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REVIEW ARTICLE

Atopic dermatitis and vitamin D

Dermatite atópica e vitamina D

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Abstract

Atopic dermatitis (AD) results from the interaction between dysfunction of the skin barrier, dysregulation of the immune system, and alteration of the skin microbiome. As the most common inflammatory skin disease worldwide and still increasing, it is a real health problem. Vitamin D deficiency is also considered a global problem affecting 13 out of 100 people in Europe. Since vitamin D is involved in the formation of the epidermal barrier, by the synthesis of structural proteins and regulation of keratinocyte proliferation and differentiation, there is a rational to evaluate the relation between vitamin D levels and the prevention or treatment of AD. The authors performed a review of the existing scientific literature on the role of vitamin D in AD. Although studies are scarce not very robust with no consensual results, most studies report lower serum levels of vitamin D in patients with AD. In addition, there seems to be an inverse relationship between plasma levels of vitamin D and clinical severity, a hypothesis that is reinforced by studies that demonstrated a statistically significant benefit of vitamin D supplementation for improving clinical symptoms and signs of AD. Some studies also suggest a possible influence of prenatal vitamin D levels on the onset of AD during childhood. Therefore, vitamin D supplementation may play a relevant role as a complement to the treatment of AD or for its prevention, but more and better scientific evidence is needed to confirm this.

Keywords: Atopic dermatitis. Vitamin D. Vitamin D deficiency. Skin.

Resumo

A dermatite atópica resulta da interação entre a disfunção da barreira cutânea, a desregulação do sistema imunitário e a alteração do microbioma da pele. Sendo a doença inflamatória da pele mais comum a nível mundial e com incidência crescente é um verdadeiro problema de saúde. O défice de vitamina D é também um problema de saúde global, que afeta cerca de 13 em cada 100 cidadãos europeus. Uma vez que a vitamina D está envolvida na formação da barreira epidérmica, pela síntese de proteínas estruturais e pela regulação da proliferação e diferenciação dos queratinócitos, é expectável que os níveis séricos de vitamina D possam ter um papel na prevenção e/ou no tratamento da dermatite atópica. Neste artigo de revisão narrativa foi revista a literatura científica existente sobre o papel da vitamina D na dermatite atópica. Apesar de escassos, pouco robustos e não consensuais, a maioria dos estudos relatam níveis séricos de vitamina D mais baixos em doentes com dermatite atópica, com uma relação inversa entre os valores plasmáticos da vitamina e a gravidade da doença, hipótese reforçada por estudos que demonstraram uma relação estatisticamente significativa entre a suplementação e a melhoria dos sintomas e sinais clínicos. Existem também evidências que sugerem uma possível influência de valores pré-natais de vitamina D

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no surgimento de dermatite atópica durante a infância. Desta forma, a suplementação com vitamina D poderá ter um papel relevante como complemento do tratamento da dermatite atópica, mas são necessárias mais e melhores evidências científicas para o comprovar.

Palavras-chave: Dermatite atópica. Vitamina D. Deficiência de vitamina D. Pele.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease with increasing incidence, affecting nearly 15-20% of children and up to 10% of adults worldwide[1,2]. It is characterized by eczema and itching[3], with a complex and not fully understood pathophysiology influenced by genetic and environmental factors, involving the interaction between an inappropriate immune response, skin barrier dysfunction, and alteration of the skin microbiome[4].

The treatment goal in AD is to reduce skin inflammation, and disease management is based on the use of emollients, topical corticosteroids calcineurin inhibitors, and, in severe cases, also systemic immunomodulators[5,6]. Treatment allows a decrease in severity and exacerbations but there is no cure and its signs and symptoms have a negative impact on the patient's quality of life[7].

Vitamin D, classically known for its role in bone metabolism and calcium homeostasis, is a steroid hormone with several extraosseous actions. This vitamin is mainly obtained from the skin through the action of ultraviolet B (UVB) radiation, through the conversion of 7-dehydrocholesterol (7-DHC) into vitamin D3, but also through food or supplementation[8,9].

The full consequences of vitamin D deficiency at cutaneous and immunological levels are not yet known. A possible relationship between vitamin D and the development of allergic diseases emerged when an increased incidence of allergic diseases was noticed at higher latitudes, where vitamin D deficiency is more common[10].

