VITAMIN D
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The complex (and unknown) interaction between vitamin D and intestinal microbiota

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Summary

Both developed and developing countries are witnessing a critical increase in chronic inflammatory diseases that target different organs and especially affect productive age people. Therefore, it is implicit that environmental factors – modes of delivery and breastfeeding, nutrition, pollution, food additives, medicines, and smoking, to name just a few – play an important role in the origin and persistence of organ damage. The main way by which these factors carry out their actions is represented by intestinal microbiota, which constitutes a complex and changing living ecosystem located in the digestive tract and which performs basic functions of homeostasis not only for the intestine but also for the entire human organism. Parallel to this phenomenon, in the last few years, researchers have become aware of the extra-skeletal effects of vitamin D, above all regarding the maintenance of immunological tolerance and strengthening of the intestinal barrier. In addition, a large portion of circulating vitamin D comes through diet and must therefore be absorbed at the intestinal level. The hypothesis of an interaction between vitamin D and intestinal microbiota, therefore, seems plausible, especially in cases of qualitative or quantitative alterations of the latter. Likewise, the possible effects of vitamin D supplementation on the composition of the microbiota itself must be taken into consideration. These are the topics discussed in this article.

INTRODUCTION

When we talk about vitamin D, or calciferol, we are referring to a family of lipid compounds that derive from steroids, which are indispensable for the human organism, whose recommended serum levels are > 30 ng/mL [1]. Daily requirements are satisfied both through exposure to sunlight and diet. In the first case, the 7-dehydrocholesterol at the skin level is transformed into vitamin D_3 (cholecalciferol) by means of a photochemical reaction, while in the second the vitamin is absorbed from foods of animal origin (D_3, cholecalciferol), such as milk and dairy products, and vegetables (D_2, ergocalciferol), such as fresh or dried mushrooms [1].

The latter forms are structurally different – because of the characteristics of the lateral chain connected to the sterol – but functionally similar. They need to be emulsified and incorporated into micelles through the activity of lecithin and bile salts to be absorbed by the intestine. Here they cross the apical membrane of enterocytes by means of both a passive diffusion mechanism and specific protein transporters (Niemann-Pick C1-Like 1, Scavenger receptor class B type 1, *CD36*, ATP-Binding Cassette transporter A1) [2]. Once inside the enterocyte, vitamin D is incorporated into the chylomicrons, which cross the basal membrane and reach the lymphatic circulation. Whether it is produced in the skin or absorbed through nutrition, vitamin D is biologically inactive: for this reason, it is considered a prohormone. To become active, it requires two-step-hydroxylation, which is first carried

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out by the 25-hydroxylase at the 25(OH) position in the liver and later by the vitamin D 1alpha-hydroxylase enzyme at the 1(OH) position in the kidneys, giving rise to the form 1,25(OH)$_2$ D (calcitriol) [1].
From this basis, we see that any disturbance to the digestive tract – meant not anatomically as a mucosal layer but rather functionally as the intestinal barrier, microbiota, and bile salts – has effects on vitamin D availability. In addition, the effect of oral vitamin D supplementation on intestinal microbiota is little known. The aim of this article is therefore to summarise our current state of knowledge on the interaction between vitamin D and intestinal microbiota, considering that both carry out important roles in modulating the immune system and in the pathogenesis of many chronic inflammatory diseases.

