VITAMIN D
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Immunomodulatory role of vitamin D in coeliac disease

Rachele Ciccocioppo, Luca Frulloni
Gastroenterology Unit, Department of Medicine
A.O.U.I. Policlinico G.B. Rossi & University of Verona

Abstract

Quite recently, a growing number of studies have shown the extra-skeletal effects of vitamin D, especially in maintaining immunological homeostasis and preserving the intestinal barrier. As a result, the hypothesis of the involvement of vitamin D in the pathogenesis of many immune-mediated conditions seems now plausible. Among these, coeliac disease is a chronic inflammatory condition targeting the small intestine, that is triggered and sustained by the ingestion of gluten contained in some cereals by genetically susceptible individuals. Coeliac disease is the world's most frequent noncommunicable illness, whose prevalence ranges between 0.5 and 1.0%. However, in spite of the high – if not absolute – reliability of diagnostic tests, its real prevalence is much lower (roughly 1‰) due to the variability of clinical features, including pauci-symptomatic cases, that is coupled with the limited knowledge of this condition among general practitioners. This generates the so-called "iceberg" phenomenon, in which diagnosed cases represent only the upper visible fraction of the total. In any case, our current understanding strongly recommends evaluation of serum vitamin D levels in both young and adult patients with coeliac disease, given that both the enteropathy and the possible bacterial overgrowth of the small intestine can lead to malabsorption of vitamin D, with obvious consequences on bone health. In addition, recent studies have proven its immunomodulatory role on all cell populations involved in immune response, while protecting the intestinal barrier and regulating the enterokinesis. Vitamin D deficiency may, therefore, represents an environmental factor that, together with gluten and genetic predisposition, is necessary for triggering and maintaining intestinal lesions in this pathological condition.

INTRODUCTION

Very recent studies have given rise to the intriguing idea of the role of vitamin D in regulating immune response and preserving the intestinal barrier, one which is no less important than its known involvement in bone metabolism [1]. What is indeed emerging from research is the connection between vitamin D status and immune-mediated diseases, such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus [2,3], to cite the best known. These illnesses constitute the true medical emergency in both western and developing countries: their prevalence is continuously on the rise and responsible for high direct costs, as well as for indirect ones linked to decreased quality of life and to disabilities in a significant percentage of the population, above all working age adults [4]. They include chronic inflammatory intestinal diseases triggered by the complex interaction between genetic, immunological and environmental factors, a circumstance which accounts for their clinical variability [5].

Coeliac disease (CeD) is the most frequent enteropathy in the world, given that its prevalence reaches between 0.5 and 1.0% [6], with a large proportion of cases remaining undiagnosed [7]. Improved diagnostic capabilities combined with the pressure of environmental factors are contributing to a significant increase in its incidence [8]. Indeed a dual connection exists between CeD and vitamin D: on the one hand, intestinal lesions

Send correspondence to
Rachele Ciccocioppo
rachele.ciccocioppo@univr.it

Conflict of interest
Rachele Ciccocioppo and Luca Frulloni declare that they have no conflicts of interest.