Some studies have shown that lower serum levels of vitamin D are related with more severe AD presentations and that vitamin D supplementation may be an effective treatment for AD[3,11,12]. Furthermore, as several data support the involvement of vitamin D on several aspects of the pathogenesis of AD, namely, on epidermal barrier dysfunction and dysregulation of the immune system[8,10], a relationship between vitamin D levels and the risk and severity of AD has been hypothesized.

Objectives

This work aims to review existing scientific literature on the relationship between vitamin D levels and AD, after performing a review on vitamin D and its metabolism.

Vitamin D metabolism

Vitamin D is a fat-soluble vitamin that exists in two forms: vitamin D3 (cholecalciferol), produced in the skin or obtained from the diet, and vitamin D2 (ergocalciferol), obtained from the diet. Few foods naturally contain vitamin D (oily fish, cod liver oil, egg yolk, shiitake mushrooms, liver), so its synthesis in the skin is the principal way to obtain vitamin D, responsible for 90% of vitamin D replacement[10,13].

Pre-vitamin D3 is synthesized in the epidermis from 7-DHC, an intermediate in the synthesis of cholesterol, by the action of UVB radiation (290-315 nm). It is then converted into vitamin D3 through a temperature-dependent reaction[13-15].

Vitamin D, whether obtained through the diet or through skin synthesis, is biologically inactive and requires two hydroxylation reactions to become active. The first occurs in the liver, by the enzyme 25-hydroxylase, to form calcidiol (25(OH)D), the main circulating form of vitamin D, which has a half-life of 2-3 weeks. It then goes through hydroxylation again by the enzyme 1α-hydroxylase, in the kidney, to be converted into calcitriol ($1,25(OH)_2D$), the most active form and which has a half-life of 4-6 h. This process depends on parathyroid hormone (PTH), serum phosphate values, and growth hormone. The enzyme 1α-hydroxylase is expressed in extra-renal organs, so the second hydroxylation of vitamin D may happen in extra-renal locations such as alveolar macrophages, osteoblasts, lymph nodes, placenta, colon, breast, and keratinocytes, suggesting an autocrine-paracrine action of calcitriol[14,16,17].

Calcium homeostasis is the most important function of vitamin D. When calcium receptors of the parathyroid glands detect low levels of ionized calcium, the gland increases the secretion of PTH, which will stimulate the renal production of calcitriol from circulating calcidiol, and enhance calcium transport at intestinal, bone, and renal levels. PTH secretion will decrease when serum calcium values return to normal. Therefore, normal serum calcidiol values are important to guarantee calcitriol synthesis and, consequently, a normal plasma calcium level. Vitamin D deficiency results in low levels of calcidiol, and, consequently, a decrease in calcitriol synthesis and calcium absorption, and an increase in PTH levels[13,14,18].

Vitamin D deficiency

Insufficient amounts of circulating vitamin D constitute a global health issue. In Europe, the prevalence rates of vitamin D deficiency are alarming and require measures both from a public health and clinical point of view. Although vitamin D levels may vary depending on the age group, ethnicity, and latitude of the study population, 13 out of every 100 European citizens have serum 25(OH)D concentrations lower than 30 nmol/L (12 ng/mL)[16,19,20].

The best indicator of vitamin D status in the body is the serum 25(OH)D concentration, which reflects the free fractions of vitamin D metabolites but there is no consensus regarding an optimal value among different scientific societies and institutions[16,18].

According to the recommendations of the global consensus on the prevention and guidance of nutritional rickets from 2016, serum 25(OH)D values lower than 30 ng/mL indicate vitamin D deficiency[21]. The American academy of pediatrics has postulated values of 25(OH) D levels > 20 ng/mL as sufficient, while the pediatric endocrine society has defined 25(OH)D levels below 30 ng/mL as insufficiency and below 20 ng/mL as deficiency[18].

In Portugal, Direção-Geral da Saúde issued a clinical guideline on the "Prevention and Treatment of Vitamin D Deficiency" (Prevenção e Tratamento da Deficiência de vitamin D), establishing similar plasma concentration values of 25(OH)D that define vitamin D insufficiency or deficiency, in adults and children[22].

Vitamin D and skin physiology

Keratinocytes are the only cells in the body capable of synthesizing vitamin D from 7-DHC. They express vitamin D receptors (VDR) that respond to the active form of vitamin D, which, along with calcium, is one of the main regulators of epidermal differentiation. Vitamin D has a dose-dependent effect on keratinocyte proliferation and differentiation: at low concentrations it increases keratinocyte proliferation, whereas at high concentrations it reduces keratinocyte proliferation and promotes their differentiation by increasing the expression of structural components of the cornified envelope and the synthesis of ceramides, which potentiate the pro-differentiating effect of calcitriol on keratinocytes (feedback loop)[13,14,23,24].

Differentiation of epidermal cells, specifically the keratinocytes, is mediated by vitamin D through the VDR. It is a sequential process that requires the selective binding of the VDR to two main coactivators: the VDR-interacting proteins (DRIP) and the receptor coactivators steroids (SRC). DRIP selectively binds to VDRs and is predominantly expressed during keratinocyte proliferation. As cells differentiate, DRIP expression decreases and SRC expression increases, and VDR begin binding to SRC[13,15,23].

Vitamin D and skin's immune system

The skin's innate immune system is constituted by immune cells (such as neutrophils, monocytes, macrophages, natural killer cells, and innate lymphoid cells), the physical barrier, and antimicrobial peptides (AMPs)[14]. The presence of VDR in different cells of the immune system demonstrates the importance of vitamin D in their regulation[24,25], namely in keratinocyte expression of proinflammatory cytokines.

Calcitriol modifies the function of adaptive immune cells: it suppresses the maturation of dendritic cells (DC), inhibits the secretion of Th1 and Th17 proinflammatory cytokines, and promotes the production of Th2 cytokines. In addition, it induces the production of Treg cells, CD4+ and CD25+, which suppress proinflammatory responses from other immune cells and prevent exaggerated or autoimmune responses[8,13,24,25].

Monocytes and other antigen-presenting cells, such as DC, are important targets of the immunomodulatory effects of vitamin D. Calcitriol modifies the maturation and differentiation of DC, giving them a more adherent spindle cell morphology and a less mature and more immunologically tolerant phenotype, both in the production of cytokines and surface markers, therefore decreasing the activation of adaptive immunity[18,24,25].

Vitamin D plays a significant role in the defense against opportunistic infections, by directly activating the production of AMPs, such as cathelicidin and beta-defensin, and stimulating the synthesis of proteins that contribute to the integrity of the epidermal barrier, such as filaggrin[14,19,23,25].

The role of vitamin D in AD

AD patients have skin barrier disruption and dysregulation of the innate immune system, which leads to inappropriate responses to allergens and microbial pathogens[3]. As previously mentioned, vitamin D promotes the differentiation of keratinocytes, stimulates the synthesis of structural components of the epidermal barrier, and increases the expression of AMPs. Therefore, low serum concentrations of vitamin D can lead to a defective epidermal barrier and immunological

changes that may contribute to AD worsening[3,14,19]. Nevertheless, contrary to psoriasis, topical use of vitamin D has not shown to be successful in AD.

More than 90% of vitamin D in the body is synthesized in keratinocytes by UVB radiation. Variables such as season, latitude, and air pollution can significantly alter vitamin D levels, as can direct sun exposure, skin phototype, lifestyle, and cultural factors (type of clothing)[10]. Geographic areas with less UVB exposure have a higher prevalence of AD and it has been found that there is a relationship between the onset and/or worsening of AD and winter. Furthermore, UV phototherapy is one of the treatment options for moderate to severe AD. Therefore, seasonal factors such as climate, UVB radiation, and vitamin D status are expected to influence the clinical course of AD[9,11,26].

VDR gene, located on the long arm of chromosome 12, has polymorphisms in various diseases which may influence vitamin D function. Some of these VDR polymorphisms influence the severity and susceptibility of AD, as confirmed by the identification of a polymorphism present in patients with severe AD, therefore indicating that VDR and vitamin D may contribute to AD control[14,15,27-29].

Low vitamin D serum levels in AD

Different studies have identified decreased serum levels of 25(OH)D in patients with inflammatory skin diseases, specifically AD, comparatively to healthy people[3,28,30].

A systematic review by Kim et al. selected seven observational studies to infer a possible relationship between serum 25(OH)D levels and AD which included in total of 986 AD patients and 657 healthy controls. One study included only adults, four studies included only children, and two included patients of all ages. The AD group had lower serum 25(OH)D values than the control group, if patients of all ages were included, especially in the subgroup with pediatric patients ($p = 0.0006$) but not in the adult subgroup ($p = 0.50$). However, the studies were considered statistically heterogeneous ($I2 = 98\%$)[3].

Fu et al. conducted a meta-analysis of 22 studies, which concluded that serum 25(OH)D levels in children with AD were significantly lower than in the healthy control group ($p = 0.001$), and values in patients with mild disease were significantly higher compared to patients with severe disease, according to SCORAD ($p < 0.001$)[31].

A study by Lipińska-Opałka et al. showed that vitamin D deficiency was significantly more frequent in children with allergic diseases, AD and asthma than in the control group ($p = 0.007$) and, again, serum vitamin D values were statistically higher in the group of children with mild compared to severe disease ($p = 0.03$)[32].

A small cross-sectional study carried out by Barlianto et al. investigated a possible association between serum vitamin D values, cytokine profile, and AD severity in 36 children aged up to 12 months, 19 with mild and 17 moderate disease, according to SCORAD. There was a high prevalence of vitamin D deficiency and insufficiency in children with AD with mean 25(OH) D values significantly lower in patients with moderate disease compared to mild disease ($p = 0.001$)[33].

Prenatal vitamin D serum levels and AD in childhood

Since 25(OH)D crosses the placenta, maternal 25(OH) D serum levels are the best indicator of the level of exposure of the fetus to vitamin D, so an insufficient value in the mother translates into an insufficient value in the fetus. Low levels of 25(OH)D during pregnancy are associated not only with complications in maternal and fetal health but also in the neonatal period and during childhood. Vitamin D is important for lung maturation and fetal immunity development. Thus, altered values of vitamin D may have a causal relationship with the development of allergic diseases in childhood[10,34,35].

Nevertheless, studies attempting to show a causal relationship between fetal exposure to vitamin D in utero and the development of AD in childhood obtained contradictory results.

Palmer et al. evaluated the influence of vitamin D levels in the umbilical cord on the development of allergic diseases in 270 children and concluded that the risk of eczema at 1 year decreased as 25(OH)D values increased: a 10 nmol/L increase in 25(OH)D concentration was associated with a 12% decrease in risk ($p = 0.002$). Cumulative incidence at 3 years old also showed a significant association with 25(OH)D values: an increase of 10 nmol/L reduced risk by 8% ($p = 0.005$)[36].

In a prospective cohort study by Baïz et al., a significant association was found between 25(OH)D values in the umbilical cord and the risk of developing AD at 1 ($p = 0.05$), 3 ($p = 0.02$) and 5 years old ($p = 0.005$). However, no significant association was found at 2 years old[37].

Another prospective cohort study of 288 pregnant women, carried out by Smith et al., identified a

significant association between maternal 25(OH)D values in early pregnancy and risk of atopy at 2 years old: children whose mothers had 25(OH)D values lower than 30 nmol/L at 13 weeks of pregnancy had a significantly higher risk of developing AD at 2 years than children of mothers with values above 50 nmol/L ($p < 0.05$)[35].

El-Heis et al. performed a double-blind randomized trial to study the effect of vitamin D supplementation (cholecalciferol 1000 IU/day) from 14 weeks until the end of pregnancy on the development of AD at different pediatric ages. Children in the supplementation group had an odds ratio of developing AD at 1, 2, and 4 years lower than those in the placebo group, although the difference was not statistically significant. No association was identified between serum 25(OH)D values during pregnancy and the development of AD in children, at any age. However, although no statistically significant, a relationship was found between supplementation and breastfeeding duration: the risk of AD at 12 months was reduced in the group of children that were breastfed for more than 1 month ($p = 0.03$), compared to those that were breastfed for > 1 month ($p = 0.66$), suggesting protective effect of supplementation with increasing the concentration of cholecalciferol in breast milk[38].

Although several studies indicate a negative association between maternal 25(OH)D values during pregnancy and the development of AD at an early age, other studies have not identified a significant relationship[39,40]. A meta-analysis combining seven randomized controlled trials to investigate a possible association between vitamin D supplementation in pregnant women or children and the development of allergic diseases, including AD in five of these studies, found no statistically significant differences, even though the length of follow-up and the dose of supplementation varied[39].

Shimizu et al. in a prospective cohort study intended to describe risk factors for the development of AD in the 1st year of life, found no association with vitamin D levels during pregnancy or at delivery or prenatal and postnatal vitamin D supplementation[40].

Vitamin D supplementation in the treatment of AD

Vitamin D supplementation is the most used strategy to restore vitamin status[16]. The efficiency of vitamin D supplementation in decreasing AD severity and improving its symptoms and clinical signs has been shown in some studies but is not consensual.

