Chronic Atrophic Autoimmune Gastritis: The Evolving Role of Vitamin D

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Abstract

Vitamin D possesses a crucial role in preserving bone health, modulating the immune system responses, and supporting various physiological functions throughout the body. Chronic atrophic autoimmune gastritis (CAAG) constitutes an autoimmune condition marked by inflammation and damage to the stomach cells, often resulting in a decreased ability to absorb certain nutrients, including vitamin B12 and iron. Although, vitamin D is not directly affected by this condition, the sufficiency of this micronutrient seems to have important implications for overall health and management of the disease. The aim of the current review was to assess the incidence and related features of vitamin D deficiency in patients with CAAG and to elucidate the complex regulatory role of this nutrient, in an effort to improve patient outcomes. Vitamin D greatly contributes to the regulation of the immune system. In patients with CAAG, the immune system attacks the stomach lining; thus, the maintenance of a healthy and balanced immune response is important. In autoimmune conditions such as CAAG, where inflammation plays a decisive role in disease progression, vitamin D could potentially exert a role in managing and controlling the associated symptoms. Adequate vitamin D levels may help in regulating the immune response and reducing inflammation. In addition, patients with CAAG are at risk of nutrient deficiencies, including vitamin B12 and iron, which can lead to anemia and bone health issues. As vitamin D is critical for calcium absorption and bone health, assurance of sufficient levels of this micronutrient can be beneficial in preventing or mitigating bone-related complications. In conclusion, regular monitoring of vitamin D levels, among other nutrients, and appropriate supplementation, when necessary, can help improve overall health and well-being in these patients.

Keywords: chronic atrophic autoimmune gastritis; autoimmune gastritis; parietal cell; vitamin D; vitamin D receptor; T cells; inflammatory response

1. Introduction

Chronic atrophic autoimmune gastritis (CAAG), also known as type A gastritis or autoimmune metaplastic atrophic gastritis, is a chronic immune-mediated, inflammatory condition that affects the stomach lining and especially the gastric oxyntic mucosa [1,2]. The disease is characterized by the auto-immune-induced depletion of gastric parietal cells, resulting in their substitution by atrophic and metaplastic tissues [1,2]. Specifically, CAAG undergoes histopathological changes across three distinct phases [3,4]. Initially, there is evidence of sporadic damage to oxyntic glands, caused by the infiltration of plasma cells and lymphocytes. This infiltration is frequently observed in a gradient from top to bottom, accompanied by a pseudo-enlargement of the parietal cells that remain akin to those under proton-pump inhibitor therapy [4,5]. Subsequently, during the florid phase, the dense infiltration of lymphocytes and plasma cells occurs in the lamina propria, accompanied by evident atrophic glandular alterations and replacement of native parietal cells by muco-secreting epithelia resembling antral glands (termed oxyntic antralization) [6]. The advanced stages of CAAG feature "oxyntic mucosa desertification", marked by fibrosis of the lamina propria replacing oxyntic glandular units. This stage is also distinguished by foveolar hyperplasia accompanied by microcystic changes underneath, as well as the emergence of inflammatory and hyperplastic polyps. Furthermore, there is a widespread occurrence of intestinal, pancreatic, and pseudopyloric metaplasia, typically accompanied by minimal inflammation [4].

The parietal cells are responsible for producing stomach hydrochloric acid and intrinsic factor, a protein necessary for vitamin B12 absorption [7]. CAAG often leads to micronutrient deficiencies due to the autoimmune-mediated destruction of gastric parietal cells, impairing the absorption of essential nutrients such as vitamin B12 and iron [8]. This can result in symptoms such as fatigue and bone health issues, necessitating careful monitoring and supplementation to address specific deficiencies and prevent complications [9].

Beyond autoimmune inflammation, *Helicobacter pylori* infection is also acknowledged as the primary etiological contributor for the progression of chronic atrophic gastritis [10]. However, in the autoimmune etiology of gastritis, the inflammation is confined to the glands of the corpus and fundus in the stomach, while the antrum remains unaffected [8]. Inflammation of the oxyntic mucosa and its subsequent atrophic development are distinctive features of

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CAAG, which are essential for a definitive diagnosis [8]. The incidence of CAAG is approximately estimated to be around 1–2% and is more common in females than in males, with a ratio of 3:1 between women and men, and increasing occurrence with advancing age [11,12].

Apart from vitamin B12 and iron deficiency, patients with CAAG exhibit deficiencies in various vitamins and micronutrients including vitamin C, vitamin D, and calcium [13–15]. The underlying pathogenetic mechanism driving these alterations seems to entail either heightened degradation or diminished nutrient absorption in the gastric mucosa, potentially stemming from elevated pH levels and bacterial overgrowth [14]. Vitamin D greatly contributes in regulating the absorption of calcium and upholding bone health by facilitating the deposition of calcium in bones. Additionally, it has important immunomodulatory effects, helping to regulate the immune system and reduce inflammation [16–19]. In autoimmune diseases, including CAAG, dysregulation of the immune system responses leads to tissue damage. The function of vitamin D to modulate the immune system balance is essential for maintaining immune equilibrium. Insufficient vitamin D levels might worsen immune regulation, potentially contributing to the onset or advancement of CAAG. Additionally, vitamin D deficiency can impair calcium absorption, which may further exacerbate gastric mucosal damage and contribute to CAAG pathology.

The aim of the current review was to assess the occurrence of vitamin D deficiency among CAAG patients and to elucidate the intricate regulatory function of this nutrient. In parallel, we attempted to elucidate the role of vitamin D role in modulating immune dysregulation and improving overall patient outcomes in this setting.

2. CAAG Pathophysiology

The pathophysiological processes of autoimmune gastritis entail a multifaceted interplay of genetic, environmental, and immunological parameters [20]. The stimulation of autoreactive T cells that identify and attack parietal cells and intrinsic factor is a key player in CAAG pathogenesis. Stimulation of T cells initiates the destruction of parietal cells, which occurs as a consequence of the activity of anti-parietal cell antibodies (PCAs); PCAs identify subunits of the proton pump, H+/K+ ATPase, a distinctive feature found exclusively in parietal cells [8]. *In vitro* studies have shown that PCAs bind to the proton pump, leading to direct cellular damage of parietal cells through complement-dependent cytotoxic activity [21]. The destruction of parietal cells leads to a decrease in the secretion of hydrochloric acid, higher pH of the stomach, and reduction in intrinsic factor, which in turn, results into vitamin B12 and iron malabsorption, causing pernicious anemia and iron deficiency anemia, respectively [8]. These conditions constitute prevalent clinical manifestations of CAAG; specifically, iron deficiency anemia is observed in approximately 25–50% of CAAG patients [22,23], whereas

pernicious anemia may be identified in up to 15–25% of patients [22,24].

Vitamin B12, an indispensable nutrient crucial for various physiological processes such as development of red blood cells, synthesis of DNA, and function of the nervous system faces reduced absorption in this scenario [1]. Autoantibodies against intrinsic factor (IFAs) targets intrinsic factor, a protein secreted by parietal cells necessary for vitamin B12 absorption [25]. The reduced absorption of vitamin B12 presents with various symptoms, such as anemia and neurological issues, which could escalate if left untreated.

However, PCAs in the circulation are not likely to present a direct pathogenic role in CAAG [8]. CAAG patients have been found to be PCA-negative, and a considerable number of individuals diagnosed with common variable immunodeficiency also experience CAAG, with the majority testing negative for PCA antibodies [26,27]. In such cases, cell-mediated immunity appears to greatly contribute to CAAG development, and the diagnosis is confirmed through histological examination. IgG4-secreting plasma cells have been noted in the mucosal tissue of patients with CAAG, specifically in individuals with pernicious anemia, yet their presence does not confirm a potential pathogenic effect [28]. Thus, although PCAs and IFAs are typically viewed as indicators of autoimmunity in CAAG, they do not directly influence the apoptosis of parietal cells and are not consistently detected in CAAG [8].

Genetic predisposition is a major contributor to the onset of CAAG. Specific alleles of the human leukocyte antigen (HLA), notably HLA–DR isotype (HLA-DR) and HLA–DQ isotype (HLA-DQ) have been linked to an elevated risk of developing this condition [29]. Additionally, genetic factors associated with impaired immune regulation and autoimmunity, including specific gene polymorphisms, may further contribute to the susceptibility of this disease [30]. In individuals with a genetic predisposition, exposure to specific dietary components or *H. pylori* infection can trigger the autoimmune response. The involvement of infectious agents as triggers for the disease occurrence has been debated. There are data indicating that *H. pylori* infection serves as a catalyst for the disease in individuals with genetic susceptibility, based on the theory of molecular mimicry between *H. pylori* and the H+/K+ ATPase of parietal cells [31]. Specifically, microbial antigens resembling self-antigens are able to stimulate autoreactive immune cells that target the gastric mucosa [31–35].

