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Inflammatory Bowel Diseases and the Vitamin D Axis: Role, Current Uses, and Future Prospects

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Abstract

The idea that the vitamin D axis has immunoregulatory functions is gaining traction, with Vitamin D Receptor (VDR) status being the most important determinant of vitamin D's pleiotropic effects. Vitamin D stimulates the formation of antimicrobial peptides such as -defensins and cathelicidins, as well as autophagy and epithelial barrier integrity, as well as the shift toward Th2 immune responses. Vitamin D deficiency has been linked to a variety of chronic inflammatory disorders, including Inflammatory Bowel Disease (IBD). Inhibition of vitamin D pathways causes dysbiosis of the gut microbiome, which has been linked to the development of IBD in a molecular approach. The significance of the vitamin D axis in immune-mediated disorders is examined in this paper, with a focus on its interaction with the gut microbiome in the pathogenesis of IBD.

Keywords: Vitamin D receptor • Dysbiosis • Immune system

Introduction

Vitamin D is a steroid/thyroid superfamily pleiotropic hormone best recognised for calcium homeostasis, but it also has various non-calcemic actions, including immunological regulation, cell differentiation, and intercellular adhesion. After a two-step hydroxylation of the inactive precursor, cholecalciferol, the active form of the vitamin is formed. Cholecalciferol is hydroxylated at position 25 to produce calcifediol [25(OH)D3], an inactive intermediate that is then hydroxylated at position 1 to produce calcitriol [1,25(OH)2D3]. Vitamin D, both inactive and active forms, circulates through the bloodstream coupled to vitamin D-binding protein (VDBP). The active form has an effect through attaching to the vitamin D receptor, a transcription-regulating protein (VDR). Vitamin D deficiency has been linked to a number of immune-mediated disorders, as well as altered immunological responses to pathogens and an increased risk of infection and cancer [1-4]. Furthermore, its binding protein can directly mediate some immunoregulatory functions [5], and its receptor, which is also expressed on immune cells, is involved in inflammatory pathway modulation. Inflammatory Bowel Diseases (IBD) are chronic inflammatory illnesses that can affect the entire gastrointestinal system and are thought to be caused by inappropriate and persistent immune activation in genetically susceptible individuals in response to gut luminal chemicals [6-8]. Vitamin D insufficiency is widespread in Crohn's disease (CD) and ulcerative colitis (UC), the two most common forms of IBD [9,10]. In this context, we examined the current literature to highlight accumulating information about the crucial function of the vitamin D axis in the setting of IBD, with a focus on the interplay between the gut microbiome and Vitamin D/VDR-mediated genetic and immunological responses. Our findings suggest that a balanced intervention on VDR function, including both vitamin D analogues and probiotics, could be a complementary strategy to IBD treatment.

Why is the vitamin d axis being targeted in IBD?

