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Review

Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature

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ABSTRACT

Objective: To evaluate whether vitamin D levels are related to the risk of developing autoimmune diseases and whether supplementation with vitamin D can modify the course of the diseases.
Methods: We reviewed the most relevant papers published from January 1973 to October 2011, using Medline and EMBASE and the search terms "vitamin D"; "autoimmune disease"; "autoimmunity"; "rheumatoid arthritis"; "systemic lupus erythematosus"; "scleroderma"; "systemic sclerosis"; "type 1 diabetes"; "multiple sclerosis"; and "undifferentiated connective tissue disease". We selected studies on the environmental, genetic and epidemiologic association of vitamin D with autoimmune diseases.
Using the strategy described, we identified 1268 articles. 331 articles were eliminated on the basis of the title and another 703 on the basis of the abstract, since they were considered irrelevant for the purposes of the study. Full-text examination was performed on the remaining 234 studies, and a further 15 studies were excluded from the review, since the results had been confirmed or superseded by more recent research. Finally, a systematic review was conducted on 219 articles concerning cross-sectional data on: vitamin D levels and autoimmune diseases; interventional data on vitamin D supplementation in autoimmune diseases; prospective data linking vitamin D level or intake to autoimmune disease risk.
Results: Physiopathology studies confirm that hypovitaminosis D, in genetically predisposed subjects, can impair self tolerance by compromising the regulation of dendritic cells, of regulatory T-lymphocytes and of Th1 cells. Cross-sectional studies show that levels of vitamin D <30 ng/mL are present in a significant percentage, not only in patients with autoimmune disease, but also in healthy subjects (30–77%), and link profound deficiency (<10 ng/mL) with aggravation of symptomatology, while genetic studies associate polymorphism of vitamin D receptors to various autoimmune diseases. Among experimental studies on humans, only those on type-1 diabetes prove that the risks are significantly reduced in infants treated with vitamin D after the 7th month (OR 0.71, 95% CI, 0.60 to 0.84) and that a dose–response effect exists.
Conclusions: Basic, genetic, and epidemiological studies indicate a potential role of vitamin D in the prevention of autoimmune diseases, but randomized and controlled trials are necessary to establish the clinical efficacy of vitamin D supplementation in ill or at-risk subjects.

Contents

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1. Introduction

The cause of the loss of immune tolerance towards self antigens that leads to the development of autoimmune diseases (AIDs) is not yet known. It is considered that environmental causes [1–3], genetic polymorphisms [4,5], and epidemiological risk factors [6,7] favor the emergence of autoimmunity in susceptible individuals, but the event that triggers the different pathologies remains unknown. AIDs are widespread throughout the world and their incidence is continually increasing [8]. For reasons that have not yet been clarified, in industrialized countries the incidence is higher among women, for whom these diseases represent the third cause of death [9,10]. There is as yet no general consensus about the possible strategies for prevention and treatment of most autoimmune diseases; treatment frequently involves the use of corticosteroids, immunosuppressive agents and biological drugs aimed at various inflammatory cytokines [11].

Vitamin D (vit D) is a prohormone that also exerts an endocrine action on the cells of the immune system, generating antiinflammatory and immunoregulatory effects [12,13]. Macrophages, dendritic cells (DCs) and T and B cells possess the enzymatic machinery to produce vit D, and an enzyme expressed in these cells (1 alfa hydroxylase) can be induced by several factors, including interferon-γ (IFN-γ) and is down-regulated during DC maturation [14]. This suggests that vit D is capable of physiologically contributing to the autocrine and paracrine regulation of both innate and adaptive immunities, by means of the vit D receptor (VDR) expressed in the nucleus of these cells. Numerous studies confirm that $1,25(OH)_2D_3$ (calcitriol; the active form of vit D) enhances the innate immune response whereas it exercises an inhibitory action on the adaptive immune system, in which it regulates the interaction between lymphocytes and antigen presenting cells (APCs) and modulates the effector mechanisms [15–17].

$1,25(OH)_2D_3$ causes direct regulatory effects on the functions of T lymphocytes by: inhibiting the proliferation of Th1, capable of producing IFN-γ and interleukin 2 (IL-2), and activating macrophages [18]; increasing the quantity of Th2 through a direct effect on native CD4s [19] or acting on the DCs/APCs facilitating the production of IL-4, IL-5 and IL-10, which move the T differentiation in favor of phenotype Th2 [20]; increasing the quantity of $CD4^+/CD25^+$ T-regulators cells (Tregs) which produce IL10, by means of which they block the development of Th1 and inhibit the secretion of IL-17 by the T-effectors [21].