The primary pathogenic role in CAAG is attributed to autoreactive CD4+ T helper 1 (Th1) cells and CD8+ cytotoxic T cells, both identified in the mucosal tissue of patients with CAAG [36]. Nevertheless, the specific stimuli prompting the proliferation of these cell clones remain unidentified. D'Elios *et al.* [36] have shown that the *ex vivo* proliferation of gastric mucosa CD4+ T cell clones is induced by H+/K+ ATPase, predominantly Th1 cells. Fur-

thermore, these cells produced interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α), indicating a characteristic Th1 cytokine pattern. Troilo *et al.* [37] delved into the immune reaction triggered by intrinsic factor in a cohort of 7 individuals with pernicious anemia. In the gastric mucosa of these patients, stimulated autoreactive Th1 cells targeting intrinsic factor were identified, with a majority displaying either a Th17 or a Th1 phenotype and producing TNF and interleukin 21 (IL-21) [37]. Moreover, intrinsic factor was capable of activating CD8$^+$ cells against parietal cells. Importantly, these autoreactive T cell clones were absent in *H. pylori* patients [37].

Patients with CAAG may progress to intestinal metaplasia. Moreover, the clinical manifestations of CAAG are intricate due to its common correlation with various autoimmune conditions, particularly Hashimoto's thyroiditis [38]. Additionally, there exists an increased likelihood of developing gastric adenocarcinoma and type 1 gastric neuroendocrine tumors associated with CAAG [27,29,39]. Autoimmune gastritis involves diverse molecular and cellular mechanisms, encompassing genetic susceptibility, autoantibodies, and the development of a pro-inflammatory microenvironment [8]; however, the comprehensive pathophysiological mechanism remains unclear.

The widely discussed potential influence of vitamin D in hindering the progression of inflammatory diseases, stems from the emerging recognition of its antiproliferative and anti-inflammatory properties. The role of vitamin D in autoimmune gastritis is a subject of ongoing research, and while the precise mechanisms are not fully elucidated, there is evidence suggesting a potential association (Fig. 1).

3. Vitamin D Physiology and Metabolism

Vitamin D, a fat-soluble vitamin, plays a major role in various functions in the human body. Its main role is in regulating calcium and phosphorus metabolism, vital for bone health [40]. Additionally, vitamin D is pivotal in modulating the immune system, as well as influencing cell growth and differentiation [40]. These physiological effects of this nutrient are orchestrated through a series of metabolic transformations, primarily occurring in the skin, hepatic tissue, and kidneys [40] (Fig. 2A).

Two primary forms of vitamin D exist, each with distinct chemical structures: either as vitamin D2, also known as ergocalciferol, or as vitamin D3, also referred to as cholecalciferol [41,42]. The synthesis of vitamin D initiates in the skin when exposure to ultraviolet B sunlight triggers the conversion of 7-dehydrocholesterol into previtamin D3 [41,42]. Following this, pre-vitamin D3 undergoes thermal isomerization, leading to its conversion into vitamin D3. Alternatively, vitamin D can be obtained from dietary sources; in this case, the small intestine absorbs this form in conjunction with chylomicrons. After this, vitamin D is conveyed to the liver, bound to vitamin D-binding protein. Upon synthesis or ingestion, the enzyme 25-hydroxylase (CYP2R1) in the liver, transforms vitamin D into 25-hydroxyvitamin D [25(OH)D], which is the primary circulating form of the vitamin [42]. Following that, 25(OH)D undergoes further hydroxylation in the kidneys, facilitated by the enzyme 1α-hydroxylase (CYP27B1) to produce the biologically active form of vitamin D, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] or calcitriol [42]. Although calcitriol being the active form, the evaluation of vitamin D levels typically hinges on assessing the serum levels of 25(OH)D. This inclination is attributed to its comparatively extended half-life and the consistently observed levels in the blood circulation. Elements such as parathyroid hormone, calcium, phosphorus, and fibroblast growth factor [43] intricately regulate the metabolism of vitamin D. The production of the active form takes place both in renal tissue and extra-renal tissues [44].

4. Assessment of Vitamin D Prevalence and Status

Vitamin D insufficiency/deficiency is a significant health concern worldwide and a common feature not only among elderly people and patients with chronic diseases but also in the general population, affecting individuals of all ages and demographic groups. Its prevalence can vary based on factors such as geographical location, lifestyle, age, and skin pigmentation [45]. About 1 billion individuals have insufficient serum levels of 25(OH)D [46]. Cui *et al.* [47], assessed the prevalence of vitamin D deficiency both globally and regionally among individuals aged 1 year or older from 2000 until 2022. The global prevalence was estimated at 15.7% in patients with 25(OH)D <30 nmol/L, 47.9% in those with 25(OH)D <50 nmol/L and lastly 76.6% in patients with 25(OH)D <75 nmol/L, between 2000 and 2022 [47]. The study described a slight decrease in the vitamin D prevalence deficiency from 2000–2010 to 2011–2022, but the levels were still notably high [47]. Season and latitude have emerged as significant risk factors for vitamin D deficiency, with more pronounced rates observed among individuals residing in the Eastern Mediterranean and lower middle-income countries [47]. Moreover, females exhibit greater susceptibility to vitamin D deficiency [47]. The impact of vitamin D deficiency extends beyond bone health, with links to chronic conditions such as cardiovascular disease, cancer, autoimmune disorders, compromised immune function, and mood disorders [48]. Addressing this issue through monitoring and supplementation, particularly in high-risk groups, is vital for public health and well-being.

The physiological range of vitamin D levels has been a subject of debate. It is suggested that combining both 25(OH)D2 and 25(OH)D3 to determine the total 25(OH)D serum levels is an indicator of vitamin D status. In general, diagnostic thresholds defining serum 25(OH)D concentrations are outlined as follows: 25(OH)D levels ranging from $\geq$30 ng/mL/75 nmol/L to 50 ng/mL/125 nmol/L
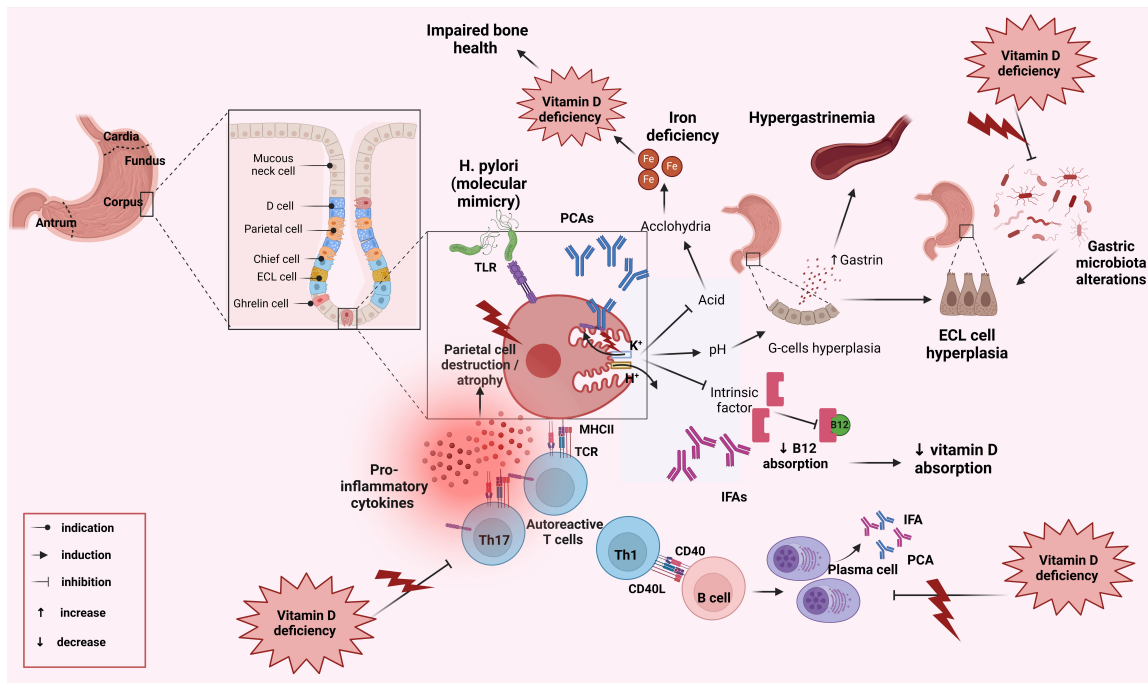
Fig. 1. CAAG impacts the corpus and fundus, which results in atrophy of the mucosal tissue. The antrum remains unaffected. The parietal cells, which constitute the primary targets in CAAG, are exclusively situated in the oxyntic mucosa and are responsible for the production of hydrochloric acid and intrinsic factor. Alongside parietal cells, oxyntic mucosa involves many other cells including mucous neck cells, chief cells, enterochromaffin-like cells, ghrelin cells, and D cells. CAAG is mainly characterized by the secretion of autoantibodies, particularly anti-PCAs and anti-IFAs. These antibodies target specific proteins expressed by parietal cells within the gastric mucosa. Parietal cells greatly contribute to gastric acid secretion through the action of the proton pump (H+/K+ ATPase). The autoantibodies produced in CAAG target components of this proton pump, leading to atrophy or destruction of parietal cells. This results in decreased production of hydrochloric acid and intrinsic factor, which are essential for digestion and absorption of nutrients such as B12 and iron, causing pernicious anemia and iron deficiency anemia, respectively. These conditions may lead to impaired absorption of vitamin D and thus vitamin D deficiency. The increased secretion of gastrin by G-cells leads to hypergastrinemia. In parallel, elevated gastrin levels stimulate ECL proliferation, leading to hyperplasia and subsequently to the development of gastric neoplastic lesions. Increased pH leads to ECL hyperplasia due to increased gastrin levels and to alterations in the gastric microbiota composition and favors adverse outcomes. The composition of the gastric microbiota might also be influenced by the occurrence of vitamin D deficiency, further aggravating these effects. The autoimmune attack on parietal cells triggers an inflammatory response in the gastric mucosa. Activated autoreactive T cells including Th1 and Th17 cells release pro-inflammatory cytokines, which further contribute to tissue damage and inflammation. Chronic inflammation and damage to the gastric mucosa result in tissue remodeling including thinning of the mucosal layer and loss of gastric glandular architecture. Vitamin D deficiency hampers the ability of this micronutrient to repress the Th1 and Th17 immune responses and the cytokine production, further worsening the inflammatory microenvironment. *H. pylori* may contribute to the autoimmune process via molecular mimicry, leading to an autoimmune response, particularly in patients carrying specific TLRs. Created with BioRender.com. Fig. 1 abbreviations: CAAG, chronic atrophic autoimmune gastritis; ECLs, enterochromaffin-like cells; PCAs, parietal cell antibodies; TLRs, Toll-like receptors; MHC, major histocompatibility complex; TCR, T cell receptor; Th cell, T helper cell; CD, cluster of differentiation; IFAs, intrinsic factor antibodies.