The vitamin D axis is made up of vitamin D, its binding protein, and its receptor, and it has a lot of intriguing qualities in terms of gastrointestinal physiology. Vitamin D's physiological activities are mediated by the VDR, a nuclear receptor superfamily ligand-dependent transcriptional regulator expressed in a range of cell types, including mucosal immune cells and the intestinal epithelium. Furthermore, the enzyme Cyp27B1, which transforms inactive vitamin D [25(OH)D3] into its active, VDR-binding form [1,25(OH)2D3], is expressed in a variety of immune cell types as well as the intestinal epithelium. The presence of such essential actors in diverse cells of the gastrointestinal tract shows that active vitamin D functions as a paracrine chemical whose levels are adjusted in response to local demands. Intestinal bacteria have been found to modulate the vitamin D axis in the gut, operating on both the intestinal epithelium and local mucosal immune cells. The expression of Cyp27B1, as well as the expression of several genes involved in innate immunity (e.g., antibacterial peptides, tight junction proteins, cytokines and their receptors), has been reported to be reduced in the intestinal epithelial cells of germ-free and antibiotic-treated mice, suggesting that the synthesis of active vitamin D by the "microbiota-dependent" Cyp27B1 enzyme may be a requirement for the proper development of local innate immunity. Probiotics and pathogenic microorganisms, on the other hand, have been demonstrated to alter VDR expression in different directions, with the former increasing and the latter lowering it. In an attempt to evade immune monitoring and modify host genes to promote their survival, viruses target VDR in particular. The VDR gene (VDR, 12q12-14) is one of the candidate genes that has been researched intensively for possible links to IBD. The risk of CD is enhanced in the presence of the VDR ApaI polymorphism and the TaqI tt genotype, whereas the risk of UC may be reduced in the presence of the VDR TaqI polymorphism, especially in Caucasians, according to the findings of two recent meta-analyses. The VDR FokI polymorphism has been linked to UC susceptibility in Asians. VDR knockout (VDR KO) mice were more susceptible to experimental colitis in animal models, as evidenced by worse histology scores, increased expression of proinflammatory cytokine genes, and the development of intestinal dysbiosis. The latter, in turn, has been shown to drastically alter the composition of bile acids in faeces, which could have a significant impact on future molecular communication, with a specific focus on immune-related cellular responses. Vitamin D binding protein (VDBP), also known as Gc globulin (human group-specific component (Gc)), is a 55-kDa serum protein released by the liver that transports active and inactive vitamin D in the plasma. It belongs to the albumin superfamily. SNPs in the VDBP gene have been reported to impact circulating amounts of this protein as well as circulating 25(OH)D3. VDBP is required for the proper operation of the endocytic pathway, which is required for the renal absorption of 25(OH)D3 into renal tubular cells and subsequent vitamin activation. Specific SNPs in VDBP (VDBP 420 variant Lys; 416 Asp 420 Lys) have been linked to IBD, albeit their exact role in pathogenesis is unknown. VDBP has proven that it can operate as a chemotactic and scavenger agent, as well as a macrophage activator, in addition to being a vitamin D carrier. Plasma VDBP, in fact, effectively scavenges G-actin produced at necrotic cell sites and prevents actin polymerization in the circulation. It also serves as a co-chemotactic factor for C5a, a highly potent chemotactic factor for all leukocytes and a variety of other cell types that are produced by restricted proteolytic cleavage of C5 during complement activation. VDBP is also changed into macrophage-derived macrophage activating factor (GcMAF) after stepwise modification of its sugar moiety, which not only has a completely active ingestion function and cytotoxic capability after 3 hours but also exhibits anticancer and antiangiogenic effects. As a result, cloned GcMAF constructs and GcMAF-mimicking peptides have been created for use as immunopotentiators in clinical trials.

The interplay of the vitamin D axis, gut microbiome and gut mucosal immune system at the intestinal level

The intestinal epithelial barrier, the gut microbiota, and components of the innate and adaptive immune systems all play a role in maintaining intestinal homeostasis, which is regulated by the interaction of several variables linked by complicated molecular signalling. The vitamin D axis has been shown to have interesting impacts on each of these components. The differentiated intestinal epithelium acts as a barrier between the intestinal lumen and the gut mucosa, preventing molecules from freely flowing between them. Indeed, the presence of adhesion structures between adjacent epithelial cells, such as tight junctions (occludin, zonula occludens proteins, and claudins), adherens junctions (E-cadherin, catenins, nectin), desmosomes, and gap junctions, ensures the sealing of the paracellular space and regulates mucosal barrier permeability. The integrity of the gut mucosa is also important for microbial protection. In fact, disrupting barrier function makes it easier to become infected with enteropathogenic bacteria and develop intestinal inflammation and IBD. In diverse models of intestinal inflammation, probiotics have been found to reduce paracellular permeability, as measured by transepithelial electrical resistance (TEER), as well as epithelial death. In the setting of several infectious and immune-mediated diseases of the lung (cystic fibrosis, interstitial lung disease, asthma, tuberculosis, chronic obstructive pulmonary disease), skin (atopic dermatitis), oral mucosa, and eyes, where impairment of the vitamin D axis has been described, impaired mucosal barrier function with hyperpermeability is also common. Furthermore, intestinal epithelial cells collaborate with hematopoietic compartments to regulate enteric infections and are critical in the beginning of type 2 immune responses. Paneth cells, goblet cells, and the specialised phagocytic, antigen-presenting M cells found in the follicle-associated epithelium overlaying organised lymphoid structures are all epithelial-derived immunocompetent cells. Vitamin D and its receptor defend epithelial barriers in a variety of organs, including the intestinal mucosa. In fact, active vitamin D has been shown to boost the expression of a number of tight junction and adherent junction proteins. At various anatomic sites, including the corneal epithelium, podocytes, and enterocytes, active vitamin D stimulates the expression and/or membrane translocation of occludin, the zonula occludens proteins ZO-1 and ZO-2, claudins 2, -7, and -12, and vinculin. In vitro studies showed that pretreatment with 1,25(OH)2D3 protects intestinal epithelial cells from dextran sulphate sodium (DSS)-induced increased permeability, and in vivo studies using VDR KO mice revealed increased susceptibility to DSS-induced colitis when compared to their wild-type littermates. Adherent proteins are active in signal transduction in addition to their sealing capabilities, and VDR can regulate such pathways by acting on VDR-regulated promoters. For example, by inducing E-cadherin and inhibiting -catenin signalling through the VDR, active vitamin D inhibits colon cancer cell proliferation and promotes differentiation. These findings support the significance of the vitamin D axis in the formation, integrity, and healing capacity of the mucosal barrier.