Calcitriol has powerful and direct effects also on the B cell response, causing induction of apoptosis, inhibition of B cell proliferation, generation of B memory cells, plasma cell differentiation and immunoglobulin production [22].

Moreover it influences the phenotype and function of APCs and mainly of DCs, a highly specialized system of APC critical for the initiation of the $CD4^+$ T-cell response, promoting tolerogenic properties that facilitate the induction of Treg instead of T-effectors [23].

The administration of VDR agonists facilitates the proliferation of DCs with tolerance properties: (a) inhibiting the differentiation and maturation of DCs [24]; (b) decreasing the expression of CD40, CD80 and CD86 co-stimulatory molecules [25]; (c) significantly reducing the production of IL-12 while increasing the production of IL-10 [26], and finally, (d) inducing the expression of immunoglobulin-like transcript 3 (ILT3), an inhibitory molecule associated with tolerance induction [27]. Immature DCs differentiated in monocytes in the presence of calcitriol respond poorly to inflammatory chemokines that regulate their maturation and migration to lymph nodes [18]. This explains the inhibitory effect of the active hormone on the maturation of DCs and on their production of proinflammatory mediators [28]. Consequently, the active synthesis of calcitriol within DCs not only inhibits their differentiation in monocytes but also blocks their ability to undergo a final differentiation in response to maturation stimuli [29]. In addition, vit D regulates monocyte differentiation in macrophages, prevents them from releasing inflammatory cytokines and chemokines, and reduces their capacity to present antigens to lymphocytes by decreasing MHC-II molecule cell surface expression [30]. During inflammatory processes calcitriol negatively regulates the expression of the kB nuclear factor, fundamental both for the differentiation and maturation of DCs and to trigger the inflammatory response [31]. DCs with tolerance properties induced by VDR agonists are capable of inducing differentiation of $CD4^+CD25^+$ Tregs capable of stopping the development of autoimmune diabetes (T1DM) [24]. DCs inducing tolerance, produced after a short treatment with calcitriol, lead to the development of $CD4^+CD25^+$ Tregs able to mediate the tolerance to transplants and to block the development of T1DM [32]. Therefore DCs can be immunogenic, but can also induce tolerance both in the thymus and in the periphery through the vit D action.

Taken together, these data suggest that VDR agonists regulate the activation and differentiation of T-cells, either by acting directly or by modulating DC function. Since DCs are central to the maintenance of both protective immunity and self-tolerance [33,34], it is legitimate to assume that a deficiency of vit D could have consequences on their maturation and function and consequently on the risk and/or progression of autoimmune disease. In experimental animal models the supplementation with $1.25(OH)_2D_3$ forestalls the development of inflammatory arthritis, autoimmune encephalomyelitis (a model for multiple sclerosis), T1DM, and autoimmune thyroiditis [35–38]. Treatment with a low calcemic vit D analog had a prophylactic and therapeutic effect on a murine model of Th1-like colitis [39] and administration of $1.25(OH)_2D_3$ or its analogs to non-obese diabetic mice modulates the expression of chemokines and cytokines and prevents diabetes [40]. Following these experimental indications, the hypothesis was formulated that the dosage and/or administration of this hormone can be effective in the clinical management and treatment of the patient suffering from an autoimmune disease.

Over recent years it has been demonstrated that vit D plays an important role in the immune system and it has been hypothesized that: (a) vitamin D deficiency can act as an environmental trigger that increases the prevalence of AIDs, especially in populations featuring geographical, climatic and ethnic particularities [41]; (b) serum levels of the hormone may play a role in their pathogenesis [42]; and (c) the administration of high doses of vitamin D may perform a preventive action [16]. For these reasons, we performed a systematic review of the literature published over the last 38 years, with the aim of evaluating whether low levels of vit D in humans can be correlated with the risk of developing AIDs and whether the administration of the hormone can modify the incidence of the disease or modify the course of autoimmune pathologies.