indicate optimal vitamin D status [49]. Vitamin D insufficiency has been defined as serum 25(OH)D levels between 20 ng/mL/50 nmol/L and 30 ng/mL/75 nmol/L, whereas vitamin D serum 25(OH)D levels ≤20 ng/mL/50 nmol/L indicate a vitamin D deficiency [49]. Concentrations exceeding 50 ng/mL/125 nmol/L up to 100 ng/mL/250 nmol/L suggest an excess of vitamin D, whereas concentrations greater than 100 ng/mL/250 nmol/L indicate an elevated risk of intoxication [49].

5. Vitamin D Receptor

Calcitriol exerts its influence by binding to the vitamin D receptor (VDR), which is found in various tissues in the human body [50]. Encoded by the VDR gene and classified within the nuclear receptor superfamily, the VDR function relies on its molecular composition and structure. In the majority of cases, VDR serves as a transcription factor, impacting the expression of genes associated with diverse biological processes in reaction to vitamin D [51].
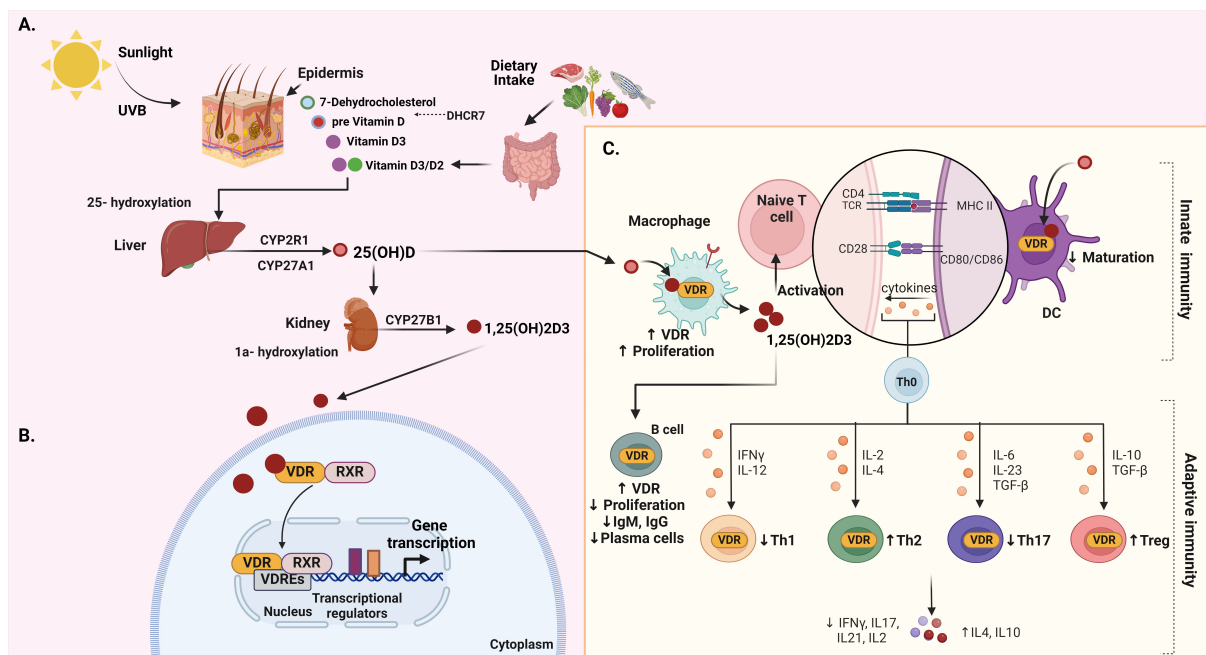
Fig. 2. Integrated overview of vitamin D: biosynthesis, metabolism, VDR signaling, and immune function. (A) The biosynthesis and metabolism of vitamin D. (B) The signaling of vitamin D–VDR. (C) The function of vitamin D in both innate and adaptive immunity. Created with BioRender.com. Fig. 2 abbreviations: UVB, ultraviolet B; DHCR7, 7-dehydrocholesterol reductase; CYP2R1, cytochrome P450, family 2, subfamily R, polypeptide 1; CYP27A1, cytochrome P450, family 27, subfamily A, polypeptide 1; CYP27B1, cytochrome P450, family 27, subfamily B, polypeptide 1; VDR, vitamin D receptor; RXR, retinoid X receptor; VDRE, vitamin D response element; TCR, T cell receptor; MHC, major histocompatibility complex; CD, cluster of differentiation; DC, dendritic cell; Th, T helper; IL-2, interleukin 2; IFN-γ, interferon gamma; TGF-β, transforming growth factor beta; Treg, regulatory T cell.

Vitamin D–VDR complex has the potential to promote various biological actions through both genomic and nongenomic mechanisms [52,53] (Fig. 2B). Upon activation, the VDR establishes a complex with the retinoid X receptor (RXR), and this composite binds to vitamin D response elements (VDREs) found in the promoter regions of target genes [52,53]. In this manner, the activated VDR assumes a crucial role in the transcriptional activation or suppression of diverse target genes by a vitamin D-mediated signaling or by heterogeneous mechanisms, which involve interplay with transcription factors [54]. Target genes encompass calcium channels and transient receptor potential vanilloid member 6 (TRPV6) [55], which are crucial for triggering capsaicin-dependent apoptosis in gastric cancer cells [56]. Moreover, various vitamin D target tissues have been revealed in the gastrointestinal tract including colon, stomach, and small intestine, in various animal species [44]. Furthermore, VDR is expressed in the gastrointestinal tract of humans, rats, and mice [57–59]. The functions of vitamin D and VDR in the intestine have been extensively investigated. Vitamin D target genes like intestinal plasma membrane calcium ATPase and TRPV6 play crucial role in maintaining adequate calcium absorption in the intestinal tissue [60].

Beyond the gastrointestinal tract, the expression of VDR is extensive across various tissues, encompassing kidneys, bones, and immune cells, emphasizing its participation in a range of physiological processes [61,62]. Notably, VDR is expressed in various immune cells engaged in gastrointestinal immune response, such as in stimulated T cells, B cells, cytotoxic natural killer (NK) cells, dendritic cells (DCs), monocytes, and macrophages [61,63–67] (Fig. 2C). Scattered cells located in the pyloric antrum and the isthmus within the corpus have been identified as target tissues for 3H-1,25(OH)2D3 [68]. However, the precise role of vitamin D in the normal stomach function remains to be investigated.