Intestinal microbiome

The Human Microbiome Project has generated unparalleled information about the diversity and function of microbial communities and their genes, sometimes known as the human microbiome, in recent years. The quantity and relative distribution of distinct microbial species defined health and disease states in people, according to the sequencing of microbial ribosomal RNA taken from various body regions; for example, decreased diversity in the gut was reported in IBD. The intestinal microbiome has a role in metabolism, mucosal barrier physiology, immunology, and inflammatory signalling, and its disturbance, or dysbiosis, is linked to the onset, maintenance, and perpetuation of a variety of intestinal and extraintestinal clinical disorders. Vitamin D and its receptor have been demonstrated to impact the makeup and functions of bacterial communities in the gut, protect from dysbiosis, and prevent IBD and its symptoms by modulating the expression of antimicrobial peptides, mucosal barrier function, and innate immunity. In the absence of vitamin D, downregulation of particular -defensins from ileal Paneth cells, as well as tight junction genes, was demonstrated to be a co-factor for dysbiosis in the setting of a high-fat dietary regimen, with subsequent endotoxemia and systemic inflammation. Pathogens may potentially use DNA methylation on specific sequences, such as micro-RNAs, to manipulate the monocyte/macrophage vitamin D axis in their favour (miRs). MiR-21, for example, can bind to CYP27B1 mRNA and inhibit its action, lowering the localised synthesis of active vitamin D in monocytes. Probiotics, which are ingestible non-pathogenic live microbes that can give some therapeutic benefits to the host when ingested in sufficient levels as food components, have been widely employed in clinical trials for the treatment of IBD, with mixed results. It was recently discovered that a fully functioning VDR pathway is essential for probiotic protection against colitis, which is relevant because VDR expression in IBD patients can be drastically reduced as a result of chronic inflammation or dysbiosis. In fact, compared to littermates, VDR KO mice did not respond to probiotics such as Lactobacillus rhamnosus strain GG (LGG) and Lactobacillus plantarum (LP) and exhibited worse Salmonella-induced colitis. In wild-type mice, the same probiotics were able to boost VDR expression and transcriptional activity, as well as antimicrobial peptide expression, and provide physiological and histologic protection from Salmonella-induced colitis. The interaction of the vitamin D axis with the gut microbiome is an exciting, yet understudied subject of research with therapeutic consequences.

Conclusion

Vitamin D's role in immunological-mediated disorders appears to be closely linked to bacterial metabolism, with chronic dysbiosis inducing VDR malfunction and setting off a vicious cycle in which a weakened immune system perpetuates disease. As a result, restoring VDR function at various cellular levels should be considered a therapeutic possibility. Probiotics and olmesartan have shown to be effective in this regard in animal trials, but further testing in human studies in specific therapeutic circumstances is required. In reality, little study has been done on the mutual effects of probiotics and vitamin D in people to far. 127 otherwise healthy hypercholesterolemic adults were assigned to take L. reuteri NCIMB 30242 or placebo capsules for a 9-week intervention period in a double-blind, placebo-controlled, randomised experiment. In comparison to placebo, oral probiotic supplementation resulted in a significant increase in circulation vitamin D (p=0.003). Olmesartan is an angiotensin-converting enzyme inhibitor that also binds to the VDR. According to some data, it functions as a VDR agonist, restoring appropriate VDR activity by displacing inhibiting bacterial products bound to the receptor. Olmesartan has been proposed as a treatment for autoimmune illnesses in combination with pulsed, low-dose, broad-spectrum, bacteriostatic antibiotics. By lowering IEC apoptosis, increasing epithelial VDR levels with vitamin D analogues or anti-TNF medication could be another way to alleviate IBD. Several VDR ligands with low calcemic effects but great therapeutic potential have also attracted attention as potential substitutes for active vitamin D. In fact, despite the fact that major side effects of vitamin D supplementation, such as hypercalcemia, have been reported infrequently and are usually only seen after exposure to high doses of the active hormone, the risk of vascular calcifications, hypercalciuria, and renal complications after long-term vitamin D exposure remains unknown. Finally, current breakthroughs in understanding in the fields of microbiomics and nutraceuticals have interesting implications in the treatment of immune-mediated disorders. Despite continuing gaps that hinder recommendations to include modulation of the vitamin D axis and microbiota in clinical practise guidelines, recent study findings urge the pursuit of this objective for better, focused therapy for patients with IBD.

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