2. Methods

2.1. Data sources

The research was carried out in the PubMed and EMBASE databases in October 2011 using the key words “vitamin D”; “autoimmune disease”; “autoimmunity”; “rheumatoid arthritis”; “systemic

lupus erythematosus"; "scleroderma"; "systemic sclerosis"; "type 1 diabetes"; "multiple sclerosis"; and "undifferentiated connective tissue disease". We deliberately did not include primary biliary cirrhosis and celiac disease since in patients suffering from these pathologies malabsorption leads to loss of liposoluble vitamins and hence of vit D [43,44].

2.2. Study selection

It was decided to divide the studies into two groups, one consisting of geo-epidemiological studies on the levels of vit D and autoimmune diseases in different geographical areas, and the other comprising physiopathological-clinical studies of the incidence and prevalence of autoimmune diseases in relation to the levels of vit D. The articles of this second group were then broken down into sub-groups depending on the type of study: cross-sectional studies that set in relation to the levels of vit D and/or their effects on the clinical course of already diagnosed AID; prospective studies correlating the levels of vit D with the risk of developing AID; studies relating to the administration of vit D and the risk of developing AID; studies evaluating the effect of the administration of the hormone on patients known to have AIDs. Studies of basic science, genetics and experimental studies on animal models which highlighted the role of vit D in the pathogenesis of AID were also taken into consideration.

The studies included were those that:

- scheduled the dosage of levels of 25(OH)D_3, because this stable and dosable metabolite reflects the status of vit D in the organism (values <30 ng/mL indicative of insufficiency; <10 ng/mL of serious deficiency);
- used for the determination of the hormone quantitative immunometric methods [radioimmunoassay (RIA), chemiluminescent assay (CLIA), enzymeimmunoassay (EIA)] and chromatographic methods [high-performance liquid chromatography (HPLC), liquid chromatography–tandem mass spectrometry (LC–MS)] [45].

2.3. Data extraction

From the analysis of the literature present in PubMed and EMBASE we identified 1268 articles. 331 articles were eliminated on the basis of the title and another 703 on the basis of the abstract, since they were considered irrelevant for the purposes of the study. Full-text examination was performed on the remaining 234 studies and a further 15 studies were excluded from the review since the results had been confirmed or superseded by more recent research (Fig. 1). The remaining 219 studies were sub-grouped into: (a) 27 studies on the correlation between vit D deficiency and the development of AID in subjects with predisposing genetic and environmental factors; (b) 21 ecological–geographical studies linking vit D levels with autoimmune disease risk; (c) 99 studies on vit D levels in patients with autoimmune diseases; (d) 41 studies on experimental vit D supplementation in patients with AID; (e) 2 studies on vit D levels and the risk of developing autoimmune diseases; and (f) 29 studies on vit D intake and the risk of developing autoimmune diseases.

In the epidemiological studies, factors such as age, sex, race, ethnic origin, drug use, familial and genetic risk of the patients were taken appropriately into consideration in order to avoid bias in the conclusions.

3. Results

3.1. Environmental and genetic association studies (27 studies)

HLA-DR and HLA-DQ alleles within the HLA class II region are the highest-risk-conferring genes. Less robust susceptibility effects have been identified for MHC class I alleles and for non-MHC regions [46]. Polymorphisms in the VDR gene have been associated with increased risk of multiple autoimmune diseases [47]. A vit D response element is found in the promoter region of the HLA DRB1*1501, this allele being strongly associated with MS susceptibility pathogenesis in Caucasians [48,49]. Genetic differences in vit D binding protein (DBP) gene have been found to influence vitamin D levels [50]. Infectious diseases [46] and behavioral–cultural variations are considered environmental risk factors for AID [51].

3.2. Ecologic studies linking vitamin D with autoimmune disease risk (21 studies)

As the prevalence of certain autoimmune diseases varies with latitude, it has been theorized that sunlight exposure, and therefore vitamin D, may play a role in their pathogenesis. It has been shown that 15% of the global population living above the 40° north parallel and below the 40° south parallel, where sun exposure is reduced, are more prone to AIDs, such as inflammatory bowel disease, multiple sclerosis (MS), T1DM, and rheumatoid arthritis (RA) [52–58]. The strongest ecologic evidence linking vit D with autoimmune disease risk is for MS [51,59,60]. MS has also been associated with birth during the winter compared with other seasons and it is hypothesized that this could reflect low maternal vit D during pregnancy [60]. Seasonal variation in MS relapses (increased flare ups during the winter) detected by magnetic resonance imaging has been observed [61].