VDR is expressed in low levels in gastric cancer [69] and Barrett's esophagus [57]. Interestingly, VDR expression has been found higher in premalignant gastric tissues with moderate differentiation compared to those exhibited poor differentiation [57,69]. Moreover, vitamin D deficiency has been related to other gastrointestinal diseases such as inflammatory bowel disease [70,71], colorectal cancer [72], and *H. pylori* infection [73].

6. Immunoregulatory Effects of Vitamin D–VDR

Vitamin D has been linked to the modulation of bone metabolism; however, growing evidence suggests that it also greatly contributes to numerous biological processes governing immune responses [61,62,74]. Interest in the po-

tential immunomodulatory effects of vitamin D has been growing since the discovery of VDR in monocytes [74,75], followed by their presence in DCs and activated T cells [76–78] (Fig. 2C). VDR agonists selectively hamper exaggerated type 1 Th1-driven inflammatory reactions and limit subsequent Th cell differentiation towards a pro-inflammatory state [79]. Vitamin D suppresses the pro-inflammatory activity of Th1 cells and the secretion of proinflammatory cytokines such as IL-2, IFN-γ, and TNF-α [80–82] (Fig. 2C). The active form of vitamin D also inhibits T cell proliferation and the expression of IL-2 [83] and IFN-γ at both the mRNA and protein levels in T cells [84]. This inhibition may be attributed to binding of the VDR–RXR heterodimer to the VDREs, present in the promoter regions of genes that encode IL-2 and IFN-γ [82]. Beyond the vitamin D anti-inflammatory role, this nutrient also induces Th2 responses by fostering the secretion of IL-4, IL-5, and IL-10 (Fig. 2C). This shift in the T cell balance from an inflammatory Th1 to an anti-inflammatory Th2 response is facilitated by vitamin D [85]. Additionally, certain studies have indicated that vitamin D might dampen Th17 responses [86] and enhance the activity of regulatory T cells (Tregs) [87]. The presence of vitamin D in immature DC culture has suggested that it induces their differentiation towards a tolerogenic phenotype; tolerogenic DCs authorize the differentiation of effector T cells into forkhead box protein 3-positive (Foxp3+) Tregs [88]. Subsequently, Tregs become activated and undergo proliferation upon exposure to VDR ligands [88]. Lastly, vitamin D is essential for the maturation of NK T (NKT) cells and for the secretion of IL-4 and IFN-γ, by these cells [89]. Consequently, the wide-ranging influence of vitamin D on various immune cell types strongly indicates its potential significance in immune-related conditions, particularly in autoimmunity [16,90,91].

7. Role of Vitamin D in CAAG

To date, there are limited data on the relation between CAAG and vitamin D deficiency. Studies evaluating vitamin D levels in patients with CAAG are presented in Table 1 (Ref. [92–97]).

The assessment of vitamin D levels in postmenopausal women with pernicious anemia as a potential risk factor for osteoporosis has been first explored in 1992 [92]. This study revealed no correlation between vitamin D and the presence of pernicious anemia in a cohort of 21 patients compared to controls. However, the small sample size and the inclusion of postmenopausal women may restrict the reliability of the results [92]. In a subsequent study, significantly lower levels of 25-hydroxy vitamin D were observed in CAAG patients compared to those with nonspecific gastritis or healthy controls [93]. In CAAG subjects, the mean vitamin D levels were 9.8 ± 5.6 ng/mL (95% confidence interval [CI] 8.4–11.2) versus 21.3 ± 12.2 (95% CI: 19.7–22.9) in healthy individuals. The significantly diminished vitamin D levels in CAAG compared to patients with nonspecific gastritis or the healthy individuals suggested a potential link between hypovitaminosis D and autoimmune disease development [93]. In another study, the elevated prevalence of hyperparathyroidism secondary to vitamin D deficiency was observed in individuals with CAAG [94], indicating that the modulation of vitamin D metabolism and/or calcium could be compromised in CAAG patients, possibly due to impaired vitamin D absorption in the intestine [94]. The limitation of that study was the inclusion of patients with gastric carcinoid type 1 (24 of 107), which may have compromised the results. Massironi *et al*. [96] showed significantly lower mean 25(OH)D levels in patients with CAAG compared to healthy controls (18.8 vs. 27.0 ng/mL; $p < 0.0001$). Moreover, a significant association was found between vitamin B12 values at diagnosis and 25(OH)D levels ($p = 0.01$) [96]. Notably, CAAG patients with moderate or severe gastric atrophy showed lower 25(OH)D levels than those with mild atrophy (11.8 vs. 20 ng/mL; $p = 0.0047$), whereas 25(OH)D levels were significantly decreased in CAAG patients with gastric cancer versus those without (11.8 vs. 19.8 ng/mL; $p = 0.0041$) [96]. The relatively small sample size and assessment of 25(OH)D throughout the year, during outpatient examination, is a potential drawback of that study. The prevalence of vitamin D deficiency in patients with CAAG and the potential association of this deficiency with the grade of gastric atrophy or hyperplasia of enterochromaffin-like cells were evaluated in an observational study [97]. The results showed that vitamin D deficiency presented in 76 of 122 patients with CAAG [97]. 25(OH)D levels exhibited a direct correlation with B12 levels and were notably reduced in patients with macronodular hyperplasia compared to those with linear or micronodular hyperplasia [97]. This finding suggests the possible pathogenetic effect of vitamin D deficiency in the initiation and progression of CAAG [97]. However, the determination of 25(OH)D throughout the year may limit the results of that study.

In addition, the vitamin D role has been assessed in the setting of gastro-entero-pancreatic neuroendocrine neoplasms (NENs) [95]. The results showed 25(OH)D median levels at 12.9 ng/mL (ranging from 2 to 32 ng/mL) [95]. Specifically, 94 patients (68%) exhibited levels ≤ 20 ng/mL, with 46 cases (33%) displaying levels ≤ 10 ng/mL, suggesting a high prevalence of vitamin D deficiency among patients with NENs [95]. A negative association was noted between 25(OH)D levels and overall survival ($p = 0.03$, rs = –0.18) as well as progression-free survival ($p = 0.01$, rs = –0.22) [95]. In Cox proportional hazards regression analysis, overall survival was strong correlated with 25(OH)D supplementation ($p < 0.002$) [95].

Both vitamin D and calcium are critical for maintaining bone health, and their deficiency consist of an essential risk factor for osteoporosis development [98]. Although there is no evidence on the prevalence of osteoporosis wit-

Table 1. Biochemical characteristics and demographics of patients with CAAG and vitamin D deficiency.

Author (ref)	Date	Study population (n)	Age	M/F	Vitamin D deficiency	Vitamin D levels (ng/mL)	Design	Other outcomes	Exclusion criteria
Eastell *et al.* [92]	1992	21 pernicious anemia vs 24 controls	68 ± 7 *vs.* 65 ± 9	0/21 *vs.* 0/24	NA	19.78 ± 1.2 *vs.* 16.47 ± 0.9	NR	Patients with pernicious anemia → ● Normal fractional calcium absorption ● Normal serum parathyroid hormone levels ● Normal 1,25(OH)2D levels	Osteoporosis-causing conditions
Antico *et al.* [93]	2012	62 CAAG *vs.* 54 NSLG *vs.* 21 HPG vs 212 controls	37–80 *vs.* 20–80 *vs.* 20–80 *vs.* 20–80	NR	NA	9.8 ± 5.6 *vs.* 22.2 ± 13.5 *vs.* 11.1 ± 8.4 *vs.* 21.3 ± 12.2	Case control study	● Vitamin D levels in CAAG → significantly lower *vs.* NSLG or controls ● Hypovitaminosis D → risk factor for autoimmune disorders ● Low vitamin D levels in HPG → predisposes for a more severe Th1 type attack to the mucosa epithelium	NR
Massironi *et al.* [94]	2013	107 CAAG	57.4 (21–88)	21/86	22.96 ng/mL in CAAG with PHPT 8.86 ng/mL in CAAG with SHPT	14.1 (2.9–33.7)	Monocentric prospective study	● ↑ HPT prevalence secondary to vitamin D deficiency in CAAG	● *H. pylori* infection ● Ongoing treatment with PPIs ● Medications affecting calcium metabolism or PTH secretion ● Renal failure ● Severe liver failure ● Malignancy
Massironi *et al.* [95]	2017	138 NENs	63 (26–90)	77/61	94 of 138 (68%) → 25(OH)D ≤20 ng/mL 46 of 138 (33%) → 25(OH)D ≤10 ng/mL	12.9 (2–32)	Monocentric study	● Inverse association between 25(OH)D & OS (*p* = 0.03, rs = –0.18). ● Inverse association between 25(OH)D & PFS (*p* = 0.01, rs = –0.22) ● Strong association between 25(OH)D supplementation & OS (*p* < 0.002)	● Ongoing vitamin D supplementation ● Advanced neoplasia ● Primary hyperparathyroidism ● Renal insufficiency

Table 1. Continued.

Author (ref)	Date	Study population (n)	Age	M/F	Vitamin D deficiency	Vitamin D levels (ng/mL)	Design	Other outcomes	Exclusion criteria
Massironi *et al.* [96]	2018	87 CAAG *vs.* 1232 controls	63.5 ± 12.8 *vs.* 62.3 ± 13.2	16/71 *vs.* 276/976	57 out of 87 (66%) *vs.* 438 of 1232 (36%) → 25(OH)D <20 ng/mL 27 of 87 (31%) *vs.* 160 out of 1232 (13%) → 25(OH)D <12.5 ng/mL	18.8 ± 9.7 *vs.* 27.0 ± 16.3	Monocentric prospective study	● Correlation between B12 at diagnosis & 25(OH)D (rs = 0.25, $p = 0.01$) ● CAAG patients with moderate or severe gastric atrophy → reduced 25(OH)D compared to those with mild atrophy (11.8 *vs.* 20 ng/mL; $p = 0.0047$) ● 25(OH)D → significantly reduced in CAAG patients with gastric cancer *vs.* those without (11.8 *vs.* 19.8 ng/mL; $p = 0.0041$)	● Ongoing vitamin D supplementation ● Ongoing medication affecting calcium metabolism ● Abnormal calcium levels ● Renal failure ● Primary hyperparathyroidism ● Severe liver failure ● Pancreatic insufficiency ● Malignancy ● Gastrointestinal disease leading to malabsorption
Zilli *et al.* [97]	2019	122 CAAG	65 (25–90)	22/100	76 of 122 (62%)	18 (4–35)	Monocentric observational study	● 25(OH)D related to B12 ● 25(OH)D → significantly reduced in patients with macronodular vs those with linear or micronodular hyperplasia	● *H. pylori* ● Renal failure ● Pancreatic insufficiency ● Severe hepatic failure ● Current or past use of vitamin or mineral supplements ● Current gastric antisecretory treatment ● Advanced neoplasia ● Primary hyperparathyroidism

Footnotes: Data are presented as n (%) or median (range) or mean ± standard deviation. ↑ means increase; à means association.

Abbreviations: Ref, reference; n, number; M/F, male/female; NA, not assessed; NR, not reported; CAAG, chronic atrophic autoimmune gastritis; NSLG, nonspecific lymphocytic gastritis; Th1, T helper 1; HPG, *H. pylori* gastritis; PHPT, primary hyperparathyroidism; SHPT, secondary hyperparathyroidism; PPIs, proton pump inhibitors; PTH, parathyroid hormone; NENs, neuroendocrine neoplasms; OS, overall survival; PFS, progression-free survival; rs, spearman's rank correlation coefficient.

-hin CAAG patients, there are data reporting a strong correlation between chronic atrophic gastritis and osteoporosis in a study of 401 postmenopausal women [99]. Moreover, since vitamin D is critical for absorbing calcium, a lack of vitamin D could also explain a decline in calcium levels in CAAG patients [15].

In a mechanistic study, the role of cluster of differentiation 24 (CD24), an antigen that has been used as a marker to indicate tumor invasiveness in gastric cancer [100], has been explored in patients with chronic atrophic gastritis [101]. The study indicated a gradual increase in CD24 expression across samples obtained from normal gastric mucosa, non-atrophic chronic gastritis, chronic atrophic gastritis, chronic atrophic gastritis with intestinal metaplasia, dysplasia, and gastric cancer [101]. Moreover, the data demonstrated that CD24 knockdown resulted in significantly increased expression of E-cadherin and VDR in gastric cancer cells, whereas CD24 overexpression led to converse effects [101]. VDR has been found to mediate E-cadherin expression, whereas the receptor expression has been eliminated during the progression of colon cancer [102,103]. Thus, VDR-mediated reduction in E-cadherin expression indicates a pivotal stage in tumor metastasis and represents a key occurrence in the epithelial–mesenchymal transition (EMT) [104]. The EMT may be considered a pathological mechanism that takes part in tumor progression, particularly during the invasion and metastasis of tumor cells [105]. Consequently, CD24 might stimulate invasion by controlling the VDR-mediated onset of EMT.

Vitamin D has emerged as a significant factor in various autoimmune diseases, as indicated by numerous epidemiological studies. Its ability to bind to VDR and act as a transcriptional factor allows it to modulate gene expression and influence the immune cells through its immunoregulatory role. Emerging data suggest a close association among VDR polymorphisms, serum vitamin D levels, and the risk of autoimmune diseases such as multiple sclerosis, type 1 diabetes mellitus, and systemic lupus erythematosus [106,107]. Thus, disruptions in vitamin D signaling or impaired vitamin D intake, influenced by genetic and environmental factors may be a contributing factor for initiation and progression of autoimmune conditions. Given the high prevalence of vitamin D deficiency observed in patients with autoimmune conditions, vitamin D supplementation has been considered a potential therapeutic approach for this setting. The findings of our study confirm this hypothesis to some extent. First, all of the aforementioned studies presented in the current review report vitamin D deficiency in patients with CAAG, proposing a potential pathogenetic effect of vitamin D deficiency in the initiation and progression of CAAG. Antico *et al*. [93] supported the notion that hypovitaminosis D could potentially serve as a risk factor for the onset of CAAG, as vitamin D levels in patients with CAAG were notably lower compared to patients with non-specific gastritis or healthy individuals.

The study explored the impact of vitamin D in the gastro-entero-pancreatic NENs showed ameliorated clinical outcomes for patients who received vitamin D supplements, enhancing the theory on the antiproliferative role of vitamin D supplementation on NENs [95]. The evidence on the role of vitamin D supplements in patients with CAAG remain scarce; however, our findings support the regular assessment of vitamin D and provide supplementation when necessary. However, specific recommendations should be made on a case-by-case basis by healthcare professionals, considering individual patient needs and medical history to conclusively establish the effectiveness of vitamin D supplementation in preventing and alleviating CAAG.

8. Conclusion

Vitamin D has been greatly associated with various autoimmune diseases in multiple epidemiological studies. Vitamin D–VDR binding enables this complex to act as a transcriptional factor, regulating gene expression and exerting immunomodulatory effects on immune cells. Research has demonstrated the potential of vitamin D to repress Th17 cytokine secretion, promote Treg activity, stimulate NKT cell action, inhibit Th1 responses, and induce Th2 cytokine secretion, thereby influencing T cell polarization towards a Th2 phenotype. Moreover, growing data suggest a close association between serum vitamin D levels, and polymorphisms in the VDR gene with the risk of autoimmune diseases. Consequently, dysregulated vitamin D signaling or impaired vitamin D intake may contribute to the initiation and progression of autoimmunity.

In the setting of CAAG, the current body of literature lacks sufficient evidence to definitively establish a direct correlation between vitamin D status and the pathogenesis or prognosis of disease. It is plausible that vitamin D deficiency could either be a secondary manifestation of the disease or contribute to impaired tissue responsiveness to both physiological and pathological signals. Moreover, to date, the underlying mechanism of vitamin D deficiency in patients with CAAG remains unclear. However, similar to other micronutrients [14], it is plausible to consider a reduced absorption or increased degradation of vitamin D in the gastrointestinal tissue due to hypochlorhydria and overgrowth of bacterial population. The existing evidence suggests a direct link between the extent of atrophy in the mucosal tissue and vitamin D concentrations. A hypothesis could be that in individuals with mild atrophy, the remaining gastric acid secretion may sustain adequate absorption of vitamin D, which becomes insufficient as the disease progresses to more advanced stages. Moreover, vitamin D deficiency in patients with NENs [95,96] enhances the potential role of hypovitaminosis D in the development of such neoplasms. Additionally, there are data on the expression of VDR in neuroendocrine cells. Moreover, vitamin D analogue demonstrated the ability to induce cell cycle arrest in the G0/G1 phase and apoptosis in a murine insulinoma

cell line [108]. The precise mechanism underlying this correlation remains incompletely understood. Nevertheless, vitamin D has demonstrated involvement in various cellular processes including growth regulation, immune modulation, differentiation, adhesion, angiogenesis, apoptosis, and metastasis in epithelial tissues [109].

