Immunomodulation by vitamin D

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Vitamin D exerts several immunological functions in addition to its homeostatic functions on calcium and bone metabolism. Current data show that relative vitamin D deficiency (<75 nmol/l 25-hydroxyvitamin D) as well as acquired seasonal vitamin D deficiency (<50 nmol/l) are frequent in Germany. As confirmed by our own data, UV exposure plays a major role for maintenance of vitamin D status, e.g., in patients with UV-triggered diseases, vitamin D deficiency is more frequent, even throughout the year. The beneficial impact of vitamin D on immune functions is highlighted by epidemiologic, genetic, and experimental evidence. In the past years, numerous publications have presented associations between vitamin D deficiency, on the one hand, and severity and prevalence of allergic asthma in children and adults, on the other hand.

Immunomodulation by vitamin D

Vitamin D is a steroid hormone produced by the human body from 7-dehydrocholesterol when exposure to UV radiation is present [20]. After enzymatic hydroxylation, it is available in its active form 1α25-dihydroxyvitamin D (also called calcitriol) (Figure 1) [20]. It is essential for bone homeostasis as it promotes the resorption of nutritional calcium in the intestine and the kidney [19]. Although today the nutritional situation in the general population is very good, a relative vitamin D deficiency can occur, particularly in winter. A report by Hinzpeter et al. [18], for example, shows that in more than 80% of Germans the daily vitamin D intake with nutrition is below the recommended dose of 5 mg/day. Accordingly, more than 55% of Germans have a relative vitamin D deficiency (serum concentration of 25-hydroxyvitamin D < 50 nmol/l) [18]. Current research shows an increasing frequency of relative vitamin D deficiency over the past decade despite the widespread use of vitamin D supplementation [27]. It is very probable that an insufficient UV exposition due to indoor working and increasing use of sunscreens plays an important role [27]. Our own investigation in more than 1,900 patients from Berlin [16] showed that in summer a relative vitamin D deficiency was present in 39.4% of the investigated patients and in winter, where there is only little UV radiation, this rate was as high as 73.4% (Figure 2) [16]. In the human body, vitamin D is mainly produced by UV radiation biosynthesis [21]. In autoimmune patients with cutaneous lupus erythematosus, who have to avoid UV exposure due to its disease-promoting effects, a relative vitamin D deficiency is present in 85.7% of patients, even in the summer months, and in winter this rate increases to 97.1% [16]. These data underline that a relative vitamin D deficiency is frequent in Germany, particularly in individuals whose daily exposure to UV radiation is limited due to various reasons.

Vitamin D and immune system

Extensive investigation has suggested an immunomodulatory effect of vitamin D [2, 5, 13, 31]. It also seems to play a role in allergic diseases like allergic bronchial asthma [24, 26]. Epidemiological data show that in the northern parts of the USA a higher prevalence of allergic diseases is present than in the southern parts where there is more UV radiation [7]. Numerous reports suggest a relationship between vitamin D deficiency and the prevalence of allergic diseases as well as a relationship with the severity of allergic asthma and a hyperreactive bronchial system in children, adolescents [6, 9], and...
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Maternal vitamin D supplementation was shown to reduce the prevalence of juvenile wheezing in 3-year-old children [8]. However, the existing data is not unambiguous [22, 40]. It is thought that vitamin D deficiency increases glucocorticoid resistance, as an increased glucocorticoid consumption in the body and a reduced pulmonary function could be shown in vitamin D-deficient children and adults [37, 38]. Furthermore, gene analyses support the hypothesis that vitamin D plays a role in the pathogenesis of allergic asthma. For example, point mutations in the vitamin D receptor gene with a possible loss of function were found in two independent cohorts in the USA [33, 34], but not in a comparable German cohort [39]. The therapeutic use of vitamin D is limited by its hypercalcemic side effects. Nevertheless, the administration of 2 × 0.25 mg calcitriol p.o. for 7 days resulted in an improvement of glucocorticoid resistance in asthma patients, probably due to the induction of IL-10 producing regulatory Tr1 cells [42]. In parallel, increased IL-10 serum concentrations were measured in patients with congestive heart failure after supplementation with 2,000 IU of vitamin D [36]. Also, in patients with multiple sclerosis, an increase of the TGF-β production by CD4 T-helper cells could be detected after the administration of 1,000 IU/day of vitamin D [28], and after high-dose vitamin D supplementation even positive effects on disease severity could be demonstrated [23]. Vitamin D can act directly on immune cells, like antigen-presenting cells, but also on T and B lymphocytes [1, 29, 31]. Among the numerous possible effects are an altered, pro-tolerogenic activation of dendritic cells [3] or the regulation of the humoral immune response [12]. Our own investigation showed that vitamin D, on the one hand, inhibits IgE production, e.g., in B cells [14] and, on the other hand, induces the tolerogenic cytokine IL-10 (Figure 3) [15]. Interestingly, B cells can independently produce active calcitriol [15] so that immunoregulatory effects on B cells can also be obtained by supplementation of the precursor form. In a first clinical investigation, we could demonstrate that the supplementation of 2,000 IU of vitamin D in winter significantly increases the vitamin D concentration, and that this does not negatively (i.e., in the sense of an immunosuppression) influence a robust recall response, as measured by peripheral immune responses at the T cell and
Vitamin D analogs