3.3. Studies of vitamin D levels in patients with autoimmune diseases (99 studies)

The case–control studies present in literature were examined to evaluate whether in patients suffering from T1DM, MS, systemic lupus erythematosus (SLE), RA, and systemic sclerosis (SSc) the level of vit D was lower than that of the control group and/or whether its concentration affected the course of the disease.

10 articles were selected, evaluating a total of 2550 patients with T1DM and 1142 controls: 8 studies [62–69] documented lower levels of 25(OH)D in the patients as compared to the control group, with a percentage varying from 43 to 90%; levels of vit D also proved to be lower in subjects with decompensated diabetes, ketoacidosis incipient nephropathy, or tubulointerstitial damage [63,67,70]. Two studies did not confirm this datum, since no significant differences were observed in the levels of vit D between patients with T1DM and controls [71,72].

In the 11 studies on MS, there were 9 studies (involving 1135 patients and 1115 controls) reporting that 25(OH)D levels are lower in MS (20–84%) than in healthy controls [73–81]. Two studies did not find any difference [82,83]. Lower vit D levels were found in MS patients with progressive forms of the disease, with increased disability and clinical activity and risk of relapse [75,78,84].

As regards SLE, 6 studies (409 patients and 617 controls) demonstrated in the patients' levels of 25(OH)D <30 ng/mL in 56–75% of cases, while in the healthy population the percentage was lower (36–55%) [85–90]. The studies were carried out in European and non-European countries and at different latitudes; the association between insufficiency and disease was significant, but could be correlated to the fact that subjects with SLE cannot expose themselves to sunlight.

RA is the disease that demonstrated the lowest association between levels of vit D and prevalence of the pathology: 2 studies out of 7 [90–96] (534 cases, 465 controls) revealed lower levels of vit D in sufferers than in healthy controls and 5 did not detect this difference: the percentage of patients with hypovitaminosis (42–67%) was comparable to that of the control group (75%).

For SSc, 4 studies out of 7 (123 cases, 190 controls) detected lower levels of vit D in patients suffering from the disease, in percentages varying from 46 to 84%, as compared with the healthy controls (40%) [97–103].

In summary, in many but not all case–control studies, circulating levels of 25(OH)D have been found to be lower in subjects with