A systematic review and meta-analysis carried out in China with 32 randomized controlled trials and 2347 pediatric patients concluded that supplementation significantly reduced SCORAD and EASI in children with AD compared to the control group ($p = 0.009$)[41].

Imoto et al. carried out a prospective study including 152 AD children, 116 (76.3%) with insufficient or deficient plasma concentrations of 25(OH)D. During the first 4 weeks, the vitamin D deficiency group received 50 IU/week and the insufficiency group received 15 IU/week, after which all patients received a maintenance dose of 15 IU/week during the next 2 months. After 3 months, vitamin D values were significantly higher ($p < 0.001$), SCORAD was reduced ($p < 0.001$) and bacterial infections were less common in the group with improvement after supplementation ($p = 0.01$)[42].

In a double-blind, placebo-controlled study for 12 weeks in 86 children with severe AD treated with topical corticosteroid (1% hydrocortisone cream, twice a day), randomized 1:1 to receive cholecalciferol (1600 IU/day or placebo), the experimental group achieved significantly higher plasma 25(OH)D values compared to the control group ($p < 0.001$) and the mean EASI score was significantly lower than in the placebo group ($p = 0.035$)[43].

Four randomized, double-blind, placebo-controlled studies with no statistical heterogeneity between studies ($I^2 < 50\%$) gathered to perform a meta-analysis concluded that both EASI and SCORAD significantly decreased after vitamin D supplementation ($p < 0.00001$)[3].

As vitamin D regulates the production of AMPs, through induction of cathelicidin expression in keratinocytes[8,10,12], Albenali et al. evaluated the clinical severity and cathelicidin LL-37 levels in patients with AD after 2 months of vitamin D supplementation. Concurrent with a 42% SCORAD reduction ($p < 0.001$) there was a significant increase in LL-37 levels, both in lesioned and non-lesioned skin ($p = 0.0004$). This study also reinforced the correlation between AD severity and low LL-37 levels ($p = 0.01$), and suggested that vitamin D deficiency can lead to a decreased antimicrobial defence and, consequently, increased AD severity due to enhancing *Staphylococcus aureus* colonization[44]. SCORAD and EASI reduction after vitamin D supplementation is concordant with the meta-analysis conducted by Fu et al., but as the dose and time of supplementation differed between studies and there were several confounding factors, studies do not allow concluding about the true effect of supplementation on AD[31].

On the contrary other studies have not confirmed the beneficial effect of vitamin D supplementation. A randomized controlled trial concluded that disease severity did not significantly decrease after vitamin D supplementation at a dose of 2000 IU/day for 3 months ($p = 0.7$), despite a significant correlation between lower vitamin D values and disease severity ($p = 0.015$)[45].

Another randomized controlled study evaluating allergic diseases in children after cholecalciferol supplementation in doses of 10 μg (400 IU) or 30 μg (1200 IU), from 2 weeks of life up to 24 months, showed that, although at 12 months 25(OH)D concentrations were significantly higher in the group supplemented with 30 μg of cholecalciferol, there was no statistically significant difference in the development of allergic diseases between the 2 groups[46].

Conclusion

A possible relationship between AD and vitamin D has been a subject of interest by the scientific community, as a deficiency in vitamin D seems to occur frequently in the population, and vitamin D has a role in the regulation of epidermal differentiation and the immune response. Therefore, there is a rational to study the influence of vitamin D in the course of AD and try to understand how vitamin D may influence several factors involved in its pathogenesis, specifically in the dysfunction of the skin barrier, immune dysregulation, and antibacterial defence[26].

Despite scarce and not very robust, many studies have shown a statistically significant association between low serum vitamin D levels and AD, especially in children, with correlation with disease severity, but this does not necessarily suggest a cause-effect relationship between the two variables. UVB phototherapy, recommended for AD treatment, may at least in part act through the increase of vitamin D levels. Nevertheless, although many studies have shown that oral vitamin D supplementation can improve vitamin D status, enhance the expression of AMPs in the skin of AD patients[26], and improve AD severity scores, the results are not always concordant on the capacity to reduce the risk of developing AD or reduce its severity, and topical vitamin analogs have not been approved for the treatment of AD.

Moreover, although several studies have pointed out that vitamin D supplementation may have a potential role in improving the severity and symptomatology of AD, there is no consensus on the dose, treatment duration, or the best time for supplementation. