Vitamin D in autoimmune bullous diseases*

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Numerous epidemiological studies have suggested a link between vitamin D deficiency and the development of various autoimmune diseases, including diabetes mellitus type 1, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis or systemic lupus erythematosus. More recently, such a link has been also proposed for autoimmune bullous diseases (AIBD). This is a relatively rare and potentially life-threatening, organ-specific group of inflammatory skin diseases characterized by the presence of tissue-bound and circulating autoantibodies against various molecules present in desmosomes (in pemphigoid diseases) or hemidesmosomes (in pemphigoid diseases). In addition to the well-known role of vitamin D in calcium and phosphate homeostasis, the hormone active vitamin D metabolite, 1,25-dihydroxyvitamin D₃ (calcitriol), exerts potent effects on cellular differentiation and regulation of immune responses via binding to the vitamin D receptor present in most cells of the immune system. Since cells of both, the innate and adaptive immune systems, are known to be relevant in AIBD, the role of vitamin D analogues in the treatment of patients with these disorders deserves much attention. This mini-review summarizes recent epidemiological and experimental studies on vitamin D involvement in the autoimmune bullous diseases.

Key words: calcitriol; 1,25(OH)₂D₃; vitamin D; 25(OH)D; autoimmune bullous diseases.

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Abbreviations: AIBD, autoimmune bullous diseases; 1,25(OH)₂D₃, 1α,25-dihydroxyvitamin D₃; 25(OH)D, 25-hydroxyvitamin D; VDR, vitamin D receptor; APC, antigen presenting cell; IVIG, intravenous immunoglobulin; PV, pemphigus vulgaris; PF, pemphigus foliaceus; BP, bullous pemphigoid; EBA, epidermolysis bullosa acquita; COL17, collagen type XVII; COL7, collagen type VII

VITAMIN D: PRODUCTION, METABOLISM, AND MECHANISMS OF ACTION

In a canonical metabolic pathway, the cholesterol-derived vitamin D is present in two major forms: ergocalciferol (D₂) and cholecalciferol (D₃), the latter being synthesized in the skin upon sunlight exposure (UV radiation) and converted to 25-hydroxyvitamin D₃ [25(OH)D₃; calcidiol] and 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃; calcitriol] in the liver and kidneys, respectively, by the vitamin D-25-hydroxylase (CYP2R1) and CYP27A1 and the 25(OH)D-1α-hydroxylase (CYP27B1) (Holick et al., 2011; Bikle, 2014). Active form of vitamin D₃ [1,25(OH)₂D₃] binds to the vitamin D binding protein (DBP) in circulation and is delivered to the target tissues, such as the intestine, bone and kidneys, to regulate the calcium and phosphate homeostasis (Bikle, 2012). In addition, 1,25(OH)₂D₃ is also synthesized locally in the epidermis and various immune cells (Bikle, 2012; 2014). Alternatively, vitamin D₂ and D₃ can be supplemented by a balanced diet of plant and animal origin, respectively. Vitamin D, whether produced in the skin from 7-dehydrocholesterol or absorbed from the diet, must be activated first to 25(OH)D and then to 1,25(OH)₂D (Bikle, 2014). Nevertheless, numerous agencies and scientific organizations highly recommend vitamin D supplementation to maintain health and prevent development of metabolic, cancerous, and immune-related diseases (Pludowski et al., 2018). Recent studies have revealed that the vitamin D metabolites can be also synthesized and activated through a CYP11A1-driven non-canonical metabolic pathway (Slominski et al., 2012; Slominski et al., 2014a; Slominski et al., 2015a; Slominski et al., 2015b).

While 25(OH)D is the major (inactive) circulating form of vitamin D, commonly used as a serological indicator to evaluate the vitamin D status in patients (Holick et al., 2011), calcitriol represents the biologically active vitamin D metabolite which serves as the primary ligand for the vitamin D receptor (VDR) expressed in the bone, gastrointestinal tract, skeletal muscle or skin, as well as in various immune cells, including dendritic cells, monocytes/macrophages or lymphocytes (Yang et al., 2013; Mazzaferrro et al., 2014; Mostafa & Hegazy 2015). The 1,25(OH)₂D₃/VDR complex binds to the vitamin D response elements (VDRs) in the genome to activate or suppress transcription of hundreds of genes in a cell-specific manner. In general, the functions of vitamin D analogues are characterized as genomic, i.e. mediated through VDR transcriptional effects inside the cell nucleus, and non-genomic, when VDR induces rapid signaling, including the ability to stimulate calcium transport across the plasma membrane (Bikle, 2014).