INTESTINAL MICROBIOTA

At birth, a multitude of microorganisms populates the human body: these include bacteria, funguses, viruses, phages, and archaea, collectively known as microbiota. Along its surface of approximately 400 m^2, the digestive tract hosts the most abundant and diverse microbial community of our organism, which is made up of more than 100 trillion microorganisms [3]. These encode more than three million genes, which in turn are responsible for synthesising thousands of metabolites [4]. This ecosystem plays an important role in basic functions for the homeostasis of our organism, such as resistance to colonisation by pathogenic microorganisms, maintenance of the integrity of the intestinal barrier and epithelial turnover, synthesis and absorption of nutrients and metabolites (vitamins, amino acids, lipids, bile salts, and short-chain fatty acids), development and modulation of the peripheral immune system, and regulation of nutritional status [3].
Thanks to the possibility to identify the hypervariable regions of the 16S subunit of bacterial rRNA [5], the best known is the bacterial population, which is classified based on its taxonomy in phyla, classes, orders, families, genera, and species [4]. Studies focusing on its qualitative and quantitative characterisation have shown that its composition changes according to the section of the digestive tract (Fig. 1), as it is affected by both intrinsic factors (such as pH, oxygen tension, and intestinal motility) and extrinsic ones (modes of delivery, types of breastfeeding, diet, urban or rural environment, number of components of the nuclear family, physical activity and exposure to xenobiotics) [3,4]. Although each individual develops specific microbiota, numerous studies have allowed researchers to establish the profile of "healthy" ("eubiotic") microbiota, characterised by a relative abundance of the phyla *Bacteroidetes* (in particular the *Bacteroides* and *Prevotella* genera) and *Firmicutes* (in particular the *Lactobacillus*, *Clostridium*, *Enterococcus*, and *Faecalibacterium* genera), and above all possessing richness and diversity [3,4]. On the other hand, all conditions which contribute to disturbing this state are called "dysbiotic".
Due to the extraordinary ability of intestinal microbiota to affect the homeostasis of the human organism, it is not surprising that dysbiosis has been identified in various pathological conditions, both intestinal – such as irritable bowel syndrome (IBS), inflammatory bowel diseases (IBDs), celiac disease – and extra-intestinal – such as obesity and metabolic syndrome, rheumatological diseases, psoriasis, Alzheimer's disease, and Parkinson's disease, to name only a few [3,4]. To date, however, it is still not completely clear whether alterations of the intestinal microbiota are the cause or effect of pathological conditions, and above all by which mechanisms microbiota trigger and maintain a pathological state. In this regard, because of the immunomodulatory role of vitamin D, we cannot exclude the possibility that the influence of microbiota in the pathogenesis of many chronic inflammatory conditions occurs at least in part through variations in the availability of vitamin D and/or that the latter can cause qualitative and quantitative modifications in the composition of the microbiota.

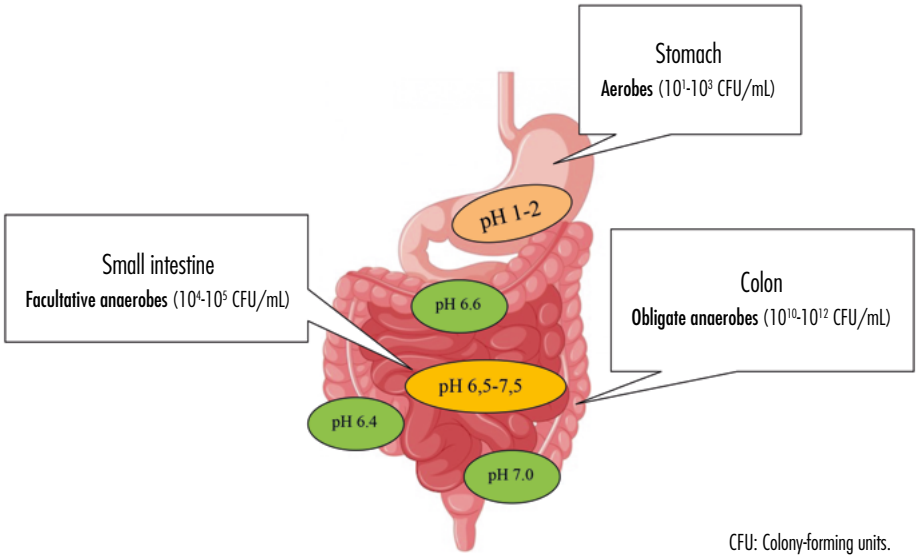


FIGURE 1.
The qualitative/quantitative composition of intestinal microbiota changes in different sections of the digestive tract according to such variables as pH, partial oxygen tension and intestinal motility. Alterations in these factors result from such conditions as gastric hypochylia, intestinal dysmotility, presence of blind loops and modifications of the ileocecal valve. They cause bacterial overgrowth of the small intestine via the descending or ascending pathway.