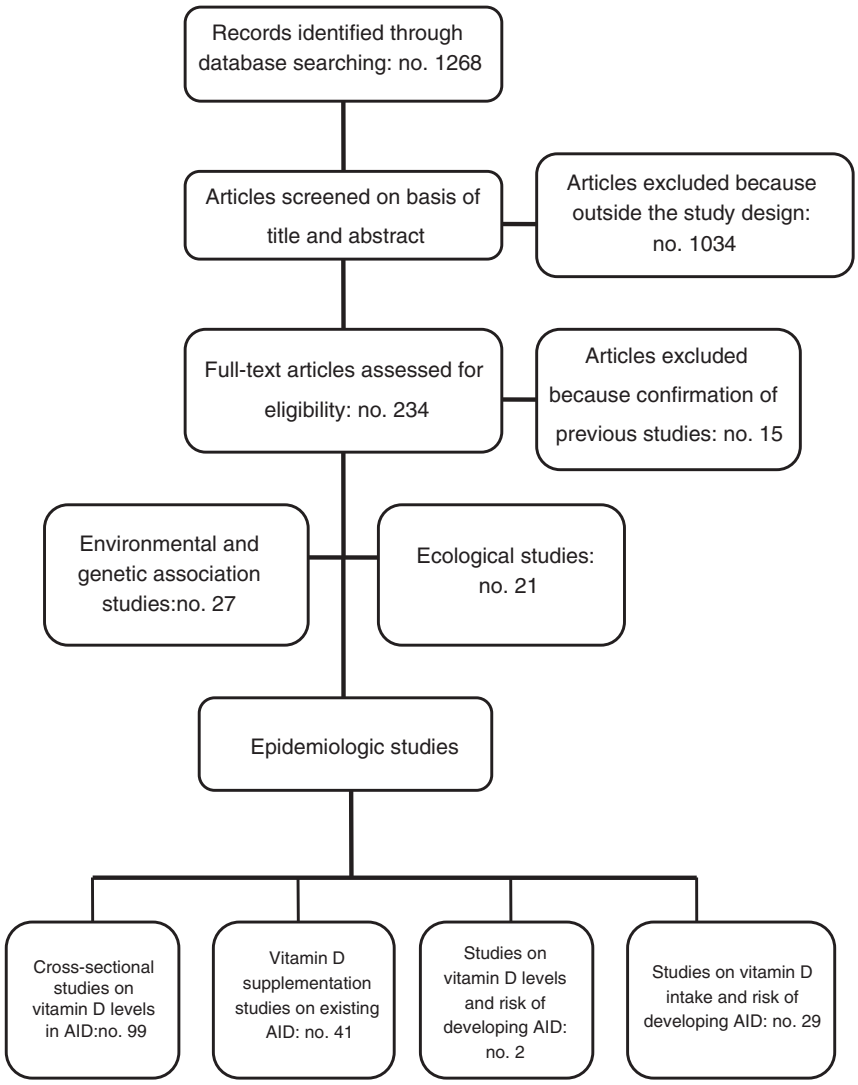

Fig. 1. Flow diagram of literature search and review.

various autoimmune diseases than in matched healthy controls. The evidence pointing to lower vit D levels in existing disease is not equally strong for all autoimmune diseases and some diseases have yet to be studied.

The differences between similar studies of a specific disease may relate to their different sizes and the heterogeneity in their statistical power, as well as to adjustment for confounding factors. Taken together, it is also evident from these studies that ethnic origin [99], season of the year [104], and disability [76,79] have strong effects on circulating vit D levels and it is not clear that all of these cross-sectional studies controlled for these important confounders. Nevertheless, in all these studies it emerges clearly that a significant percentage of the subjects enrolled in the control cohort demonstrate values <30 ng/mL of the hormone in the absence of autoimmune diseases. This evidence confirms studies related to the status of vit D carried out on the healthy population in various countries and/or at various latitudes: indeed 14 recent works, which evaluated a total of 85,629 subjects resident in the U.S.A., Italy, Pakistan, India, Egypt, Netherland, Spain, Saudi Arabia and the Lebanon demonstrated that percentages of recruited subjects which varied from 30 to 77% in the various groups examined had values <30 ng/mL (between 2.5 and 25% levels <11 ng/mL), but above all they demonstrated that in these subjects there is no increase in the prevalence of AID [87,105–118]. In these studies too, the confounders (different geographical locations, different races, different analytical methods, different selection criteria, different statistical analyzes) were not specifically stated as optimized; nevertheless, the review of all these works suggests that vit D deficiency is extremely widespread, is not an etiopathogenetic factor of AIDs but could favor the occurrence of it in subjects that are genetically predisposed.

The studies have confirmed that a serious vit D deficiency (<11 ng/mL) is correlated with the increase of autoimmune aggression in all the diseases studied, including RA, which leads to an exacerbation of the clinical symptoms; this demonstrates that vit D has an immunomodulator effect on the inflammation and an immunoregulatory effect on the attack against the self [119–136].

3.4. Vitamin D supplementation in patients with autoimmune diseases (41 studies)

Studies carried out on animal models have shown that the administration of $1.25(OH)_2D_3$ (5 mcgr/kg on alternate days) or analogous compounds (BXL-219, MC 1288, Ro 63-2023, Ro 26-2), inhibits IL-12 production and infiltration of Th1 cells, while increasing the frequency of $CD4^+CD25^+$ regulatory T-cells, arresting the immunological progression and preventing the clinical onset of AID. This evidence

has been demonstrated in T1DM [137–139], MS [140,141], RA [35,142] and in SLE [143,127].

In man, the observational and/or uncontrolled studies on patients with SLE (60 cases) [144], RA (44 cases) [145,146], MS (113 cases) [147,148] and SSc (51 cases) [149–152] demonstrated that the administration of cholecalciferol and/or alfacalcidol (2 mcg/d) to patients had no effect or determined improvement in the symptoms of the disease, the radiological situation of the lesions and the number of relapse episodes. On the other hand, these studies did not demonstrate any positive effect in relation to the clinical onset of the disease or its immunological evolution after supplementation with this dose of hormone [74,144,153,154].

Among the randomized controlled trials, only 2 studies carried out on T1DM (51 cases) indicated a positive outcome for the disease with administration of vit D: 1 alfa-OH D_3 at a dosage of 0.5 mcg/d reduced the insulin requirement and protected the β-cell function [155,156].