Apart from the classic role of vitamin D in the calcium and phosphate homeostasis, many in vivo studies have shown that active vitamin D metabolites regulate several physiological processes, such as the cell proliferation, differentiation, and immune modulation. Active vitamin D metabolites display immunomodulatory activity manifested by reduction in the antigen presenting cells’ (APC) activity or pro-inflammatory T helper 1 (Th1) and T helper 17 (Th17) frequencies, as well as expansion of the T- and B-regulatory cells (Takeda et al., 2010; Bikle, 2014; Alhassan Mohammedi et al., 2017; Tukaj et al., 2018).

In addition, it has been proven that CYP11A1-derived vitamin D metabolites serve as ligands for VDR or can act as inverse agonists on retinoic acid orphan receptors (ROR) α and γ (Slominski et al., 2014b; Slominski et al., 2017), which are known to play key roles in regulation of the immune and metabolic pathways. More recently,
the top signaling pathways for CYP11A1-driven analogues, such as 20,23(OH)2D, were linked to activation of the aryl hydrocarbon receptor (AhR), representing an alternative receptor to VDR (Slominski et al., 2018). It is worth to mention that despite the importance of UVB radiation in the 25-hydroxyvitamin D synthesis, this radiation is also a key agent that induces DNA damage in the skin. Both, 1,25(OH)2D and CYP11A1-derived vitamin D analogues, protect the epidermal keratinocytes against UVB-induced damage via activation of the Nrfl2-dependent antioxidant response and p53-phosphorylation, as well as by induction of the DNA repair system (Chaiprasongsuk et al., 2019). In addition, both - the classical 1,25(OH)2D and non-calcemic CYP11A1-driven analogues, exert anti-inflammatory effects on keratinocytes by inhibiting the nuclear factor-xB (NF-xB) activity (Janjetovic et al., 2009; 2010; Tukaj et al., 2016).

Because regulatory effects of vitamin D analogues on proliferation and differentiation have been also confirmed for cells outside the immune system, topical application of vitamin D analogues has been considered and approved for the treatment of psoriasis - one of the most common chronic inflammatory skin disease which affects approximately 2% of the general human population (Umar et al., 2018). In addition, some reports indicate that topically applied vitamin D analogues are also effective in vitiligo (Xing & Xu, 2012). Because skin is the main source of vitamin D in our body (approximately 90%) and most of the available data point to this vitamin’s significant impact on the health of skin and other organs (Mostafa & Hegazy 2015), the potential impact of hypovitaminosis D on the development of dermatological diseases, including autoimmune bullous skin diseases, deserves special attention.

AUTOIMMUNE BULLOUS DISEASES

Autoimmune bullous diseases (AIBD) are characterized by the presence of tissue-bound and circulating autoantibodies that are directed against different structural molecules present in the skin and adjacent mucous membranes. AIBD are divided into three different subgroups, such as the pemphigoid, pemphigus, and dermatitis herpetiformis, the last being the cutaneous manifestation of the celiac disease with autoantibodies directed against the tissue and the epidermal transglutaminase (Witte et al., 2018). Pemphigus is a group of autoantibody-mediated autoimmune diseases of the skin and oral mucosa, in which the loss of cell adhesion (acantholysis) causes blisters and erosions. Patients with pemphigus are characterized by the presence of autoantibodies directed against desmoglein 1 and desmoglein 3, which are cell-cell adhesion molecules found in desmosomes in the epidermis. There are two major subtypes of pemphigus diseases: pemphigus vulgaris (PV) and pemphigus foliaceus (PF), the first being the most common form of pemphigus (Kasperkiewicz et al., 2017). While the etiology of pemphigus diseases is largely unknown, the genetic and environmental risk factors have been proposed. Both, the PV and PF are frequently associated with other (auto)inflammatory diseases, such as psoriasis, neurological and psychiatric disorders or some malignancies. In the case of PV, genetic risk factors include either HLA alleles DRB1*04:02 and DQB1*05:03 or non-HLA genes, i.e. DS63, TAP2, II.6, and ST18. In addition, environmental risk factors, in particular use of penicillamine and captopril, as well as exposure to pesticides, metal vapor, UV, ionizing radiation, burns, undergoing surgery or stressful life events have been noted. In genetically susceptible individuals, the autoimmune reaction is driven by autoreactive T and B lymphocytes. Autoreactive T cells are educated by antigen presenting cells (APC) that present Dsg peptides via HLA class II molecules. Consequently, autoreactive T helper cells specific for Dsg molecules drive generation of autoreactive B cells and secretion of the tissue-bound and circulating autoantibodies to Dsg (Kasperkiewicz et al., 2017; Schmidt et al., 2019). Pemphigus can be treated with systemic corticosteroids and adjuvant therapies, including immunosuppressive agents, intravenous immunoglobulin (IVIG) and plasmapheresis. In addition, rituximab, a monoclonal antibody against the CD20 molecule (B cells’ marker), is another promising therapeutic option (Kasperkiewicz et al., 2017).