In light of the heightened occurrence of vitamin D deficiency among individuals with autoimmune conditions, there is growing interest in exploring vitamin D supplementation as a potential treatment in autoimmune conditions. Based on the data examined in the current review, while the precise mechanisms underlying the role of vitamin D in CAAG remain to be fully elucidated, accumulating evidence suggests that vitamin D may affect immune function and gastric mucosal integrity, making it a promising avenue for further research and potential therapeutic intervention. Thus, the routine evaluation of vitamin D levels in patients with CAAG is essential. Moreover, vitamin D supplementation in CAAG individuals suffering from vitamin D deficiency before the progression of disease may be a crucial preventive factor [110]. However, the lack of large, randomized controlled trials necessitates further well-organized studies with robust methodological design to demonstrate the causality of vitamin D in CAAG patients and thus validate the efficacy of vitamin D in preventing CAAG and determine if vitamin D supplementation can restrict the damage of gastric parietal cells.

Author Contributions

IA designed the article, collected the data, wrote the article; CK collected the data, wrote the article; CT designed the article, revised the article critically for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Iwamuro M, Tanaka T, Otsuka M. Update in Molecular Aspects and Diagnosis of Autoimmune Gastritis. Current Issues in Molecular Biology. 2023; 45: 5263–5275.

[2] Livzan MA, Gaus OV, Mozgovoi SI, Bordin DS. Chronic Autoimmune Gastritis: Modern Diagnostic Principles. Diagnostics (Basel, Switzerland). 2021; 11: 2113.

[3] Solcia E, Rindi G, Fiocca R, Villani L, Buffa R, Ambrosiani L, et al. Distinct patterns of chronic gastritis associated with carcinoid and cancer and their role in tumorigenesis. The Yale Journal of Biology and Medicine. 1992; 65: 793–804; discussion 827–829.

[4] Massironi S, Zilli A, Elvevi A, Invernizzi P. The changing face of chronic autoimmune atrophic gastritis: an updated comprehensive perspective. Autoimmunity Reviews. 2019; 18: 215–222.

[5] Stolte M, Baumann K, Bethke B, Ritter M, Lauer E, Eidt H. Active autoimmune gastritis without total atrophy of the glands. Zeitschrift Fur Gastroenterologie. 1992; 30: 729–735.

[6] Itsuno M, Watanabe H, Iwafuchi M, Ito S, Yanaihara N, Sato K, et al. Multiple carcinoids and endocrine cell micronests in type A gastritis. Their morphology, histogenesis, and natural history. Cancer. 1989; 63: 881–890.

[7] Engevik AC, Kaji I, Goldenring JR. The Physiology of the Gastric Parietal Cell. Physiological Reviews. 2020; 100: 573–602.

[8] Lenti MV, Rugge M, Lahner E, Miceli E, Toh BH, Genta RM, et al. Autoimmune gastritis. Nature Reviews. Disease Primers. 2020; 6: 56.

[9] Singh S, Chakole S, Agrawal S, Shetty N, Prasad R, Lohakare T, et al. A Comprehensive Review of Upper Gastrointestinal Symptom Management in Autoimmune Gastritis: Current Insights and Future Directions. Cureus. 2023; 15: e43418.

[10] Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut. 2015; 64: 1353–1367.

[11] Park JY, Cornish TC, Lam-Himlin D, Shi C, Montgomery E. Gastric lesions in patients with autoimmune metaplastic atrophic gastritis (AMAG) in a tertiary care setting. The American Journal of Surgical Pathology. 2010; 34: 1591–1598.

[12] Zhang H, Jin Z, Cui R, Ding S, Huang Y, Zhou L. Autoimmune metaplastic atrophic gastritis in chinese: a study of 320 patients at a large tertiary medical center. Scandinavian Journal of Gastroenterology. 2017; 52: 150–156.

[13] Aditi A, Graham DY. Vitamin C, gastritis, and gastric disease: a historical review and update. Digestive Diseases and Sciences. 2012; 57: 2504–2515.

[14] Ludden JB, Flexner J, Wright IS. Studies on ascorbic acid deficiency in gastric diseases: incidence, diagnosis and treatment. American Journal of Digestive Diseases. 1941; 8: 249–252.

[15] Cavalcoli F, Zilli A, Conte D, Massironi S. Micronutrient deficiencies in patients with chronic atrophic autoimmune gastritis: A review. World Journal of Gastroenterology. 2017; 23: 563–572.

[16] Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 2020; 12: 2097.

[17] Ismailova A, White JH. Vitamin D, infections and immunity. Reviews in Endocrine & Metabolic Disorders. 2022; 23: 265–277.

[18] Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, Hormone, and Immunomodulator. Nutrients. 2018; 10: 1656.

[19] Johnson CR, Thacher TD. Vitamin D: immune function, inflammation, infections and auto-immunity. Paediatrics and International Child Health. 2023; 43: 29–39.

[20] Conti L, Annibale B, Lahner E. Autoimmune Gastritis and Gastric Microbiota. Microorganisms. 2020; 8: 1827.

[21] De Aizpurua HJ, Cosgrove LJ, Ungar B, Toh BH. Autoantibodies cytotoxic to gastric parietal cells in serum of patients with pernicious anemia. The New England Journal of Medicine. 1983; 309: 625–629.

[22] Marignani M, Delle Fave G, Mecarocci S, Bordi C, Angeletti S, D'Ambra G, et al. High prevalence of atrophic body gastritis in

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patients with unexplained microcytic and macrocytic anemia: a prospective screening study. The American Journal of Gastroenterology. 1999; 94: 766–772.

[23] De Block CE, Van Campenhout CM, De Leeuw IH, Keenoy BM, Martin M, Van Hoof V, *et al*. Soluble transferrin receptor level: a new marker of iron deficiency anemia, a common manifestation of gastric autoimmunity in type 1 diabetes. Diabetes Care. 2000; 23: 1384–1388.

[24] Esposito G, Dottori L, Pivetta G, Ligato I, Dilaghi E, Lahner E. Pernicious Anemia: The Hematological Presentation of a Multifaceted Disorder Caused by Cobalamin Deficiency. Nutrients. 2022; 14: 1672.

[25] Al-Awami HM, Raja A, Soos MP. Physiology, gastric intrinsic factor. StatPearls Publishing: Treasure Island (FL). 2023.

[26] Lenti MV, Miceli E, Padula D, Di Sabatino A, Corazza GR. The challenging diagnosis of autoimmune atrophic gastritis. Scandinavian Journal of Gastroenterology. 2017; 52: 471–472.

[27] Lenti MV, Miceli E, Cococcia S, Klersy C, Staiani M, Guglielmi F, *et al*. Determinants of diagnostic delay in autoimmune atrophic gastritis. Alimentary Pharmacology & Therapeutics. 2019; 50: 167–175.

[28] Bedeir AS, Lash RH, Lash JG, Ray MB. Significant increase in IgG4+ plasma cells in gastric biopsy specimens from patients with pernicious anaemia. Journal of Clinical Pathology. 2010; 63: 999–1001.

[29] Neumann WL, Coss E, Rugge M, Genta RM. Autoimmune atrophic gastritis–pathogenesis, pathology and management. Nature Reviews. Gastroenterology & Hepatology. 2013; 10: 529–541.

[30] Herrera-Goepfert R, Yamamoto-Furusho JK, Onate-Ocana LF, Camorlinga-Ponce M, Munoz L, Ruiz-Morales JA, *et al*. Role of the HLA-DQ locus in the development of chronic gastritis and gastric carcinoma in Mexican patients. World Journal of Gastroenterology. 2006; 12: 7762–7767.

[31] Chmiela M, Gonciarz W. Molecular mimicry in *Helicobacter pylori* infections. World Journal of Gastroenterology. 2017; 23: 3964–3977.

[32] Wang L, Cao ZM, Zhang LL, Dai XC, Liu ZJ, Zeng YX, *et al*. *Helicobacter Pylori* and Autoimmune Diseases: Involving Multiple Systems. Frontiers in Immunology. 2022; 13: 833424.

[33] Claeys D, Faller G, Appelmelk BJ, Negrini R, Kirchner T. The gastric H+,K+-ATPase is a major autoantigen in chronic Helicobacter pylori gastritis with body mucosa atrophy. Gastroenterology. 1998; 115: 340–347.

[34] Youssefi M, Tafaghodi M, Farsiani H, Ghazvini K, Keikha M. Helicobacter pylori infection and autoimmune diseases; Is there an association with systemic lupus erythematosus, rheumatoid arthritis, autoimmune atrophy gastritis and autoimmune pancreatitis? A systematic review and meta-analysis study. Journal of Microbiology, Immunology, and Infection. 2021; 54: 359–369.