On the basis of the evidence presented in literature, we can deduce that the dose of hormone administered in the experimental studies carried out on man to date, controlled and not, could be insufficient to control autoimmune aggression or inhibit the onset of disease: indeed it was studied primarily not to cause complications in the bone-calcium metabolism. Furthermore, alfacalcidol or cholecalciferol might not possess the same therapeutic efficacy as the analogous compounds utilized in the studies in animal models [157–159]. Consequently randomized and controlled trials are necessary to evaluate the type and dose of the compound to be administered to attain pharmacological and clinical efficacy, as well as the duration of the period of supplementation and any side effects of the treatment.

3.5. Vitamin D level and the risk of developing autoimmune diseases (2 studies)

Only 2 case–control studies in literature correlate serum levels of vit D with the incidence of AIDs, as regards RA and MS. In Nielen's study, which compared 79 blood donors who had developed disease with 79 healthy controls matched for age and sex, the concentration of vit D did not prove to be correlated to the risk of developing RA [160]. In Munger's work, on the other hand, higher serum levels of 25(OH)D were associated with a significantly lower risk of incident MS, but only among whites, not blacks or Hispanics, and the effect was most pronounced for individuals under age 20 [161].

3.6. Vitamin D intake and the risk of developing autoimmune diseases (29 studies)

The main outcome measure was development of type 1 diabetes, to assess whether vit D supplementation in infancy reduces the risk of this disease in later life. Controlled trials and observational studies were included in the analysis: observational studies (case–control studies and cohort studies) met the inclusion criteria [162–165]; no randomized controlled trials were found. Meta-analysis of data from the case–control studies (Fig. 2) showed that the risk of type 1 diabetes was significantly reduced in infants who were supplemented with vit D compared to those who were not supplemented (pooled odds ratio 0.71, 95% CI 0.60 to 0.84) [166].

There was also some evidence of a dose–response effect, with those using higher amounts of vit D being at lower risk of developing T1DM [167].

Finally, there was a suggestion that the timing of supplementation might also be important for the subsequent development of T1D: children supplemented between 7 and 12 months of age demonstrated lower chances of developing T1DM in later life than those who were supplemented between 0 and 6 months of age [165,166]. This evidence could be a consequence of the fact that adaptive immunity becomes competent precisely in this period, so that the supplementation with vit D in an earlier period has no regulatory action on the effector mechanisms of the same, especially in the reactions against self-antigens. Several studies that examined the risk of developing T1DM in children whose mothers had been administered vit D during pregnancy were also included in the review. Since the complete original data of the studies evaluated were not available it was not possible to perform a meta-analysis, but the graphic illustration of the results (Fig. 3) of the RR and/or OR recorded in the individual studies clearly shows that the administration of vit D to the pregnant women in no way modified the risk of the infants developing the disease [168–170].

As regards RA, 2 studies were evaluated during the analysis: a prospective study of a duration of 11 years, conducted in a cohort of women in North America, which revealed that the subjects with higher basal values of vit D had a 33% lower risk of developing RA [171]; a more recent study with similar characteristics did not detect any association between the disease and the concentration of the hormone [172]. As regards MS, a prospective study carried out in North America [173] and a case–control performed in Holland [76] were analyzed: both demonstrated that the administration of the hormone diminishes the risk of onset of the disease. Furthermore, the second study also noted that, especially in women, the decrease is proportionate to the increase in the concentration of circulating vit D. On the other hand, no correlation was demonstrated with SLE [172].

4. Discussion

The review performed in the course of our examination of the studies published over the last 38 years concerning the correlation between hypovitaminosis D and the risk of AID leads to several considerations.

Basic science studies prove that vit D regulates the action of adaptive immunity agents and that in the presence of vit D deficiency the immune system demonstrates an increased occurrence of autoreactive T cells. The evidence that emerges from the analysis of these works makes it possible to hypothesize that the increase in autoreactive T cells could be indirectly provoked by the vit D deficiency through alteration of the maturation and/or functions of the DCs, which are crucial to the maintenance of self-tolerance [25,26]. The absence of the immunoregulatory action of vit D on the APCs that can induce tolerance could cause the loss of immunological tolerance in subjects with polymorphism of the regulatory genes of the vitamin, with significant consequences on autoimmune disease risk and/or progression. The hypothesis that genetic predisposition plays an important role is borne out by the data deriving from the cross-sectional studies examined in the course of the review, which demonstrate that circulating levels of 25(OH)D are low in subjects with AID but also in a significant percentage of healthy people (30 to 77%), hence confirming that vit D deficiency is not an independent etiological factor of AID. Moreover, the action of the hormone in the control of self-tolerance is corroborated by epidemiological and ecological–environmental studies that indicate that 25(OH)D deficiency is present in all the principal AIDs.

