464
465 **Conclusion**
466 Increasing evidence of sub-optimal or even deficient blood concentrations of a number
467 of vitamins in obesity and metabolic alterations have been consistently reported. There is
468 therefore a clinical need to increase the awareness of medical care givers and patients
469 regarding vitamin status, especially for long-term follow-up and in the context of nutritional
470 or surgical interventions. The reported evidence of modulations of both bacterial vitamin
471 production and GM composition and functionality in condition of vitamin depletion and
472 supplementation reinforce the links between vitamins and GM. In this direction, the GM
473 dysbiosis observed in metabolic alterations and obesity could participate to the altered
474 vitamin host status observed in several cohorts. The restoration of a functional ecosystem via
475 a balanced diet, colon-targeted vitamin, probiotic or prebiotic supplementation of either
476 vitamin-producing single strains or combination of strains relying on cross-feeding (Figure 1)
477 can thus contribute to an improved vitamin metabolism and status. The potential effects on
478 metabolic health of such strategies should also be studied as well as the mechanisms involved
479 in these interactions between vitamins, gut microbiota and metabolic health.
480

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Table 1 – Functions, recommended levels and deficiency consequences of B and D vitamins - Adapted from *Vitamin and mineral requirements in human nutrition* [96]

Vitamin	Name	Function	Daily recommended amounts	Optimal circulating levels	Deficiency biochemical diagnosis	Deficiency consequences
Vitamin B1	Thiamin	Coenzyme functions in metabolism of carbohydrates and branched-chain amino acids	Men: 1.2 mg/Woment: 1.1mg	75-195 nmol/L (Whitfield et al., 2018)	Thiamine Pyrophosphate effect (TPPE) > 25% (WHO,1999)	Beriberi, polyneuritis and neurological symptoms
Vitamin B2	Riboflavin	Coenzyme functions in numerous oxidation and reduction reactions	Men: 1.3 mg/Women: 1.0 mg	100-650 nmol/L	Erythrocyte glutathione reductase activation coefficient (EGRAC) >1.80 (Lanyau-Dominguez et al., 2020)	Growth, cheilosis, angular stomatitis, and dermatitis
Vitamin B3	Niacin	Cosubstrate/coenzyme for hydrogen transfer with numerous dehydrogenases	Men: 16 mgNEs/Women: 14 mgNEs (Niacin equivalents)	4100-69000 nmol/L	Urinary excretion of N1-methylnicotinamide (NMN) < 5.8 µmol (Redzic and Gupta, 2021)	Pellagra with diarrhoea, dermatitis, and dementia
Vitamin B5	Pantothenic acid	Constituent of coenzyme A and phophopantetheine involved in fatty acid metabilsm	Men: 5.0 mg/Women: 5.0 mg	1600-2700 nmol/L (NIH)	Serum : <1000 nmol/L (NIH)	Fatigue, sleep disturbances, impared coordination and nausea
Vitamin B6	Pyridoxine	Coenzyme functions in metabolism of amino acids, glycogen, and sphingoid bases	Men: 1.3 mg/Women: 1.3 mg	20-200 nmol/L (NIH)	Serum: <20 nmol/L (NIH)	Nasolateral seborrhoea, glossitis and peripheral neuropathy
Vitamin B7	Biotin	Coenzyme functions in bicarbonate-dependent carboxylations	Men: 30 µg /Women: 30 µg	0.8-1.7 nmol/L	Serum: <0.8 nmol/L	Fatigue, depression, nausea, dermatits, and muscular pains
Vitamin B9	Folate	Function in producing genetic material (RNA, DNA) and amino acids	Men: 400 µg/ Women: 400 µg	> 6.8 nmol/L	< 6.8 nmol/L	Anemia, digestive and neurological disorders
Vitamin B12	Cobalamin	Functions in the development, myelination and function of the central nervous system	Men: 2.4 µg/Women: 2.4 µg	0,185-0,600 pmol/L	Serum: < 0,18 nmol/L	Anemia, fatigue, weakness
Vitamin D	Calciferol	Maintenance of normal blood level of calcium and phosphate	Men: 10 µg/Women: 10 µg	100-200 nmol/L	Serum: <75 nmol/L	Fatigue, bone pain, muscle weakness, depression

