

Vitamin D and the Adaptive Immune System with Special Emphasis to Allergic Reactions and Allograft Rejection

Armin Zittermann*, Gero Tenderich and Reiner Koerfer

Heart Center North Rhine-Westphalia, University Hospital, Ruhr University Bochum, Bad Oeynhausen, Germany

Abstract: Tolerance induction is a fascinating option to prevent allergic diseases or allograft rejection. Calcitriol is the hormonal form of vitamin D and is produced by two hydroxylation steps: a hepatic 25-hydroxylation of vitamin D and a subsequent renal 1 α -hydroxylation. Calcitriol has important immunomodulatory properties. Calcitriol can prevent those inflammatory processes which are responsible for allograft rejection, whereas its effects on immunological responses related to allergic reactions are more complex and not fully elucidated. This article summarizes present knowledge on vitamin D and the adaptive immune system. Experimental and clinical studies support the assumption that calcitriol can decrease the risk of allograft rejection. Prospective randomized clinical trials are however needed to clarify whether administration of calcitriol, some of its analogues, or simple vitamin D supplementation is able to prevent rejection in solid organ transplanted patients. With respect to allergic reactions, human data are inconsistent at present. Some argue that vitamin D deficiency may cause allergic reactions whereas others argue that vitamin D excess leads to an increased allergy risk. In this context, current strategy of vitamin D supplementation in infants and the possibility of a bimodal effect on allergic reactions of both, vitamin D deficiency and excess are discussed.

Keywords: Vitamin D, calcitriol, allergy, allograft, rejection, inflammation, T helper cell, dendritic cell.

INTRODUCTION

In the 1960s, the prevalence of asthma and allergic reactions began to increase worldwide [1]. Despite this global phenomenon, the prevalence is higher in industrialized countries than in developing countries [2]. Nevertheless, in industrialized countries allergic reactions are uncommon in farmers children compared with the children of non-farmers [3]. It is estimated by the American Academy of Allergy, Asthma & Immunology that approximately 36 million people (11% of the US population) suffer from allergic rhinitis and approximately 3 million people (about 3% of the US population) suffer from asthma. The prevalence of atopic dermatitis has doubled or tripled in industrialized countries during the past three decades; 15 to 30% of children and 2 to 10% of adults are affected [4]. According to the hygiene hypothesis, allergic diseases are caused by inappropriate immunological responses to harmless antigens driven by an immune response mediated by specific T helper cells. However, the hygiene hypothesis of allergic reactions has recently been questioned [5]. Thus, the etiology of allergic reactions still remains largely unclear.

It was also in the 1960s that powerful immunosuppressives became available and allowed performing solid organ transplantation and helped decreasing the chance of allograft rejection. In the 1980s, new techniques and new medications helped making organ transplantation a safer, more effective and more routine procedure. So far, approximately 25,000 lung transplantations, 75,000 heart transplantations, and more than 400,000 kidney transplantations have been performed worldwide. In addition, around 11,000 to 13,000

liver transplantations are performed each year. Nevertheless, prevention of acute and chronic allograft rejection still remains a challenge.

Vitamin D has long been known for its essential role in regulating calcium and bone metabolism. Within the last 20 years, however, it became also increasingly clear that vitamin D exerts important immunomodulatory properties. This review article outlines present knowledge on vitamin D's role in the adaptive immune system. In addition, possible clinical implications with respect to allergic reactions and allograft rejection are summarized.