Furthermore, this systematic review highlights the fact that experimental studies in humans, albeit small and uncontrolled, indicate the beneficial effects of vit D supplementation in reducing the severity of disease activity, while in experimental animal models the dose of vit D administered prevents or forestalls autoimmune diseases. This datum suggests that the oral vit D intake in many of the studied populations could be too low to produce significant effects; further, variability in administration may reduce positive effects. In the observational studies evaluated, the difference between high and low oral doses is 400 IU/day at most: this supplementation [1 μg (40 IU) of 25(OH)D increases circulating hormone by 1 nmol/L] [174] results in an increment of only 10 nmol/L of 25(OH)D. Consequently, the evidence needs to be re-evaluated through the realization of randomized controlled trials that assess the type and the dose of the drug to be administered, since the failure of the administration experimented to date could be linked to the supply of a dose of hormone insufficient to control autoimmune aggression or

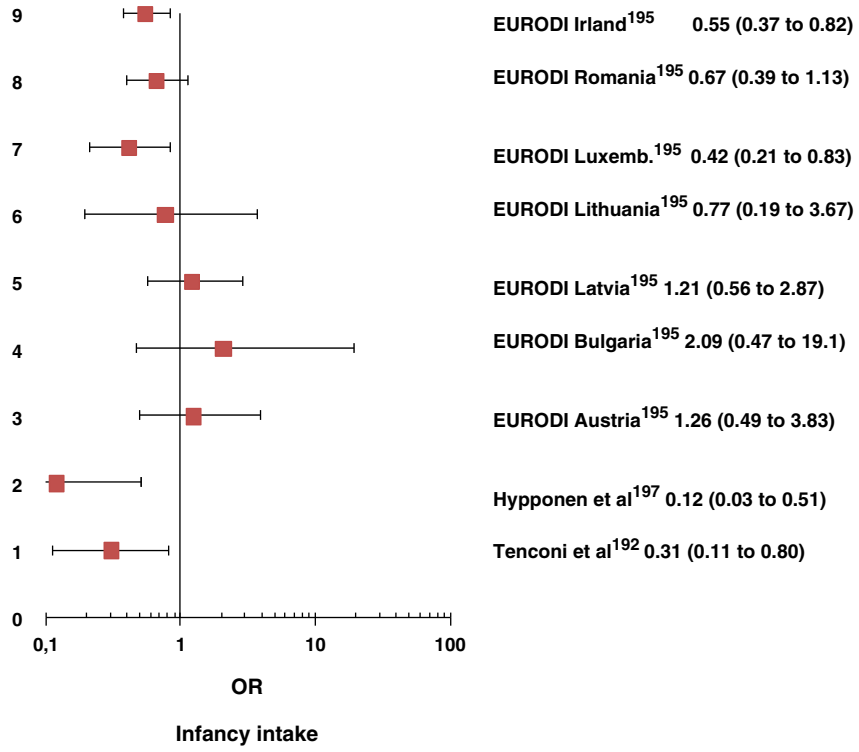

Fig. 2. Forest plot showing the odds ratio (OR) of infancy vit D intake and risk of developing T1DM in later life (mean pooled OR is 0.71).

to prevent the onset of the disease, and/or to the administration of compounds less effective than the synthetic derivatives.

The data in literature are insufficient to demonstrate that there is a significant correlation between the hormone levels and the incidence of AID. As regards the studies in which the supplementation of vit D is correlated with the prevalence of AID, only those carried out on T1DM and MS have yielded positive and robust results, illustrating a reduction in the onset of disease of up to around 30%. More specifically, in the studies dealing with diabetes, a dose–response and a precise timing of the supplementation have been highlighted.