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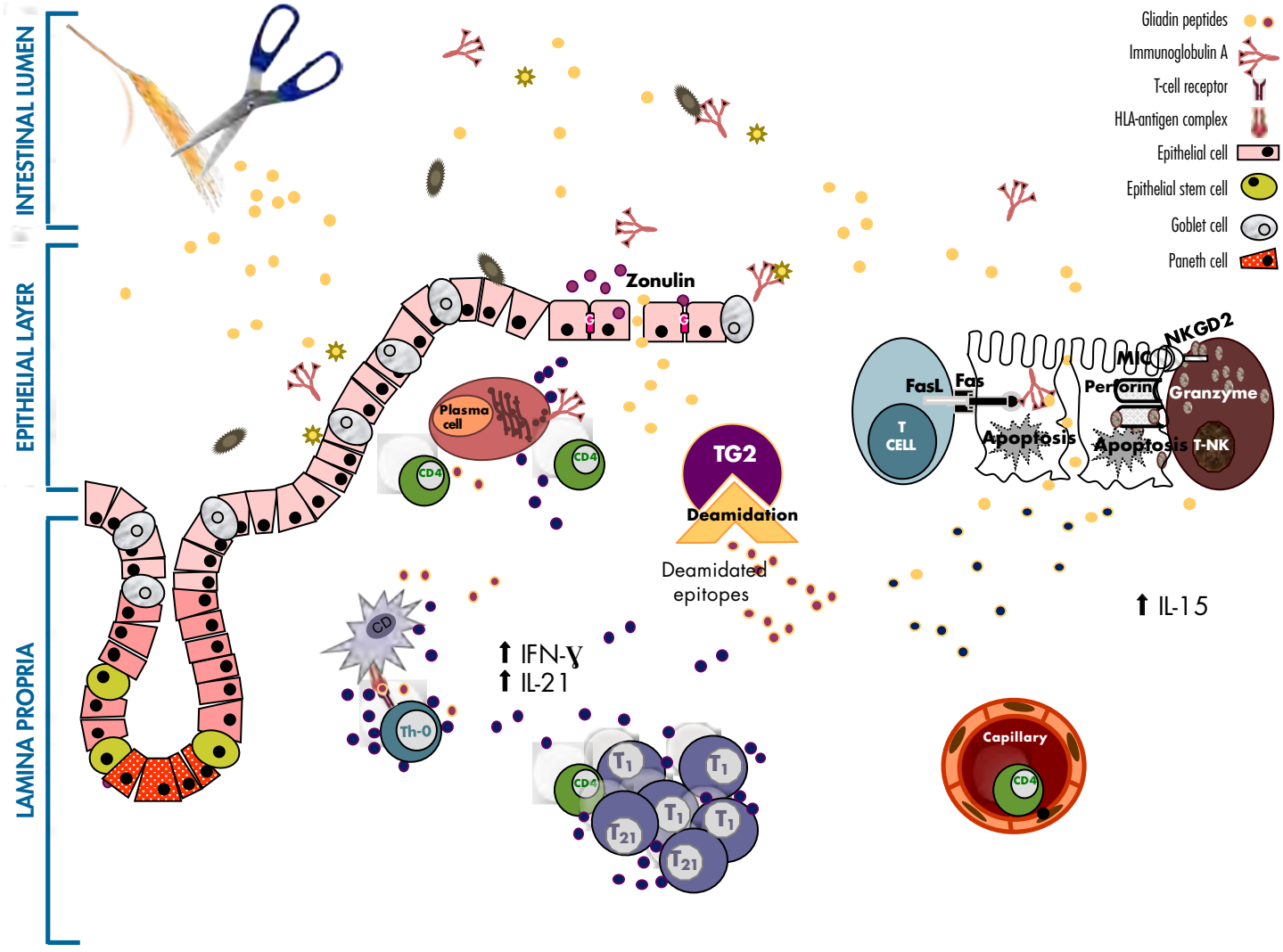