[35] D'Elios MM, Appelmelk BJ, Amedei A, Bergman MP, Del Prete G. Gastric autoimmunity: the role of Helicobacter pylori and molecular mimicry. Trends in Molecular Medicine. 2004; 10: 316–323.

[36] D'Elios MM, Bergman MP, Azzurri A, Amedei A, Benagiano M, De Pont JJ, *et al*. H(+),K(+)-atpase (proton pump) is the target autoantigen of Th1-type cytotoxic T cells in autoimmune gastritis. Gastroenterology. 2001; 120: 377–386.

[37] Troilo A, Grassi A, Petrone L, Cianchi F, Benagiano M, Bella CD, *et al*. Intrinsic factor recognition promotes T helper 17/T helper 1 autoimmune gastric inflammation in patients with pernicious anemia. Oncotarget. 2019; 10: 2921–2929.

[38] Cellini M, Santaguida MG, Virili C, Capriello S, Brusca N, Gargano L, *et al*. Hashimoto's Thyroiditis and Autoimmune Gastritis. Frontiers in Endocrinology. 2017; 8: 92.

[39] Lahner E, Zagari RM, Zullo A, Di Sabatino A, Meggio A, Ce-

saro P, *et al*. Chronic atrophic gastritis: Natural history, diagnosis and therapeutic management. A position paper by the Italian Society of Hospital Gastroenterologists and Digestive Endoscopists [AIGO], the Italian Society of Digestive Endoscopy [SIED], the Italian Society of Gastroenterology [SIGE], and the Italian Society of Internal Medicine [SIMI]. Digestive and Liver Disease. 2019; 51: 1621–1632.

[40] Giustina A, Bilezikian JP, Adler RA, Banfi G, Bikle DD, Binkley NC, *et al*. Consensus Statement on Vitamin D Status Assessment and Supplementation: Whys, Whens, and Hows. Endocrine Reviews. 2024. (online ahead of print)

[41] Triantos C, Aggeletopoulou I, Thomopoulos K, Mouzaki A. Vitamin D-Liver Disease Association: Biological Basis and Mechanisms of Action. Hepatology (Baltimore, Md.). 2021; 74: 1065–1073.

[42] Wei X, Pandohee J, Xu B. Recent developments and emerging trends in dietary vitamin D sources and biological conversion. Critical Reviews in Food Science and Nutrition. 2023; 1–17.

[43] Latic N, Erben RG. FGF23 and Vitamin D Metabolism. JBMR Plus. 2021; 5: e10558.

[44] Janoušek J, Pilařová V, Macáková K, Nomura A, Veiga-Matos J, Silva DDD, *et al*. Vitamin D: sources, physiological role, biokinetics, deficiency, therapeutic use, toxicity, and overview of analytical methods for detection of vitamin D and its metabolites. Critical Reviews in Clinical Laboratory Sciences. 2022; 59: 517–554.

[45] Dominguez LJ, Farruggia M, Veronese N, Barbagallo M. Vitamin D Sources, Metabolism, and Deficiency: Available Compounds and Guidelines for Its Treatment. Metabolites. 2021; 11: 255.

[46] Bouillon R. Genetic and environmental determinants of vitamin D status. Lancet (London, England). 2010; 376: 148–149.

[47] Cui A, Zhang T, Xiao P, Fan Z, Wang H, Zhuang Y. Global and regional prevalence of vitamin D deficiency in population-based studies from 2000 to 2022: A pooled analysis of 7.9 million participants. Frontiers in Nutrition. 2023; 10: 1070808.

[48] Passeri G, Giannini S. Benefits of Vitamin D in Health and Diseases. Nutrients. 2023; 15: 2419.

[49] Płudowski P, Kos-Kudła B, Walczak M, Fal A, Zozulińska-Ziółkiewicz D, Sieroszewski P, *et al*. Guidelines for Preventing and Treating Vitamin D Deficiency: A 2023 Update in Poland. Nutrients. 2023; 15: 695.

[50] Carlberg C. Genome-wide (over)view on the actions of vitamin D. Frontiers in Physiology. 2014; 5: 167.

[51] Carlberg C. Vitamin D Genomics: From *In Vitro* to *In Vivo*. Frontiers in Endocrinology. 2018; 9: 250.

[52] Carlberg C. Genomic signaling of vitamin D. Steroids. 2023; 198: 109271.

[53] Żmijewski MA. Nongenomic Activities of Vitamin D. Nutrients. 2022; 14: 5104.

[54] Udomsinprasert W, Jittikoon J. Vitamin D and liver fibrosis: Molecular mechanisms and clinical studies. Biomedicine & Pharmacotherapy. 2019; 109: 1351–1360.

[55] Hoenderop JG, Vennekens R, Müller D, Prenen J, Droogmans G, Bindels RJ, *et al*. Function and expression of the epithelial Ca(2+) channel family: comparison of mammalian ECaC1 and 2. The Journal of Physiology. 2001; 537: 747–761.

[56] Chow J, Norng M, Zhang J, Chai J. TRPV6 mediates capsaicin-induced apoptosis in gastric cancer cells–Mechanisms behind a possible new "hot" cancer treatment. Biochimica et Biophysica Acta. 2007; 1773: 565–576.

[57] Trowbridge R, Mittal SK, Sharma P, Hunter WJ, Agrawal DK. Vitamin D receptor expression in the mucosal tissue at the gastroesophageal junction. Experimental and Molecular Pathology. 2012; 93: 246–249.

[58] Wang Y, Zhu J, DeLuca HF. Where is the vitamin D receptor?

Archives of Biochemistry and Biophysics. 2012; 523: 123–133.

[59] Marcinkowska E. The Vitamin D System in Humans and Mice: Similar but Not the Same. Reports. 2020; 3: 1.

[60] Christakos S, Li S, De La Cruz J, Shroyer NF, Criss ZK, Verzi MP, *et al*. Vitamin D and the intestine: Review and update. The Journal of Steroid Biochemistry and Molecular Biology. 2020; 196: 105501.

[61] Gascon-Barré M, Demers C, Mirshahi A, Néron S, Zalzal S, Nanci A. The normal liver harbors the vitamin D nuclear receptor in nonparenchymal and biliary epithelial cells. Hepatology (Baltimore, Md.). 2003; 37: 1034–1042.

[62] Ding N, Liddle C, Evans RM, Downes M. Hepatic actions of vitamin D receptor ligands: a sunshine option for chronic liver disease? Expert Review of Clinical Pharmacology. 2013; 6: 597–599.

[63] Norman AW. Minireview: vitamin D receptor: new assignments for an already busy receptor. Endocrinology. 2006; 147: 5542–5548.

[64] Kamen DL, Tangpricha V. Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. Journal of Molecular Medicine (Berlin, Germany). 2010; 88: 441–450.

[65] Cantorna MT, Rogers CJ, Arora J. Aligning the Paradoxical Role of Vitamin D in Gastrointestinal Immunity. Trends in Endocrinology and Metabolism: TEM. 2019; 30: 459–466.

[66] Khashim Alswailmi F, Shah SIA, Nawaz H, Al-Mazaideh GM. Molecular Mechanisms of Vitamin D-Mediated Immunomodulation. Galen Medical Journal. 2021; 10: e2097.

[67] Sîrbe C, Rednic S, Grama A, Pop TL. An Update on the Effects of Vitamin D on the Immune System and Autoimmune Diseases. International Journal of Molecular Sciences. 2022; 23: 9784.

[68] Stumpf WE. Vitamin D and the digestive system. European Journal of Drug Metabolism and Pharmacokinetics. 2008; 33: 85–100.

[69] Wen Y, Da M, Zhang Y, Peng L, Yao J, Duan Y. Alterations in vitamin D signaling pathway in gastric cancer progression: a study of vitamin D receptor expression in human normal, premalignant, and malignant gastric tissue. International Journal of Clinical and Experimental Pathology. 2015; 8: 13176–13184.

[70] Triantos C, Aggeletopoulou I, Mantzaris GJ, Mouzaki A. Molecular basis of vitamin D action in inflammatory bowel disease. Autoimmunity Reviews. 2022; 21: 103136.

[71] Aggeletopoulou I, Marangos M, Assimakopoulos SF, Mouzaki A, Thomopoulos K, Triantos C. Vitamin D and Microbiome: Molecular Interaction in Inflammatory Bowel Disease Pathogenesis. The American Journal of Pathology. 2023; 193: 656–668.

[72] Zhou J, Ge X, Fan X, Wang J, Miao L, Hang D. Associations of vitamin D status with colorectal cancer risk and survival. International Journal of Cancer. 2021; 149: 606–614.