PATHOPHYSIOLOGY OF ALLERGIC REACTIONS AND ALLOGRAFT REJECTIONS

Pathophysiology of Allergy

During a first contact with the allergen, a sensitization takes place which is characterized by an activation of specific T helper (Th) cells. Th cells comprise a key component of the immune defense and can be differentiated into at least 4 distinct subsets (Fig. 1). Th2 cells are important in eradicating parasites, whereas Th1 cells provide protection against intracellular pathogens. T helper 17 cells (Th17) protect against bacterial and fungal infection. Regulatory T cells (Treg cells) are crucial for the maintenance of immunological tolerance. Their major role is to shut down T cell-mediated immunity toward the end of an immune reaction and to suppress auto-reactive T cells. A strong Th2 predominance leads to pathologic conditions such as overproduction of IgE and allergic diseases, whereas a strong Th1 predominance leads to autoimmunity and severe allograft rejection. Th17 also contribute to autoimmune disease. Generally, the outcome of Th cell differentiation is dictated by dendritic cell (DCs), the microenvironment, or both. DCs are highly specialized antigen presenting cells (APCs). Their main function is to process antigen materials and present it on the surface to T cells. DCs are critical for the initiation of T cell re-

*Address correspondence to this author at the Department of Cardio-Thoracic Surgery, Heart Center North Rhine-Westphalia, Ruhr University Bochum, Georgstraße 11, D-32545 Bad Oeynhausen, Germany; Tel: +49 5731 97 1912; Fax: +49 5731 97 2020; E-mail: azittermann@hdz-nrw.de

sponses. For differentiation into subsets of Th cells, naive T cells need to be first induced by macrophage-derived cytokines such as interleukin (IL)-1, IL-6, IL-12, and tumor necrosis factor (TNF)- α to differentiate into Th0 cells. Thereafter, these cells further differentiate under the influence of antigen presenting DCs to Th subsets [6]. Th1 cells produce IL-2 and interferon- γ , whereas Th2 cells produce IL-4, IL-5, and IL-13. Human Th17 produce IL-17, IL-22, and IL-26 [7]. It has been assumed that a subtle balance between Th1 and Th2 cells is provided under normal conditions [8]. However, it becomes also increasingly clear that regulation is much more complex than previously thought. There is probably more flexibility in cytokine production than would be predicted from the terminal differentiation model of Th1 versus Th2 [7].

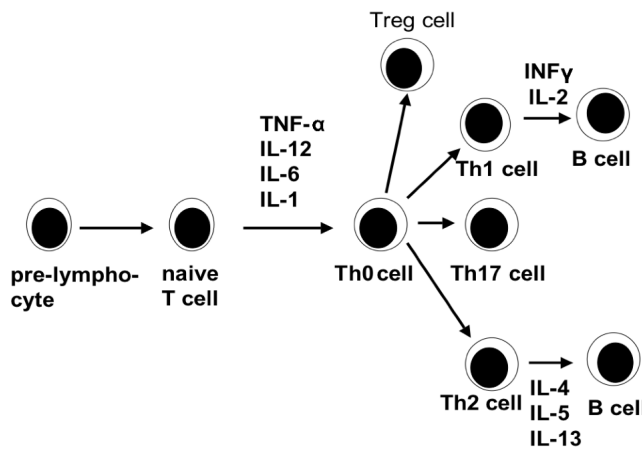


Fig. (1). Activation of T helper cells. Abbreviations: IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; Th, T helper; Treg, regulatory T.

It is present knowledge that Th2 cells induce B cells to produce specific IgE against the allergen. Allergic reactions are characterized by excessive degranulation of mast cells after activation by allergen-specific IgE, resulting in an extreme inflammatory response. It also depends on the availability of protective factors whether or not an allergic reaction occurs. IL-10 is such a protective factor. High levels of IL-10 act as an inhibitor of mast cell degranulation [9], and successful immunotherapy with bee venom is associated with a sharp increase in IL-10 production by T cells [10]. In addition, peripheral mononuclear cells from allergic individuals have lower spontaneous and stimulated IL-10 production than those from normal subjects [11].