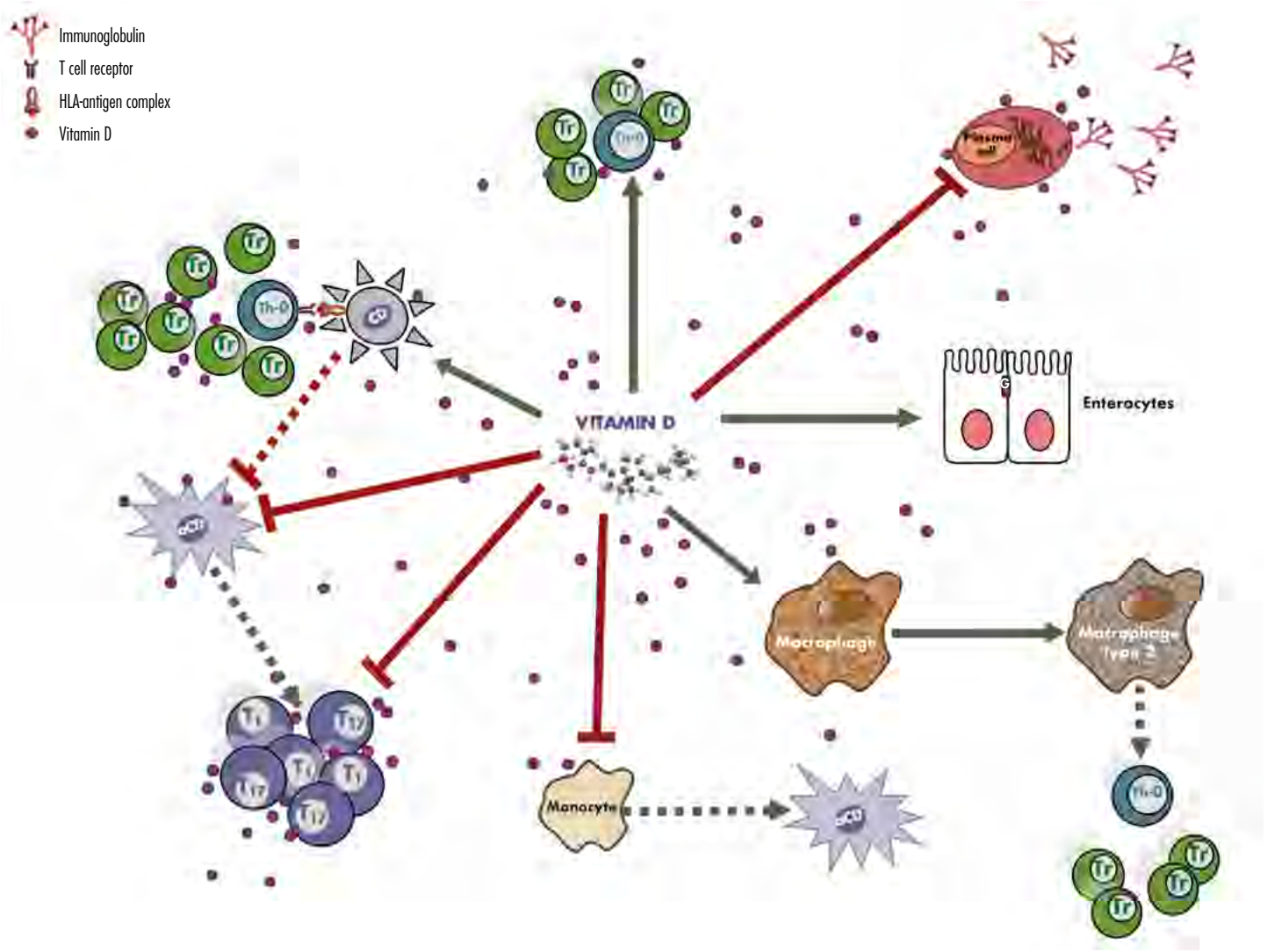
DC: dendritic cell; Th-0: T helper-0; IFN: interferon; IL: interleukin; TG2: tissue transglutaminase type 2; G: inter-enterocyte junctional complex; NK: natural killer; FasL: Fas ligand; Fas: death receptor; NKG2D: natural killer group 2-member D; MHC: Major histocompatibility complex class-I-related chain molecules; Th21: T-helper 21; Th1: T-helper 1; T-NK: lymphocyte T natural killer.

FIGURE 1.
Immunopathogenesis and intestinal lesions of coeliac disease. See text.

can lead to poor absorption of vitamin D, with negative effects on bone health [9], while on the other hand vitamin D deficiency is associated with abnormal inflammatory response [10], which may promote the onset and persistence of enteropathy, at least potentially. This mini-review begins with the immunopathogenesis of CeD (Fig. 1). We then look at the evidence that has so far been collected on the effects of vitamin D (and of its deficiency) on innate and adaptive immunity and on the intestinal barrier (Fig. 2). Finally, we review current available data on CeD.

COELIAC DISEASE

This pathology can develop in genetically predisposed subjects upon ingesting gluten; indeed eliminating gluten from their diets is the only therapy available today [11]. It is an autoimmune disease that especially targets the small intestine, although it can affect the skin (dermatitis-herpetiformis) or the cerebellum (gluten ataxia) in a certain number of cases [12]. Pathogenetic mechanisms connected with the disease cause localized lesions in the intestinal mucous membrane and are characterized by an increase in intraepithelial lymphocytes, crypt hyperplasia, various degrees of villi atrophy and polymorphic inflammatory infiltrate of the lamina propria [13]. In this regard, CeD represents a condition that is well understood, in that the haplotypes for genetic susceptibility (HLA-DQ2/8), the external trigger (gluten) and the autoantigen (the tissue transglutaminase enzyme) are all known [11]. Nonetheless, genetic predisposition concerns over 30% of the population, and gluten is a basic foodstuff in the diets of nearly all the world's peoples. It is therefore clear that other factors are involved which enable lesions to develop and persist; these other causes help



aDC: activated dendritic cell; DC: dendritic cell; G: inter-enterocyte junctional complex; Treg: regulatory T lymphocyte; Th-0: T helper 0; Th1: T helper 1; Th17: T helper 17.

FIGURE 2.
Immunomodulatory and protective effects of vitamin D on intestinal epithelium. See text.

us explain the age variability in the onset of this disease. Indeed, researchers speak of missing environmental factors [14], which include the microbiota, the type of delivery and feeding, the age of weaning, viral infections, and – recently – vitamin D levels. Each of these elements is an object of current research.