[73] Shafrir A, Shauly-Aharonov M, Katz LH, Paltiel O, Pickman Y, Ackerman Z. The Association between Serum Vitamin D Levels and *Helicobacter pylori* Presence and Eradication. Nutrients. 2021; 13: 278.

[74] Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. Science (New York, N.Y.). 1983; 221: 1181–1183.

[75] Bhalla AK, Amento EP, Clemens TL, Holick MF, Krane SM. Specific high-affinity receptors for 1,25-dihydroxyvitamin D3 in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. The Journal of Clinical Endocrinology and Metabolism. 1983; 57: 1308–1310.

[76] von Essen MR, Kongsbak M, Schjerling P, Olgaard K, Odum N, Geisler C. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. Nature Immunology. 2010; 11: 344–349.

[77] Veldman CM, Cantorna MT, DeLuca HF. Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. Archives of Biochemistry and Biophysics. 2000; 374: 334–338.

[78] Aranow C. Vitamin D and the immune system. Journal of Investigative Medicine: the Official Publication of the American Federation for Clinical Research. 2011; 59: 881–886.

[79] Scolletta S, Colletti M, Di Luigi L, Crescioli C. Vitamin D receptor agonists target CXCL10: new therapeutic tools for resolution of inflammation. Mediators of Inflammation. 2013; 2013: 876319.

[80] Lemire JM, Archer DC, Beck L, Spiegelberg HL. Immunosuppressive actions of 1,25-dihydroxyvitamin D3: preferential inhibition of Th1 functions. The Journal of Nutrition. 1995; 125: 1704S–1708S.

[81] Cippitelli M, Santoni A. Vitamin D3: a transcriptional modulator of the interferon-gamma gene. European Journal of Immunology. 1998; 28: 3017–3030.

[82] Alroy I, Towers TL, Freedman LP. Transcriptional repression of the interleukin-2 gene by vitamin D3: direct inhibition of NFATp/AP-1 complex formation by a nuclear hormone receptor. Molecular and Cellular Biology. 1995; 15: 5789–5799.

[83] Jeffery LE, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, *et al*. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. Journal of Immunology (Baltimore, Md.: 1950). 2009; 183: 5458–5467.

[84] Reichel H, Koeffler HP, Tobler A, Norman AW. 1 alpha,25-Dihydroxyvitamin D3 inhibits gamma-interferon synthesis by normal human peripheral blood lymphocytes. Proceedings of the National Academy of Sciences of the United States of America. 1987; 84: 3385–3389.

[85] Chauss D, Freiwald T, McGregor R, Yan B, Wang L, Nova-Lamperti E, *et al*. Autocrine vitamin D signaling switches off pro-inflammatory programs of T_H1 cells. Nature Immunology. 2022; 23: 62–74.

[86] Daniel C, Sartory NA, Zahn N, Radeke HH, Stein JM. Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. The Journal of Pharmacology and Experimental Therapeutics. 2008; 324: 23–33.

[87] Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1alpha,25-Dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. Journal of Immunology (Baltimore, Md.: 1950). 2001; 167: 4974–4980.

[88] Penna G, Roncari A, Amuchastegui S, Daniel KC, Berti E, Colonna M, *et al*. Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4+Foxp3+ regulatory T cells by 1,25-dihydroxyvitamin D3. Blood. 2005; 106: 3490–3497.

[89] Yu S, Cantorna MT. The vitamin D receptor is required for iNKT cell development. Proceedings of the National Academy of Sciences of the United States of America. 2008; 105: 5207–5212.

[90] Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential. Frontiers in Immunology. 2017; 7: 697.

[91] Yamamoto EA, Jørgensen TN. Relationships Between Vitamin D, Gut Microbiome, and Systemic Autoimmunity. Frontiers in Immunology. 2020; 10: 3141.

[92] Eastell R, Vieira NE, Yergey AL, Wahner HW, Silverstein MN, Kumar R, *et al*. Pernicious anaemia as a risk factor for osteoporosis. Clinical Science (London, England: 1979). 1992; 82: 681–685.

[93] Antico A, Tozzoli R, Giavarina D, Tonutti E, Bizzaro N. Hypovitaminosis D as predisposing factor for atrophic type A gastritis: a case-control study and review of the literature on the interaction of Vitamin D with the immune system. Clinical Reviews in Allergy & Immunology. 2012; 42: 355–364.

[94] Massironi S, Cavalcoli F, Rossi RE, Conte D, Spampatti MP, Ciafardini C, *et al*. Chronic autoimmune atrophic gastritis associated with primary hyperparathyroidism: a transversal prospective study. European Journal of Endocrinology. 2013; 168: 755–761.

[95] Massironi S, Zilli A, Bernasconi S, Fanetti I, Cavalcoli F, Ciafardini C, *et al*. Impact of Vitamin D on the Clinical Outcome of Gastro-Entero-Pancreatic Neuroendocrine Neoplasms: Report on a Series from a Single Institute. Neuroendocrinology. 2017; 105: 403–411.

[96] Massironi S, Cavalcoli F, Zilli A, Del Gobbo A, Ciafardini C, Bernasconi S, *et al*. Relevance of vitamin D deficiency in patients with chronic autoimmune atrophic gastritis: a prospective study. BMC Gastroenterology. 2018; 18: 172.

[97] Zilli A, Cavalcoli F, Ciafardini C, Massironi S. Deficiency of micronutrients in patients affected by chronic atrophic autoimmune gastritis: A single-institution observational study. Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2019; 51: 505–509.

[98] Fischer V, Haffner-Luntzer M, Amling M, Ignatius A. Calcium and vitamin D in bone fracture healing and post-traumatic bone turnover. European Cells & Materials. 2018; 35: 365–385.

[99] Kim HW, Kim YH, Han K, Nam GE, Kim GS, Han BD, *et al*. Atrophic gastritis: a related factor for osteoporosis in elderly women. PloS One. 2014; 9: e101852.

[100] Chou YY, Jeng YM, Lee TT, Hu FC, Kao HL, Lin WC, *et al*. Cytoplasmic CD24 expression is a novel prognostic factor in diffuse-type gastric adenocarcinoma. Annals of Surgical Oncology. 2007; 14: 2748–2758.

[101] Wang YC, Wang JL, Kong X, Sun TT, Chen HY, Hong J, *et al*. CD24 mediates gastric carcinogenesis and promotes gastric cancer progression via STAT3 activation. Apoptosis: an International Journal on Programmed Cell Death. 2014; 19: 643–656.

[102] Peña C, García JM, Larriba MJ, Barderas R, Gómez I, Herrera M, *et al*. SNAI1 expression in colon cancer related with CDH1 and VDR downregulation in normal adjacent tissue. Oncogene. 2009; 28: 4375–4385.

[103] Alvarez-Díaz S, Valle N, García JM, Peña C, Freije JMP, Quesada V, *et al*. Cystatin D is a candidate tumor suppressor gene induced by vitamin D in human colon cancer cells. The Journal of Clinical Investigation. 2009; 119: 2343–2358.

[104] Wells A, Yates C, Shepard CR. E-cadherin as an indicator of mesenchymal to epithelial reverting transitions during the metastatic seeding of disseminated carcinomas. Clinical & Experimental Metastasis. 2008; 25: 621–628.

[105] Arias AM. Epithelial mesenchymal interactions in cancer and development. Cell. 2001; 105: 425–431.

[106] Daryabor G, Gholijani N, Kahmini FR. A review of the critical role of vitamin D axis on the immune system. Experimental and Molecular Pathology. 2023; 132-133: 104866.

[107] Ruiz-Ballesteros AI, Meza-Meza MR, Vizmanos-Lamotte B, Parra-Rojas I, de la Cruz-Mosso U. Association of Vitamin D Metabolism Gene Polymorphisms with Autoimmunity: Evidence in Population Genetic Studies. International Journal of Molecular Sciences. 2020; 21: 9626.

[108] Chiang KC, Yeh CN, Pang JHS, Hsu JT, Yeh TS, Chen LW, *et al*. 1α,25(OH)2D3 Analog, MART-10, Inhibits Neuroendocrine Tumor Cell Growth Through Induction of G0/G1 Cell-cycle Arrest and Apoptosis. Anticancer Research. 2016; 36: 3307–3313.

[109] Swami S, Raghavachari N, Muller UR, Bao YP, Feldman D. Vitamin D growth inhibition of breast cancer cells: gene expression patterns assessed by cDNA microarray. Breast Cancer Research and Treatment. 2003; 80: 49–62.

[110] Adorini L. Intervention in autoimmunity: the potential of vitamin D receptor agonists. Cellular Immunology. 2005; 233: 115–124.