Pathophysiology of Solid Organ Rejection

Rejection is mediated through both T cells and humoral immune (antibodies) mechanisms. The number of mismatched alleles determines the speed and magnitude of the rejection response. Solid organ rejection involves an activation of T-lymphocytes against alloantigen by one of two pathways: a direct interaction with foreign antigens presented by endothelial cells, monocytes, or DCs in association with major histocompatibility complex (MHC) proteins and indirect interaction with foreign peptides processed and presented by recipient APCs in association with recipient MHC proteins [12]. This presentation of antigen results in an activation of Th1 cells. Other cytokines secreted such as

TNF- α , IL-4, IL-5, and IL-6, stimulate the activation and proliferation of macrophages, B cells, and other cells involved in the inflammatory response. The immune cascade leads to damage of the donor endothelial cells, vascular smooth muscle cells, and myocytes which presents clinically as acute or chronic rejection. It is also noteworthy that the cytokine IL-10 plays a pivotal regulatory role in tolerating exogenous antigens [13] by inhibiting APC function and cytokine production by macrophages and DCs, leading to profound inhibition of Th1 cell-mediated immunity.

Administration of immunosuppressive agents has reduced the risk of rejections substantially. The calcineurin inhibitors (CNI) cyclosporine A (CsA) and tacrolimus (FK506) downregulate expression of IL-2 and other proinflammatory cytokines. Azathioprine inhibits DNA synthesis in lymphocytes and mycophenolate mofetil (MMF) blocks the proliferative response. The mTOR (mammalian target of rapamycin) inhibitors sirolimus (rapamycin) and its derivative everolimus block several events downstream of the IL-2 receptor. Immunosuppressive drugs such as glucocorticoids, MMF, and mTOR inhibitors impair DC maturation and inhibit upregulation of costimulatory molecules. There is also some evidence that the CNIs CsA and tacrolimus have an inhibitory effect on DCs [14]. Immunosuppressive management is, however, associated with severe short-term and long-term adverse effects such as an increased risk of infection and malignancies. Some immunosuppressive agents such as glucocorticoids and CNIs are associated with an increased risk of osteoporosis [15]. In addition, CNIs are nephrotoxic. Due to the aforementioned various side effects of immunosuppressive agents, one can say that the ideal immunosuppression would be no immunosuppression.

VITAMIN D AND THE ADAPTIVE IMMUNE SYSTEM

Vitamin D is metabolized by a hepatic hydroxylase into 25-hydroxyvitamin D (25(OH)D) and by a renal 1 α -hydroxylase into the vitamin D hormone 1,25 dihydroxyvitamin D (calcitriol). This step is under control of parathyroid hormone (PTH). However, in case of vitamin D deficiency/insufficiency, renal synthesis of calcitriol becomes substrate dependent, i.e. dependent on the circulating 25(OH)D concentration [16]. Calcitriol is also produced by local 1 α -hydroxylases from its precursor 25-hydroxyvitamin D in various extra-renal cells, among them immune cells such as monocytes, DCs, and B cells [6,17,18]. Here, calcitriol plays an important autocrine role. Uptake of 25(OH)D into extra-renal tissues is reduced in case of low circulating calcitriol levels [19]. Although it has been assumed that extra-renal calcitriol concentrations depend on circulating 25(OH)D levels [20], there is also evidence that the activation step of 25OHD in extrarenal tissues into calcitriol is independent of serum 25OHD levels [21,22]. Receptors for the vitamin D hormone (VDR) are expressed in almost all tissues and cells, including different cells of the immune system such as T cells, activated B cells, and DCs.

Activation of the adaptive immune system is complex. Generally, it is of importance that specific pathways of the specific immune system are adequately suppressed in order to avoid autoimmune diseases, allograft rejection, and allergic reactions. Of clinical importance is the fact that DCs may