Immunopathogenesis

Gluten represents the protein component contained in some cereals, such as wheat, barley, rye and oats. It remains in flours after the bran has been eliminated by grinding and the starch by centrifugation [15]. What is actually involved is a mixture of proteins, which are soluble in alcohol: gliadins in wheat, hordeins in barley, secalins in rye and avenins in oats. Their peculiarity consists in the fact that they are rich in proline and glutamine, which gives various types of flour the properties necessary for rising and breadmaking. The human intestine does not produce enzymes (prolyl-endopeptidase) able to break the bonds between these amino acids. As a result, following chemical digestion performed by gastric acidity and enzymatic digestion by intestinal peptidases, oligopeptides remain which cannot be broken down further [16]. When the intestinal barrier is impaired as a result, for example, of a viral infection or dysbiosis [17], oligopeptides pass through the epithelium and reach the lamina precisely where the immunocompetent cells are located, whose function is to maintain immunological tolerance with respect to the myriad of bacterial and dietetic antigens present in the intestinal lumen. Furthermore, a direct mechanism

causing damage to the barrier has also been hypothesized, which therefore may lead to increased intestinal permeability by means of the release of zonulin [18]: this occurs following the bonding of oligopeptides with the chemokine CXCR3 receptor expressed on the enterocytes, which in turn causes the molecules which form the tight junctions to disassemble [19]. Together with the adherens junctions and the basal complex, these junctions bind the enterocytes together so as to guarantee an extremely selective passage of the molecules, via trans- or paracellular transport, thus contributing to the integrity of the anatomo-functional unit called the intestinal barrier [20].

Other elements that make up the barrier include secretory immunoglobulin A (SIgA), the mucus layer that lines the enterocytes, the intraepithelial lymphocytes, as well as all other cell populations present in the lamina itself, which form the so-called gut-associated lymphoid tissue, on which depends immunological homeostasis [21]. Indeed, the state of antigen cells present in the lamina – whether dormant or active – determines the fate of the immunological response: tolerogenic or inflammatory [22]. Recent studies have indeed shown that the presence of pathobiont species in the intestinal microbiota, together with gliadin peptides, causes the activation of the dendritic cells, which in turn perceive the oligopeptides as antigens: they group them with HLA-DQ2/8 molecules and present them to the T CD4+ l lymphocytes, triggering an inflammatory storm rather than a tolerogenic response [23]. The presence of an inflammatory micro-environment also results in the activation of the enzyme tissue transglutaminase. On the one hand, this enzyme represents the autoantigen of CeD [24], while on the other it makes a selective deamidation of such oligopeptides, in particular of 33-mer, substituting glutamine residues with glutamic acid. This deamidation makes oligopeptides immunodominant and therefore able to amplify the proliferative and secretory response of T-specific lymphocytes [25]. Thus stimulated, the latter produce a pro-inflammatory cytokine cascade, largely dominated by interferon γ and interleukin-15, with the subsequent activation of CD8+ cytotoxic lymphocytes, macrophages, and the natural killer cells which are ultimately responsible for villi atrophy [26].

Villi atrophy is the result of exaggerated enterocyte apoptosis due both to the cytolytic action mechanisms of Fas/LigandFas and of perforin-granzyme and to the detachment of the basal membrane, which is not balanced by increased proliferation at the crypt level [27]. This compromised condition contributes to the loss of the intestinal barrier function because the mucosa surface is now lined with immature cells that form an inefficient junction complex. Finally, T-helper lymphocytes have epitopes to B lymphocytes which produce specific antibodies after differentiating in plasma cells [28]; this count, which can be measured in a patient's serum, has very high diagnostic accuracy [29].

IMMUNOMODULATORY EFFECTS OF VITAMIN D

The vitamin D receptor (VDR), located at the level of the nucleus and responsible for the biological effects of vitamin D, is codified by a highly polymorphic gene that forms part of the superfamily of receptors for steroids [30]. Recently, the expression of this receptor has also been identified in tissues which are not involved in bone and mineral metabolism, and in particular in cells of the immune system, such as those presenting the antigen [31]. For this reason, some VDR polymorphisms may increase or decrease susceptibility to immune-mediated diseases, including CeD [32]. This fact has motivated a series of studies that have shown that vitamin D is involved in immune response, both innate and adaptive [33]. Indeed, the enzyme that converts 25-hydroxy-vitamin D into its active form is also expressed in monocytes-macrophages and is activated following the bond of the toll-like receptors on their surfaces with the respective viral and bacterial antigens, with the result that defenses are strengthened against infections [34]. In addition, vitamin D inhibits the differentiation of monocytes in dendritic cells, thereby reducing the possible appearance of the antigen to trigger an inflammatory response [35].