EFFECTS OF VITAMIN D ON MICROBIOTA

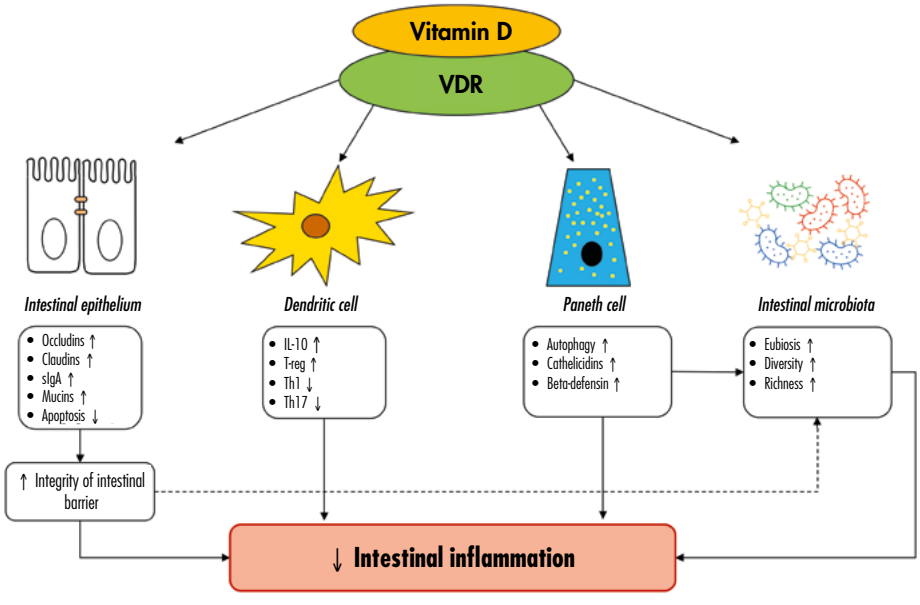
An increasing number of studies have evaluated the effects of vitamin D on intestinal microbiota, in particular regarding IBDs, a multifactorial disease in which dysbiosis plays a leading role in causing and maintaining lesions [6]. At the same time,

the find of low levels of vitamin D levels in patients affected by these conditions and, especially, the association of serum levels with disease activity, risk of relapse and response, and/or failure of therapies [7,8] have sparked a growing interest in the possible role of vitamin D in the pathogenesis of IBDs. Scientific evidence derived mainly from experimental models suggests, on the one hand, that epigenetic modifications triggered by intestinal inflammation can reduce the expression of the gene which encodes vitamin D's nuclear receptor (VDR) [9] and, on the other, that the signaling pathway of vitamin D/VDR can regulate various factors involved in intestinal inflammation [7,10]. In particular, vitamin D appears to influence the integrity of the intestinal barrier by modulating the expression of components of tight and anchoring junction [7] and stimulating the release of antimicrobial peptides (cathelicidins and beta-defensins) on the part of Paneth cells [11] and mucins; in this context, it has an immunomodulatory effect, both by inhibiting the release of pro-inflammatory cytokines and stimulating the release of anti-inflammatory cytokines and the induction of regulatory T-lymphocytes [7,10,11] (Fig. 2).