induce naïve T cells in an immunogenetic direction but also in a tolerogenic direction, depending on the state of their maturation and their cell surface receptor [23,24]. Tolerogenic DCs generally are semimature with increased expression of MHC class II and B7-2, but low expression of CD40 and no production of the proinflammatory cytokines IL-6 and TNF- α [25]. Calcitriol appears to generate tolerogenic DCs *in vivo*, as demonstrated in models of transplanted and autoimmune disease [26,27]. DCs appear to be key targets of calcitriol [28]. Calcitriol arrests the differentiation and maturation of DCs, maintaining them in an immature state, as shown by decreased expression of maturation markers and increased antigen uptake [29]. A number of studies have demonstrated that treatment of DCs with calcitriol downregulates the expression of the costimulatory molecules CD40, CD80, CD86. Calcitriol also decreases IL-12 synthesis. Calcitriol is able to enhance the secretion by DCs of the anti-inflammatory and anti-allergic cytokine IL-10 [30]. In addition, calcitriol inhibits NF- κ B, which is involved in the inflammatory response and in DC maturation [30]. Since DCs play a central role in initiating immune responses, calcitriol could play a pivotal role in reducing immune recognition and blunting the immune response. In line with this suggestion, calcitriol was shown to inhibit antigen-induced T cell proliferation [31]. This effect may at least in part also be due to an induction of T regulatory cells [26,27]. They are able to inhibit T cell response and secrete high levels of IL-10 when stimulated in the presence of dexamethasone and calcitriol [32].

Administration of calcitriol can prevent strong Th1 responses [33], whereas its effects on Th2 cells are more complex and not fully elucidated [34]. Calcitriol has been reported to upregulate [35-37], downregulate [38], or exert no effect [39,40] on IL-4 production and Th2 differentiation. Heine *et al.* [18] have demonstrated that activation of human B cells induces 1- α -hydroxylase expression. Accordingly, these B cells secrete significant amounts of calcitriol. Calcitriol enhances IL-10 expression of activated B cells more than threefold [18]. Thus, activated B cells not only produce allergic substances such as IgE but also an anti-allergic and anti-inflammatory substance like IL-10.

VITAMIN D AND ALLERGIC REACTIONS

Experimental Data

VDR deficient mice fail to display major immune abnormalities [41] and do not develop experimental allergic asthma [42], whereas mice with a deficiency in the 1- α -hydroxylase, required for calcitriol synthesis, show enlarged lymph nodes and a reduced number of CD4⁺ and CD8⁺ peripheral T cells [43]. Since it has been suggested that the VDR itself has specific regulatory effects [44], results from VDR knock-out mice must be interpreted with care and cannot be simply related to the situation in vitamin D deficient humans. In patients with steroid resistant asthma, administration of vitamin D was shown to reverse steroid resistance through induction of IL-10 secreting T regulatory cells [32]. Calcitriol can reduce airway inflammatory response in bronchoalveolar lavage in a rat model of allergic asthma [45]. This effect is at least in part due to a dose-dependent attenuation of the expression of inducible nitric oxide synthase. Calcitriol potentiates the beneficial effects of allergen

immunotherapy in a mouse model of allergic asthma [25]. Calcitriol significantly reduces antigen-specific IgE levels, airway hyperresponsiveness, eosinophilia, and Th2-related cytokines concomitant with increased IL-10 levels in lung tissue and antigen-specific IgA in serum [25]. On the contrary, early treatment with calcitriol augmented allergen induced T cell proliferation along with Th2 cytokine and IgE production in mice [46]. However, airway eosinophilia was also decreased in this murine allergic airway disease. Although investigations were performed with the vitamin D hormone calcitriol, the authors suggest from their studies that excess vitamin D supplementation could influence the development of sustained Th2 response, leading to increased prevalence of allergy.