As has been demonstrated in *in vitro* studies, vitamin D also acts directly on dendritic cells by inhibiting their maturation and therefore their antigen-presenting ability and by favoring the acquisition of a tolerogenic profile [36,37].

Regarding adaptive response, vitamin D reduces the differentiation of T lymphocytes towards a pro-inflammatory profile while promoting the expansion of their regulatory activity [38]. Furthermore, T lymphocytes that express high levels of VDR on their surfaces are believed to be sensitive to an immunomodulatory action from vitamin D, acquiring an anti-inflammatory power. This fact is of great interest in the context of the pathogenesis of CeD, in that the gliadin-specific T lymphocytes are the agents mainly responsible for damage of the mucous and for the process that favors the onset of lymphoma connected to this type of chronic inflammation [39].

Concerning its effects on B lymphocytes, *in vitro* studies have also shown that vitamin D is able to reduce their differentiation in plasma cells and to increase their apoptosis by ultimately causing a reduction in the production of immunoglobulins and therefore of autoantibodies [40].

What is more, VDR is also located on the enterocytes, where it regulates their proliferation, differentiation and apoptosis. It effectively governs the enterokinetics, thereby playing a primary role in the defense mechanisms and functionality of the intestinal barrier [41]. Along these lines, we should mention the studies of Chen et al., which show that vitamin D has a protective effect on the epithelial barrier, both *in vitro* and *in vivo*, by signaling through a myosin light-chain kinase-dependent enzyme, which in turn is activated by the increase of the kB nuclear factor caused by an inflammatory stimulus [42,43]. In particular, the myosin light-chain kinase-dependent enzyme acts directly on the assembly on the actin filaments, causing a contraction of the cytoskeleton and therefore the destruction of the tight junctions. This phenomenon is of great importance if we consider that the disassembly of the latter has already been shown in CeD [44].

Later, the research group led by Dong confirmed the protective effect of vitamin D with regard to the tight junctions of the enterocytes. These studies employed an *in vitro* model of a single layer of $CaCo_2$ cells in which the rupture of the epithelial barrier was induced by gliadin peptides, as well as an *in vivo* gluten-sensitive model [45]. In both cases, vitamin D was able to inhibit the release of the zonulin induced by gliadin and to protect the integrity of the tight junctions, thereby maintaining the function of the barrier. Yet the first study to have brought attention to the possible extra skeletal role of vitamin D in children with CeD was that conducted by Tanpowpong et al. [46]. These authors showed how vitamin D deficiency could contribute to a compromised intestinal barrier, making subjects more susceptible to

enteric infections and consequently to the risk of developing abnormal immune responses vis-à-vis antigens present in the intestinal lumen. This finding has completely revolutionized the way in which we clinical doctors think about vitamin D in CeD, in a context in which deficiency had been considered a mere effect of enteropathy and not a possible cause. Finally, in a cohort of adults with CeD, vitamin D deficiency was correlated to increased frequency of psoriasis, though not to other autoimmune diseases [47].

Taken together, these findings lead us to believe that a simple connection of serum vitamin D level to CeD is reductive. For this reason, we hope that future studies will focus on further evaluating the overall effects of this disease so as to determine the risk of developing it, of prolonging organ damage, and perhaps of developing further complications.

CONCLUSIONS

From the literature we have reviewed, it seems evident that vitamin D can play a significant role in the pathogenesis of CeD, both by means of a direct protective effect on the intestinal barrier and by modulating the immune response to promote tolerance mechanisms. These facts lead us to hypothesize that programs designed to prevent deficiency can contribute to limiting increased incidence of not only this pathology but also of many other chronic inflammatory diseases. In this light, it is worth remembering that vitamin D deficiency in women during pregnancy seems to be connected to an increased risk of developing autoimmune diseases, including CeD, above all during the first two years of life [48]. Supplementing the entire population is obviously not conceivable, in particular those who already have adequate daily vitamin D intake, given that excessive levels not only compromise bone health but also upset immunological homeostasis, with excess vitamin D stimulating Th2 polarization [49,50]. It is therefore essential to continue prevention and screening programs which are able to identify vitamin D deficiencies in the population in order to limit large-scale consequences.

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