Regarding its effects on intestinal microbiota, vitamin D supplementation in a small cohort of subjects affected by ulcerative colitis reduced *Ruminococcus gnavus*, even though it did not modify alpha diversity (the bacterial diversity index within a sample) [12]; meanwhile, in subjects affected by Crohn's disease – but not in the control group – supplementation caused a relative increase in such eubiotic bacteria as *Alistipes, Parabacteroides, Roseburia* and *Faecalibacterium* [13]. The absence of modifications in faecal microbiota following vitamin D supplementation in healthy patients was confirmed by one study [14], but not in others: in these, by contrast, an increase in eubiotic indices was found, such as alpha and beta diversity (the index of bacterial diversity between different samples). Furthermore, the latter group of studies showed an increase in the *Bacteroides/Firmicutes* ratio as well as an increase in protective strains such as *Akkermansia muciniphila* [15,16]. A possible explanation for this apparent discrepancy might be found in vitamin D's ability to especially influence the microbiota adhering to the intestinal mucous: this discrepancy would thus be evaluated by endoscopic tissue sampling more than by using luminal microbiota faecal samples. In particular, the most important effects seem to occur in the upper intestinal tract, where following eight weeks of supplementation a decrease in opportunistic pathogens (such as the *Pseudomonas, Escherichia*, and *Shigella species*), as well as an increase in richness, were found [17].

These findings have stimulated interest in investigating the potential role of vitamin D in IBS as well. This is a chronic condition that affects at least 10% of the world's population; it is characterised by symptoms such as abdominal pain or discomfort, intestinal meteorism, and alterations in defecation, especially constipation and/or diarrhoea [18]. Its aetiopathogenesis involves factors that influence the function of the gut-brain axis and which include altered intestinal permeability and dysbiosis [18,19]. In addition, vitamin D deficiency has often been detected in this condition, which is probably linked to changes in eating habits, mostly the exclusion of milk and dairy products. On the opposite, proper supplementation has been shown to contribute to an improvement in both quality of life and intestinal symptoms [19]. Nonetheless, in light of the dearth of clinical studies, differences in their designs, the heterogeneous nature of the subjects examined, and inadequate attention paid to confounding factors – such as exposure to sunlight and diet – we are not able to establish the role played by vitamin D in IBS and, above all, to determine whether this role is in part mediated by alterations in intestinal microbiota.

Intestinal dysbiosis also seems to be involved in the pathogenesis of fatty liver disease associated with metabolic syndrome [20], the main cause of chronic liver disease in the western world as well as the condition associated with a greater risk of vitamin D deficiency [21]. In particular, vitamin D supplementation in this pathology seems to contrast the fibrogenesis resulting from the activation of the transforming growth factor B pathway in hepatic stellate cells [22]. In addition, supplementation appears to improve several laboratory parameters, such as levels of transaminases, triglycerides, fasting glycaemia, and insulin [23].



IL: Interleukin; sIgA: Secretory immunoglobulin A; T-reg: Regulatory T lymphocytes; Th: T helper lymphocytes; VDR: Vitamin D receptor.

FIGURE 2.
Effects on vitamin D on intestinal ecosystem: see text.

At the same time, the possible effect of vitamin D supplementation on intestinal microbiota in this specific clinical setting has still not been investigated. Regarding the metabolic syndrome, *in vivo* studies on both animal models and humans suggest that intestinal microbiota plays a role in the pathogenesis of obesity. In this regard, transplanting the microbiota of obese subjects clearly causes obesity in experimental animals [4]. Furthermore, an increased *Firmicutes/Bacteroidetes* ratio, high levels of *Ruminococcaceae* and *Lactobacillus*, and low ones of *Bacteroidaceae*, *Bacteroides*, and *Bifidobacterium vulgatus* seem to be connected with obesity [4]. In this connection, we should recall those findings which show that vitamin D supplementation (though not the placebo) caused an increase in the genera *Lachnospira* and *Coprococcus* (which were found to be associated with a state of health) and a reduction of the genera *Blautia* and *Ruminococcus* (which are relatively abundant in inflammatory and dysmetabolic conditions) in a cohort of overweight and/or obese subjects (body mass index ≥ 25 kg/m^2) [24].