Epidemiology

At present, the vitamin D hypothesis takes two forms: Some argue that vitamin D deficiency may cause allergic reactions whereas others argue that vitamin D excess leads to an increased allergy risk. Wjst is a representative of the proponents of the latter hypothesis. He argues that the increase in allergies in Bavaria after 1960 coincided with vitamin D supplementation intervention programs to prevent rickets in childhood. Moreover, both, adherence to these programs and prevalence of allergies in children seem to be lower in farming communities in Bavaria (5). The farm protection is observed mainly during the first year of life [47], when vitamin D supplementation is also recommended. Wjst's hypothesis is based on the assumption that vitamin D may lead to Th2 predominance and increased IgE production. Wjst has also assumed that margarine fortification in Germany (2.5 μ g vitamin D/100g margarine) may contribute to allergic diseases [48]. Generally, his hypothesis is supported by findings that maternal 25(OH)D in late pregnancy was inversely associated with asthma in their 9-year-old offspring [49]. Hypönen *et al.* [50] found that regular infant vitamin D supplementation with 50 μ g/day in the first year was associated with a 66% and 46% higher risk for atopy and allergic rhinitis, respectively at age 31 years. In that investigation, asthma risk at age 31 years was 4-times higher in subjects who had received 50 μ g or more vitamin D/day during infancy compared to less than 50 μ g vitamin D daily. Examinations of 25OHD levels in 18,224 adults of NHANES III found no sensitization to a single allergen. However, the prevalence of allergic rhinitis increased across quartile groups of current vitamin D serum levels [51].

It is noteworthy that several other epidemiological studies support the vitamin D deficiency hypothesis of allergic reactions. In cord blood, 25OHD levels were twice as high in summer than in winter samples. Moreover, IL-10 levels and the ratio of IL-10 to IgE were significantly higher in the summer half year compared to the winter half year [52]. Results fit well together with observations that especially infants who are born in late autumn and winter have an increased risk of developing pollen and food allergy [53]. In a prospective cohort study of almost 1200 mother-child pairs from the Northeast of the US, a higher maternal intake of vitamin D during pregnancy was associated with a lower risk of recurrent wheeze in children 3 years of age [54]. Interestingly, a strong north-south gradient was observed for the prescription of drugs used to treat anaphylaxis in the United States, with the highest rates found in New England. It has

been assumed that these results may be due to lower vitamin D status in the Northeast than in the South of the US [55]. Xystrakis *et al.* [32] administered calcitriol to blood cells of healthy persons and steroid-resistant asthmatic patients and found that the intervention enhanced subsequent responsiveness to dexamethasone for induction of IL-10. Obese subjects with deficient 25OHD levels (<25 nmol/l) did not differ in the prevalence of allergic rhinitis and asthma compared to vitamin D replete subjects. However, deficient subjects were more likely to report atopic dermatitis than their vitamin D-replete counterparts [56].

The question arises whether one of the two aforementioned hypothesis is incorrect or whether it is possible that there is a biphasic effect of vitamin D on allergic diseases, e.g. an increased allergy risk at inadequately low and also at excessively high 25(OH)D levels? Such an effect also seems to exist with respect to vitamin D and vascular calcification [57]. It is noteworthy that in the healthy adult population vitamin D intoxications such as hypercalcemia do not occur until oral vitamin D intake and serum 25(OH)D concentrations exceed 250 µg/day and 500 nmol/l, respectively [58]. The amount of 250 µg corresponds to an intake of approximately 3-5 µg/kg body weight in adults. In Germany, the current vitamin D recommendation for infants is 10 µg/day. Vitamin D supplements for infants usually contain 12.5 µg/tablet. Since milk formula for infants are fortified with 10 µg vitamin D per liter, a non-breast fed infant receives additional 7.5 µg vitamin D with 750 ml milk formula. The resulting daily vitamin D intake of 20 µg/day is still regarded acceptable [59]. In newborn, a daily vitamin D supplement of 10 µg is equivalent to 2.2 µg/kg body weight. A re-analysis of an earlier study of our group in adults demonstrates that a daily vitamin D intake of 0.45 µg/kg body weight increases 25(OH)D levels by 50 nmol/l [60]. In small children, a daily vitamin D intake of 0.67 µg/kg/day results in similar 25(OH)D increases [61] when taking into account that vitamin D2 has lower bioavailability than vitamin D3. Data indicate that a daily vitamin D intake of 10 µg in infants (equivalent to 2.2 µg/kg/day) should result in an increase in circulating 25(OH)D levels of 164 – 245 nmol/l. A mean intake of 20 µg vitamin D may thus result in 25OHD levels of up to 500 nmol/l, whereas even higher levels may have been achieved in Finnish newborns, which were supplemented with 50 µg vitamin D daily in the 1960s. Therefore, it cannot be definitively ruled out that the strategy to prevent rickets with daily vitamin D amounts of up to 20-50 µg may have resulted in high 25(OH)D levels. However, this can only be clarified by initiating a representative cohort study in German infants in order to measure 25(OH)D levels. Beyond infancy, there is no evidence for a risk of excessive 25(OH)D levels in the general population. Available data in children and adolescents indicate that vitamin D status is rather too low than too high [62]. It should also be mentioned that 2.5 µg vitamin D (the amount which is added to 100 g margarine in Germany) is very low. Available data indicate that at least in adults 2.5 µg is irrelevant to increase 25(OH)D substantially [63].