Pemphigoid is another well-defined subgroup of AIBD that is characterized by the presence of tissue-bound and circulating autoantibodies directed against different structural molecules present in hemidesmosomes at the cutaneous basement membrane (Schmidt & Zillikens 2013). Bullous pemphigoid (BP), where autoantibodies to BP180 (collagen type XVII or COL17) and BP230 are observed, is the most common autoimmune subepidermal blistering disease, whose incidence, similarly to other autoimmune diseases, is constantly increasing (Witte et al., 2018). By contrast, epidermolysis bullosa acquisita (EBA), a subepidermal blistering disease with autoantibodies to type VII collagen (COL7), is one of the rarest AIBD, with an incidence rate of 0.2-0.5 per million per year (Vorobyev et al., 2017). The etiology of pemphigoid seems to be unclear, nevertheless either environmental or genetic risk factors have been described. Numerous data found an association between pemphigoid and other immunological disorders, including psoriasis (Schmidt & Zillikens; 2013; Ohata et al., 2015). In addition, BP has been strongly associated with neurological disorders, including cognitive impairment, Parkinson’s disease, stroke, epilepsy or multiple sclerosis (Schmidt & Zillikens; 2013). Several trigger factors, such as penicillin, vancomycin, gentamycin, trauma, burns, radiotherapy, UV-radiation, vaccination and contact allergy to metals have been described (Schmidt & Zillikens; 2013; Vorobyev et al., 2017). In addition, an association between HLA-DQBl*0301 and BP or mucous membrane pemphigoid (MMP), as well as the risk allele HLA-DRB1*1502 or association between HLA-DR2 and EBA, have been reported (Schmidt & Zillikens; 2013; Kasperkiewicz et al., 2016). The majority of studies concerning the pathophysiology of pemphigoid are based on experimental animal models and numerous evidences pointed to pathogenic importance of both, the local and systemic innate and adaptive autoimmune responses against structural proteins of the dermal–epidermal junction (Schmidt & Zillikens; 2013; Kasperkiewicz et al., 2016).

As in the case of pemphigus, the pemphigoid diseases can be controlled medically by using corticosteroids, high-doses of IVIG, rituximab, plasmapheresis, and immunoadsorption (Schmidt & Zillikens 2013; Koga et al., 2019).

VITAMIN D STATUS IN THE AUTOIMMUNE BULLOUS DISEASES

Several epidemiological studies demonstrated that the vitamin D deficiency leads to an increased prevalence of autoimmune diseases, such as the multiple sclerosis, diabetes type 1, rheumatoid arthritis or systemic lupus
Vitamin D status in patients with pemphigus vulgaris (PV), bullous pemphigoid (BP), and epidermolysis bullosa acquisita (EBA). In one case, the authors presented data concerning the vitamin D status in pemphigus patients without subdivision into PV and pemphigus foliaceus. There is no data available on vitamin D status in other rare pemphigus variants, such as the paraneoplastic pemphigus, pemphigus vegetans, pemphigus erythematosus or herpetiform pemphigus and pemphigoid diseases, such as the mucous membrane pemphigoid, pemphigoid gestationis, linear IgA disease, anti-laminin-γ1-pemphigoid, anti-p200 pemphigoid or lichen planus pemphigoides. According to the International Endocrine Society, the 25(OH)D serum concentrations of 20–29 ng/ml and below 20 ng/ml have been defined as vitamin D insufficiency and deficiency, respectively (Holick et al., 2011). The 25(OH)D values are presented in two unit forms, i.e. nmol/L or ng/mL. To convert nmol/L to ng/mL, the values should be divided by 2.5.