Ageing also represents a condition frequently linked to both vitamin D deficiency [25] and variations in the composition of intestinal microbiota [4]. A cross-sectional, multi-centric study of 567 community-dwelling elderly Americans showed that higher serum concentrations of calcitriol were connected to greater alpha and beta diversity [26]. In addition, serum levels of calcitriol were positively correlated to microorganisms belonging above all to the *Firmicutes* phylum [26], producers of butyric acid, a short-chain fatty acid with known beneficial effects on intestinal homeostasis [3,4].

Finally, an elegantly designed, randomised, double-blind study was conducted on 41 subjects affected by cystic fibrosis, a chronic, genetic disease that causes secretion thickening, especially in the lungs, skin, and digestive system (above all the pancreas) as a result of the functional loss of the cystic fibrosis transmembrane conductance regulator (CFTR), an ionic channel which regulates the flow of chloride ions – and therefore also of water – in epithelial cells. The results of this study showed a relative abundance of the Bacteroida class in subjects with normal vitamin D levels, while in those with low levels a relative abundance of *Gammaproteobacteria* was detected, a class of gram-negative bacteria which includes such pathogens as *Yersinia Pestis*, *Vibrio Cholera*, *E. coli*, and *Pseudomonas aeruginosa*; the last named is often responsible for pulmonary infections in such patients [27]. In addition, successive vitamin D supplementation to normalise serum levels caused a relative increase of the *Lactococcus* genus and a reduction of the *Veillonella* (belonging to the *Erysipelotrichaceae* family), whose detection in broncho-alveolar lavage samples was associated with a subclinical inflammatory status [27].

EFFECTS OF MICROBIOTA ON VITAMIN D

Moving to consider the consequences that qualitative and quantitative modifications of intestinal microbiota or the administration of probiotics can have on the absorption and therefore on the availability of vitamin D, an example is provided by bacterial overgrowth of the small intestine: as a result of the presence of one or more predisposing factors, such as gastric hypochylia (caused by chronic prazole therapy, atrophic gastritis, and surgeries), alterations of gut motility (mostly in diabetes, systemic autoimmune diseases such as scleroderma, diverticulosis, stenosis, and intestinal by-passes) and ileocecal valve anatomy (Crohn's disease, surgery), an overgrowth/contamination of the intestinal flora via descending or ascending way, respectively, has been found [28]. In the ascending way, in particular, the contamination of the small intestine by anaerobic and Gram-negative bacteria causes the breakdown of micelles, resulting in poor absorption of fat-soluble vitamins, including vitamin D. This results in a clinical picture characterised not only by intestinal meteorism and diarrhoea, but also – over time – osteoporosis, anaemia and peripheral neuropathies due to vitamin B12 deficiency [28]. Furthermore, the breakdown of micelles alters the enterohepatic circulation of bile salts. Upon reaching the colon in great quantities, these cause the onset of "choleretic" diarrhoea, which is linked to heightened intracellular production of cyclic AMP and GMP, which in turn increase the active secretion of water and electrolytes. Finally, microbial flora can also damage the apical portion of the enterocytes, with the loss or reduction of potential enzymatic activity, including lactase, and the consequent development of symptoms of lactose intolerance.