Intervention Trials

Very few intervention trials are available so far. In a small, randomized, double-blind, placebo-controlled trial, vitamin D₂ supplementation (25 µg/day) significantly im-

proved skin symptoms in children with winter-related atopic dermatitis [64]. In a study in heart failure patients, vitamin D₃ supplementation (50 µg/day) was able to increase blood levels of the anti-allergic cytokine IL-10 [60]. However, the effect on allergic reactions has not been elucidated in that earlier investigation.

VITAMIN D AND ALLOGRAFT REJECTION

Experimental Data

Activation of the VDR by calcitriol can prolong allograft survival in heart, kidney, liver, pancreatic islets, skin, and small bowel allografts [29]. This effect is associated with the inhibition of leukocyte infiltration into the allograft. In several studies, acute rejection has been further delayed by combining VDR activation with a suboptimal dose of CsA or other immunosuppressive agents (see below). While in kidney transplanted rats both CsA and calcitriol (1 µg/kg/d) prevented early post-transplant increases in the Th1 cell derived proinflammatory cytokine IL-2, only calcitriol resulted in an increase in the Th2 derived cytokines IL-10 and IL-4. It has been assumed that this increase may also contribute to improved graft tolerance [65]. Similar results were observed in orthotopic liver transplanted rats. However, treatment with relatively high doses of calcitriol (2.5 µg calcitriol/kg/day) resulted in hypercalcemia [66,67]. A combination of low calcitriol doses (0.25 µg calcitriol/kg/day) with 1.0 mg CsA/kg/day had an additive effect on limiting lymphocyte proliferation and prolonging liver graft survival [68]. In rat lung allotransplantation, calcitriol (0.5 µg/kg/day) and CsA (2.5 mg/kg/day) but not tacrolimus (40 µg/kg/day) administration had strong additive effects on arterial oxygen content [69]. Calcitriol markedly inhibits hepatocyte apoptosis by promoting the anti-apoptosis genes Bcl-2 and Bcl-xL and inhibiting the pro-apoptosis genes Bax and caspase-3. Calcitriol also decreases TNF-α and interferon-γ proteins in rat liver allograft [70].

Gregori *et al.* [26] have demonstrated that short treatment with calcitriol and MMF induces tolerance to fully mismatched mouse islet allografts. Peritransplant macrophages and DCs from tolerant mice expressed down-regulated CD40, CD80, and CD86 costimulatory molecules. In addition, DCs from the graft area of tolerant mice secrete, upon stimulation with CD4⁺ cells, 10-fold lower levels of IL-12 compared with DCs from acutely rejecting mice, and induce a CD4⁺ T cell response characterized by selective abrogation of interferon-γ production. In human monocytes, treatment with high amounts of calcitriol or one of its analogs was able to significantly reduce excretion of IL-12 and TNF-α. In addition, expression of major histocompatibility complex class II antigens HLA-DR and B7.1 was reduced [71].