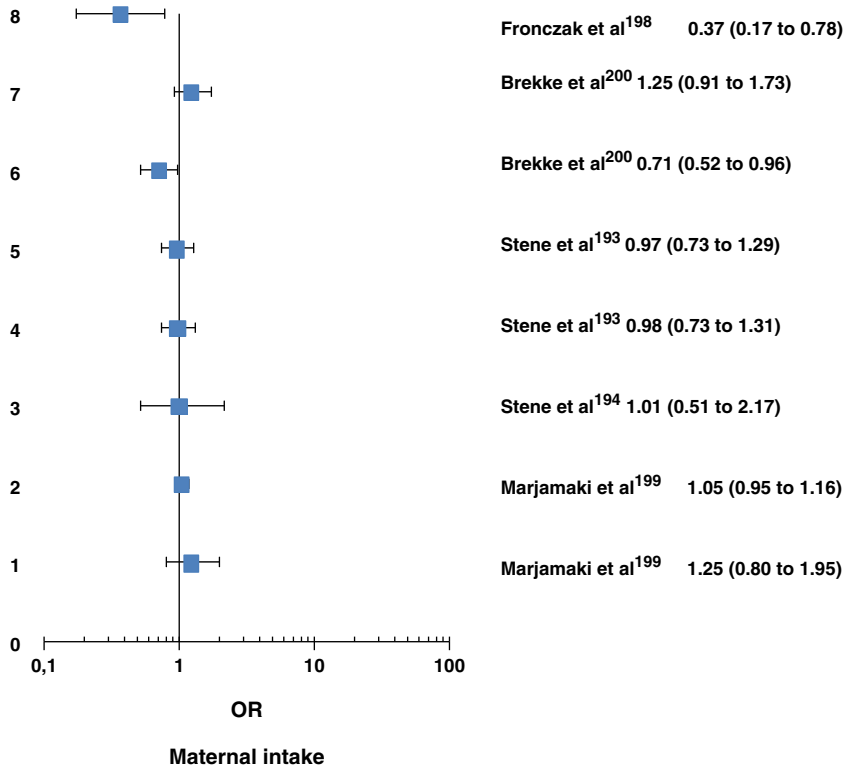

Fig. 3. Forest plot showing the odds ratio (OR) of vit D intake in pregnant women and risk of newborn to develop T1DM in later life (mean pooled OR is 0.95).

Promising clinical results together with evidence for the regulation of multiple immunomodulatory mechanisms by VDR agonists represent a sound basis for further exploration of their potential in the treatment of rheumatic autoimmune disorders. However, randomized controlled trials, adequately powered with long periods of follow-up, are lacking on vit D level and the risk of developing autoimmune disease. Such studies are crucial to establish causality (evidence that vit D supplementation can prevent or improve autoimmune diseases), and to provide information on the best formulation, dose and timing of supplementation.

Take-home messages

- Basic, genetic, and epidemiological studies indicate a potential role of vitamin D in the prevention of autoimmune diseases.
- Experimental studies in humans performed to date indicate the beneficial effects of vit D supplementation in reducing the severity of disease activity; it could be that the dose of hormone supplied is insufficient to control the autoimmune aggression or to prevent the onset of the disease.
- The data present in literature deriving from the studies linking vitamin D level and the risk of developing autoimmune diseases are insufficient to establish a direct link between deficiency of the hormone and incidence of the pathology.
- Randomized, controlled trials are necessary to evaluate the type and dose of the compound to be administered to attain pharmacological and clinical efficacy, as well as the duration of the period of supplementation and any side effects of the treatment.

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Cardiac valve replacement is a high-risk procedure in patients with antiphospholipid syndrome

Cardiac valve abnormalities are frequently observed in patients affected with antiphospholipid syndrome (APS), being detected in up to more than 80% of cases by means of highly sensitive techniques. Thus, valve replacement surgery should be adopted in some cases but data on long-term prognosis and risk factors of poor outcome are scarse and almost anecdotal. Recently, a retrospective analysis of the largest multicentric case series of cardiac valve surgery in APS patients has been published by Erdozain *et al.* (**Arthritis Care Res 2012;64:1256-60**). Operative and postoperative courses, including longterm outcome, was registered for 33 cardiac valve replacements carried out in 32 APS patients between 1981 and 2008. Heart valve involvement as well as other APS manifestations were evaluated in order to identify factors associated to valve surgery adverse prognosis. This retrospective study assessed that heart valve replacement is a high-risk surgical intervention in APS patients, linked to high mortality and morbidity rates, mainly caused by thrombotic or hemorrhagic events. The authors did not find any disease variable as a predictor of valve surgery adverse outcome.
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