Regarding the possibility that probiotics (defined by the World Health Organisation as live organisms able to produce beneficial effects) can influence circulating vitamin D levels, let us now consider the sparse evidence presented by the literature. In a post hoc analysis of a randomised controlled clinical study, administration of the probiotic *Lactobacillus reuteri* NCIMB 30242 BSH-active [expressing the enzyme accountable for the hydrolase of bile salts (BSH) and their deconjugation [29], with a resulting decreased ability to form micelles] for nine weeks to dyslipidaemic subjects produced a statistically significant increase in circulating vitamin D levels compared to those who received a placebo. It is worth noting here that the effect was selective on vitamin D and not on other fat-soluble vitamins [30]. In addition, in clinical studies conducted on patients who underwent bariatric surgery (with one anastomosis gastric bypass or with Roux-en-Y anastomosis) administration of probiotics (including the association of *Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* Bi-07) up until three months after surgery caused an increase in serum vitamin D levels [31,32]. Among possible explanations, the authors propose increased absorption of vitamin D thanks to the acidification of the intestinal content secondary to the synthesis of lactic acid, stimulation of the 25-hydroxylase vitamin D enzyme, and/or an increase of the 7-dehydrocholesterol synthesis [30]. Finally, we should note a possible functional interaction between resident microbiota and/or probiotics and VDR. In animal models of colitis, anti-inflammatory actions of butyric acid may be linked to the increased gene expression of VDR triggered by the same compound [7,33].

EFFECTS OF MICROBIOTA ON LACTOSE ABSORPTION

Lactose is the main sugar present in the milk of mammals. It is a disaccharide composed of glucose and galactose, whose intestinal absorption depends on the hydrolysis carried out by the lactase enzyme (beta-galactosidase) present on the brush borders of enterocytes. Deficiency of this enzyme, whether congenital (a quite rare condition, typically found in children) or acquired (a very frequent condition, typical of adults), causes inadequate digestion of lactose: remaining in the intestinal lumen, it is catabolized by resident flora, with the production of small, osmotically active molecules (short-chain fatty acids) and gas (carbon dioxide, methane, and hydrogen), with the resulting development of symptoms of intolerance, such as diarrhea, intestinal meteorism and abdominal cramps [34]. In particular, acquired deficiency can be primary – and therefore linked to a genetically determined deficiency, which affects roughly two-thirds of Caucasians – or secondary to enteropathies such as coeliac disease and Crohn's disease, or drug- and radiation-induced enteropathies, to cite the most frequent cases. In addition, it can also result from bacterial contamination of the small intestine because of the above-mentioned capacity of bacteria to damage the brush borders of enterocytes, where the activity of disaccharides takes place.

It is well known that the onset of ailments linked to undigested milk and dairy products induces subjects to avoid these foodstuffs, with significant nutritional repercussions resulting above all from inadequate vitamin D intake [34]. Some of these consequences are secondary to qualitative and quantitative modifications of intestinal microbiota, which are deprived of their share of *Lactobacillaceae*, with the resulting loss of their important immunomodulatory role.

Equally well known is that the development of symptoms of lactose intolerance depends not only on quantities consumed but also on the capacity of the individual's microbiota to break down disaccharides [34,35]. To date, strains with recognised lactose activity include *Bacteroides/Prevotella*, *Bifidobacterium*, and *Eubacterium rectale/Clostridium coccoides* [36]. For this reason, a possible therapeutic strategy consists of the use of probiotics, as shown in some cases in which intake of *Lactobacillus casei Shirota* and *Bifidobacterium breve Yakult* for 4 weeks [37] or *Lactobacillus reuteri* for 10 days [38] led to a reduction of intolerance symptoms and of hydrogen levels in breath tests for lactose. Finally, it is worth noting that some findings show that milk intake in subjects with lactase insufficiency is connected to increased levels of indolepropionic acid, a metabolite of tryptophan produced by intestinal microbiota, in particular by *Bifidobacterium*, and inversely linked to the risk of developing type 2 diabetes mellitus [39].

CONCLUSIONS

Growing evidence shows that vitamin D could play a physiological role in the modulation of intestinal microbiota and that several of its systemic immunoregulatory effects are linked to this latter. Nonetheless, the complexity of the universe represented by intestinal microbiota, together with the limited methods available to explore it, makes difficult a full understanding of its possible role in various clinical scenarios. As a result, identifying preventive or therapeutic strategies is problematic. We, therefore, recommend supplementation for subjects with vitamin D deficiency, since the persistence of this state over time could lead to an alteration of not only osteo-metabolic but also nutritional and immunological homeostasis.

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