The calcitriol doses administered to experimental rats are usually much higher than the amount of calcitriol administered to humans (0.25-2.5 µg/kg body weight/day versus 0.25-1.0 µg/day). Hypercalcemia is a well known adverse effect of calcitriol treatment in humans, e.g. in patients with chronic kidney disease [72]. Therefore, various vitamin D analogs such as paricalcitol and ZK 191784 have been synthesized [71,73] (Fig. 2). Besides their potent immunomodulatory properties the advantage of some of these vitamin D analogs over calcitriol is that they have a lower hypercalcemic effect. This allows administering higher doses without

increasing the risk of hypercalcemia [72], hypercalciuria [71], or vascular calcification [74].

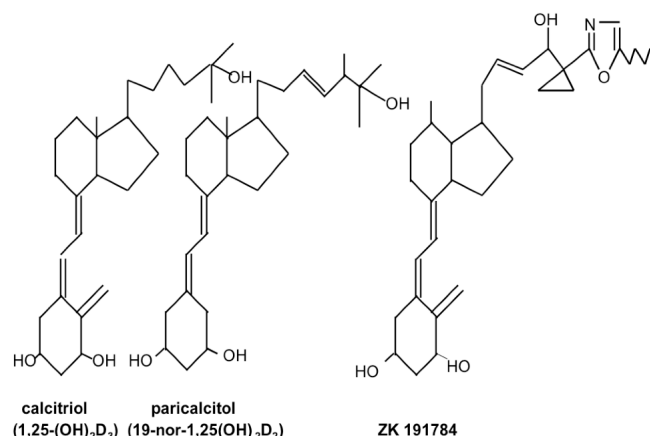


Fig. (2). Chemical structure of calcitriol and two vitamin D analogues.

Clinical Trials

Ardalan *et al.* [75] investigated the effects of calcitriol treatment (0.5 µg/day) on the immunological response in a prospective study in renal transplant recipients. Compared to a control group, calcitriol treatment started in the donor, resulted in a significant increase in Treg cells. It was assumed that this result indicates a potent immunosuppressive action of calcitriol. Four retrospective studies evaluating the effects of calcitriol on allograft function in renal transplant recipients have been published so far [76-79]. These studies included between 48 and 110 patients. Achenbrenner *et al.* [76] found a significant deceleration in the rate of loss of renal function following calcitriol treatment. O'Herrin *et al.* [77] demonstrated prolonged graft survival in calcitriol treated patients compared to controls over a period of 3 years. Tanaci *et al.* [78] reported fewer cases of acute rejection after calcitriol treatment in osteoporotic renal transplant recipients. However, mean time of graft survival did not differ between groups. In the largest of the four studies, published by Sezer *et al.* [79], the calcitriol treated group (n=53) required fewer pulse steroid doses to deal with rejection compared with the 57 non-treated patients of the control group. These results are in general agreement with a retrospective study in heart transplant recipients. In patients receiving calcitriol (0.5 or 1.0 µg/day) no change in episodes of rejection, infection, or deaths compared to patients who were not treated with calcitriol was detected [80]. However, calcitriol treated patients required substantially lower cumulative doses of CsA (29% and 28% for 1 and 2 years, respectively) for protection of organ rejection than the control group. Although cumulative corticosteroid doses from patient diaries did not differ between groups, patients administered calcitriol received significantly lower corticosteroid doses at some time points (at 3 and 24 months) [80]. These results are of clinical importance since compared to other solid organ transplant recipients cardiac transplant recipients receive relatively high doses of immunosuppressive agents. This is due to the much more fatal effects of cardiac allograft failure compared to failure of other organs such as renal allograft failure. Therefore, dose reduction in these patients is highly welcome.