Due to its hypercalcemic effects, the therapeutic use of vitamin D is limited [2, 29]. Thus, synthetic derivatives have been developed in which the calcium-mobilizing effects are dissociated from the immunologic effects. These kinds of calcitriol analogs are already being used in clinical practice for the topic therapy of psoriasis vulgaris (a chronic inflammatory skin disease) [29]. The exact molecular mechanism of these derivatives has not yet been fully elucidated, but cell-specific effects have been described. The calcitriol analog ZK.191784, for example, does not have calcium-resorbing effects on intestinal mucosal cells [32], but it has anti-inflammatory effects on T cells [43]. Our own investigation shows that in a murine model the systemic IgE response could be reduced by systemic treatment with a low-calcemic calcitriol analog [12]. Even very structurally different derivatives can be immunologically effective; the calcitriol derivative BXL-219, for example, prevents experimentally induced Type I diabetes [4], and another derivative, ZK.156979, inhibits experimental colitis [11]. In conclusion, these data underline the complex effect of vitamin D receptors on the immune response. Future data will demonstrate the therapeutic benefit of derivatives for the treatment of immune-mediated diseases in humans.

Nuclear hormone receptor ligands control IgE response

Vitamin D binds to its receptor (VDR) in the cytosol, and after translocation of this calcitriol-VDR complex into the cell nucleus, numerous genes are activated or inhibited [13]. In earlier investigations we could show that vitamin D is not the only nuclear hormone receptor ligand inhibiting IgE production. Other members of this family have the same effect: retinoids [41], liver X receptor ligands [14, 30], and PPARs [10, 35] (Figure 4). Recently, we could confirm these in vitro findings in the mouse model [12]. This may be the basis for an innovative therapeutic approach to use vitamin D in the treatment of allergic diseases. The fact that vitamin D inhibits the transcription factor NFκB, which is essential for the switching of the IgE isotype class, seems to play an important role in the mechanism [14]. Our further investigation demonstrated that the vitamin D receptor can inhibit the switching of the isotype class to IgE directly in the IgE switch promoter (e-germline promoter) by recruiting inhibitory molecules (Figure 5) [30]. Future studies will have to clarify whether this leads to a stable or unstable modulation of the allergic immune response, and how this could be used for the prevention or treatment of allergic diseases.

Conclusion and perspectives

Vitamin D deficiency is very common in higher latitudes and can be relevant for the development of osteoporosis and immunologic diseases as vitamin D can have numer-
ous protective and immunomodulatory effects. Vitamin D or its precursors might be beneficial for the prevention and therapy of diseases with a modified immune response, and this potential should be investigated in future clinical studies.

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