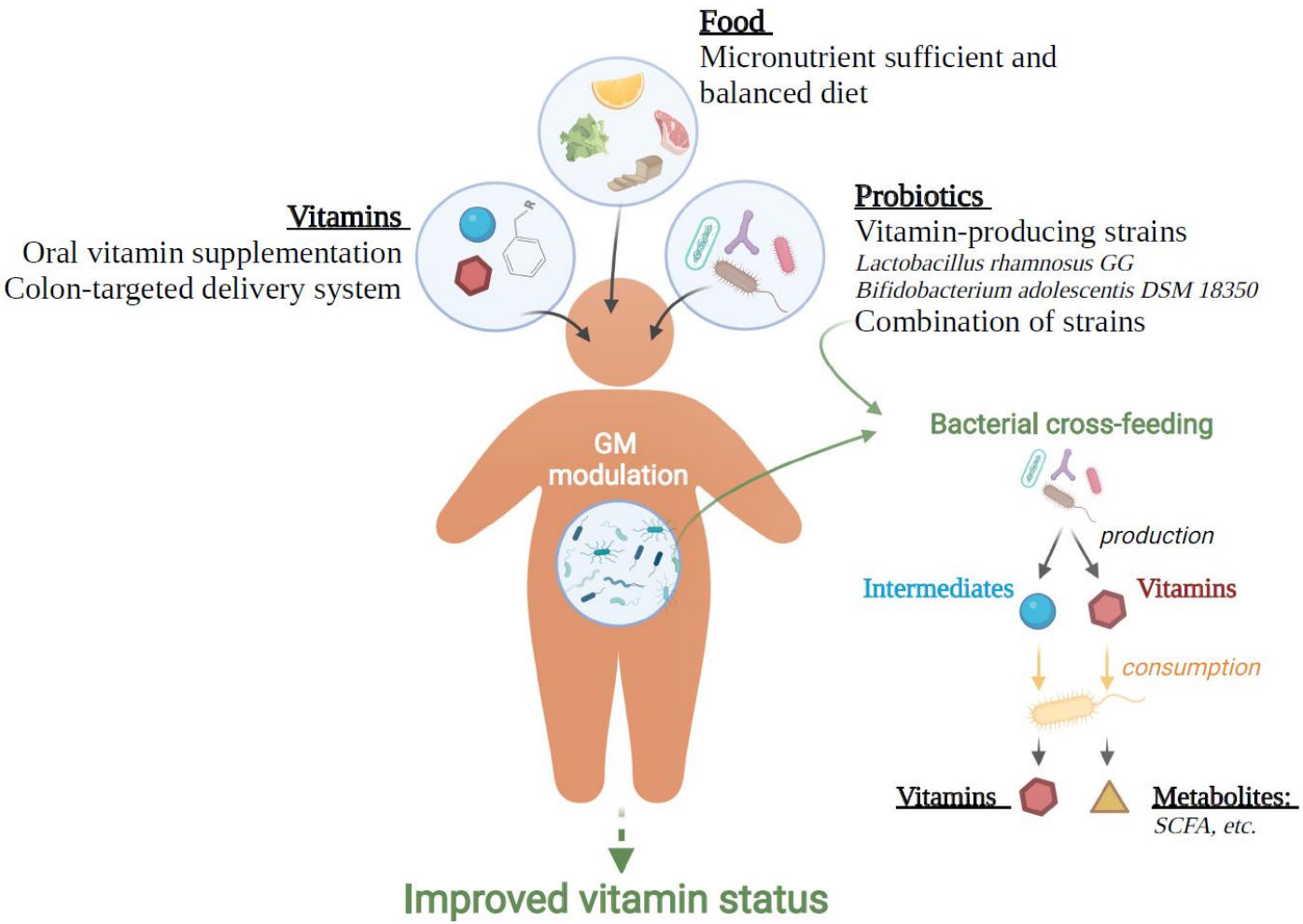

Figure 1 – **Intended strategies for host vitamin status improvement in obesity and metabolic alterations.** Improvement of vitamin metabolism can be envisioned via nutritional intervention with micronutrient sufficient and balanced diet, but also oral vitamin supplementation, for example via colon targeted system to deliver the vitamin directly to the gut microbial ecosystem and finally via probiotic administration of either single

strains known to synthesize a specific vitamin or a bacterial community capable of cross-feeding to synthesize both vitamins and other metabolites such as short-chain fatty acids (SCFA) - *Created with BioRender.com*

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