We have recently used a different approach to study the effects of calcitriol on clinical outcome in cardiac transplant recipients [81]. We did not study the effects of orally administered calcitriol but analyzed total mortality according to tertiles of circulating levels of endogenously synthesized calcitriol. Total mortality was significantly higher in the tertile with the lowest calcitriol levels compared to the tertile with the highest calcitriol levels. Since rejection and infection contributed significantly to total mortality in our study, results indicate the problem of optimal immunosuppressive therapy in clinical practise, as well as the possibility of an enhanced risk of rejection and infection in patients with low calcitriol levels.

Generally, calcitriol does not have the adverse short-term and long-term effects of immunosuppressive agents such as CsA and tacrolimus. There is evidence that calcitriol administration has protective effects on post-transplant bone loss [82] and is thus able to attenuate the bone loss caused by immunosuppressive agents such as CsA and tacrolimus. In addition, calcitriol does not appear to increase opportunistic infections [83], and may also decrease the risk of developing malignancies [84]. Since inflammatory processes may suppress circulating calcitriol levels, patients with allograft rejection may be at risk to enter a vicious circle of low calcitriol levels, the need of high doses of nephrotoxic immunosuppressive agents, and frequent allograft rejection (Fig. 3).

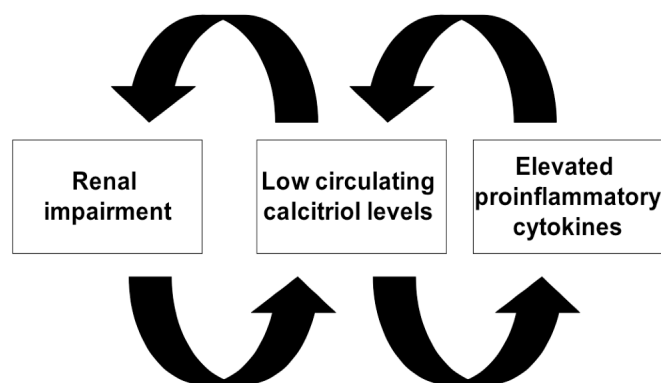


Fig. (3). Proposed vicious circle of low calcitriol levels, renal impairment, and inflammatory processes.

CONCLUSIONS

Tolerance induction is a fascinating option to prevent allergic diseases or allograft rejection. There is accumulating evidence that the vitamin D hormone calcitriol plays a pivotal role in the modulation of immune responses. Calcitriol seems to downregulate Th1 cell response and might thus prevent pathophysiological reactions associated with inflammatory processes such as autoimmune reactions and allograft rejection. Prospective clinical trials are however needed to clarify whether administration of calcitriol or some of its analogues is able to prevent rejections in solid organ transplanted patients. In addition, regulation of endogenously synthesized calcitriol in solid organ transplant recipients has to be studied more detailed. In this context, the question arises whether or not it is possible to increase circulating calcitriol levels by simple vitamin D supplementation in these patients. Moreover, the impact of renal impairment, including drug-induced nephrotoxicity, and inflammatory processes on circulating calcitriol levels needs further clarifi-

cation. Some have argued that calcitriol-mediated downregulation of the Th1 cell response might result in a strong Th2 predominance, leading to an increased allergy risk. However, data about the effect of calcitriol on Th2 differentiation are inconsistent at present. It is noteworthy that several preventive calcitriol effects suppressing allergic reactions have also been explored during recent years. During the last three decades the prevalence of both, chronic diseases which are associated with an activation of Th2 cells such as allergies and chronic diseases which are associated with an activation of Th1 cells such as rheumatoid arthritis, have increased in western societies. This does not support the hypothesis that the increased allergy prevalence is associated with a shift from Th1 predominance towards Th2 predominance. Moreover, there is evidence that vitamin D insufficiency and deficiency rather than vitamin D excess are epidemic in western societies [85]. Nevertheless, it cannot be definitively ruled out at present that especially during infancy the relatively high amounts of vitamin D that have been administered or are still given may be harmful with respect to the development of allergic reactions.

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Received: December 23, 2008

Revised: January 30, 2009

Accepted: February 3, 2009