**Table 1. Vitamin D status in patients with AIBD**

<table>
<thead>
<tr>
<th>Patients (No.)</th>
<th>25(OH)D levels (mean ± S.D.) in patients vs corresponding controls (p-value)</th>
<th>Hypovitaminosis D in patients (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV (n=13)</td>
<td>12 ± 4.4 vs 22.2 ± 11.7 ng/mL (p=0.012)</td>
<td>62</td>
<td>Marzano <em>et al.</em>, 2012</td>
</tr>
<tr>
<td>BP (n=15)</td>
<td>9.6 ± 7.2 vs 22.6 ± 18.7 ng/mL (p=0.022)</td>
<td>73</td>
<td>Marzano <em>et al.</em>, 2012</td>
</tr>
<tr>
<td>BP (n=12)</td>
<td>32.4 ± 16.9 vs 32.6 ± 16.2 nmol/L (n. s.)</td>
<td>83</td>
<td>Tukaj <em>et al.</em>, 2013</td>
</tr>
<tr>
<td>PV (n=35)</td>
<td>13.9 ± 8.3 vs 22.2 ± 11.1 ng/mL (p&lt;0.001)</td>
<td>48.6</td>
<td>Marzano <em>et al.</em>, 2015</td>
</tr>
<tr>
<td>BP (n=32)</td>
<td>9.5 ± 7.7 vs 22.4 ± 14.9 ng/mL (p&lt;0.0001)</td>
<td>75</td>
<td>Marzano <em>et al.</em>, 2015</td>
</tr>
<tr>
<td>PV (n=34)</td>
<td>74.2 ± 53.1 vs 89.7 ± 29.5 nmol/L (p=0.008)</td>
<td>50</td>
<td>El-Komy <em>et al.</em>, 2014</td>
</tr>
<tr>
<td>PV (n=30)</td>
<td>11.1 ± 5.8 vs 12.1 ± 9.2 ng/ml (n. s.)</td>
<td>100</td>
<td>Joshi <em>et al.</em>, 2014</td>
</tr>
<tr>
<td>PV (n=32)</td>
<td>11.79 ± 1.55 vs 20.69 ± 2.79 ng/ml (p=0.009)</td>
<td>Not available</td>
<td>Zarei <em>et al.</em>, 2014</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>Not available</td>
<td>78.8</td>
<td>Moravvej <em>et al.</em>, 2016</td>
</tr>
<tr>
<td>(n=52)</td>
<td></td>
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<tr>
<td>BP (n=31)</td>
<td>29.3 ± 17.3 vs 34.9 ± 19.4 nmol/L (p=0.246)</td>
<td>86.7</td>
<td>Sarre <em>et al.</em>, 2016</td>
</tr>
<tr>
<td>EBA (n=22)</td>
<td>Not available</td>
<td>73</td>
<td>Tukaj <em>et al.</em>, 2018</td>
</tr>
</tbody>
</table>

Vitamin D status in patients with pemphigus vulgaris (PV), bullous pemphigoid (BP), and epidermolysis bullosa acquisita (EBA). In one case, the authors presented data concerning the vitamin D status in pemphigus patients without subdivision into PV and pemphigus foliaceus. There is no data available on vitamin D status in other rare pemphigus variants, such as the paraneoplastic pemphigus, pemphigus vegetans, pemphigus erythematosus or herpetiform pemphigus and pemphigoid diseases, such as the mucous membrane pemphigoid, pemphigoid gestationis, linear IgA disease, anti-laminin-γ1-pemphigoid, anti-p200 pemphigoid or lichen planus pemphigoides. According to the International Endocrine Society, the 25(OH)D serum concentrations of 20–29 ng/ml and below 20 ng/ml have been defined as vitamin D insufficiency and deficiency, respectively (Holick et al., 2011). The 25(OH)D values are presented in two unit forms, i.e. nmol/L or ng/mL. To convert nmol/L to ng/mL, the values should be divided by 2.5.

**EXPERIMENTAL THERAPIES USING VITAMIN D ANALOGUES IN THE AUTOIMMUNE BULLOUS DISEASES**

The efficacy of vitamin D supplementation in experimental models of arthritis, lupus, multiple sclerosis, encephalomyelitis, diabetes type 1, and atherosclerosis has been confirmed in various studies (Deluca & Cantorna, 2001; Takeda *et al.*, 2010; Dankers *et al.*, 2017). Moreover, several clinical trials have been performed to investigate the therapeutic value of vitamin D supplementation in multiple sclerosis, rheumatoid arthritis, Crohn’s disease, type I diabetes, and systemic lupus erythematosus (Dankers *et al.*, 2017). While patients with the autoimmune bullous skin diseases suffer from vitamin D deficiency (Marzano *et al.*, 2012 and Marzano *et al.*, 2015; Tukaj *et al.*, 2013; El-Komy *et al.*, 2014; Joshi *et al.*, 2014; Zarei *et al.*, 2014; Moravvej *et al.*, 2016; Sarre *et al.*, 2016; Tukaj *et al.*, 2018), a direct link between hypovitaminosis D and the development of autoimmune bullous diseases has not been proven.

It is hypothesized that binding of bullous pemphigoid (BP)-specific IgG autoantibodies to BP180 initiates the Fc receptor-independent events leading to the excessive expression and secretion of pro-inflammatory IL-6 and IL-8 from basal keratinocytes (Schmidt *et al.*, 2000; Schmidt & Zillikens, 2013). Activation of complement at the dermal–epidermal junction (DEJ), together with the mast cells’ degranulation and inflammatory chemokines result in the infiltration of inflammatory cells, including granulocytes, in the upper dermis. The reactive oxygen species (ROS) and matrix metalloproteinases (MMP) released by the activated granulocytes induce dermal-epidermal splitting and blister formation (Schmidt & Zillikens, 2013). We have recently found that bullous pemphigoid (BP) IgG-induced IL-6 and IL-8 secretion from...
Despite growing understanding of AIBD pathogenesis, treatment of this group of skin disorders remains challenging. This is because of frequent relapses, numerous side effects due to corticosteroid usage, or simply due to lack of effective treatment (Koga et al., 2019; Izumi et al., 2019). In addition, the incidence of AIBD is constantly increasing (Witte et al., 2018), and therefore there is a growing urgency for discovering an effective treatment or prophylactic regimen in order to reduce the incidence of these autoimmune disorders. Despite the usage of topical vitamin D analogues in the treatment of autoimmune skin conditions, such as psoriasis and vitiligo (Xing & Xu, 2012; Umar et al., 2018), there is a limited number of epidemiological and experimental studies on vitamin D involvement in the autoimmune bullous diseases. This requires further research and clinical trials involving the pemphigus and pemphigoid patients. In fact, several case reports have described that the Halley-Hailey disease, also known as a familial benign chronic pemphigus, can be successfully controlled with vitamin D analogues applied either orally or topically (Bianchi et al., 2004; Rajpara & King, 2005; Megna et al., 2019). Finally, because there are many case reports describing the coexistence of AIBD and psoriasis (Ohata et al., 2015), the role of topically applied vitamin D analogues in the treatment of these disorders needs to be properly evaluated.

REFERENCES


CONCLUSION

Figure 1. Pathophysiology and the experimental therapy of AIBD.
(a) 1,25(OH)2D3 (calcitriol) inhibits secretion of the pro-inflammatory cytokines induced by bullous pemphigoid (BP) anti-COL17 IgG in a human keratinocyte culture. (b) 1,25(OH)2D3 promotes expansion of disease-regulating immunosuppressive cells (Treg and Breg), attenuates secretion of pathogenic anti-COL7 IgG, as well as down-regulates neutrophil activity and inhibits proinflammatory Th17 cell population in a mouse model of epidermolysis bullosa acquista (EBA).


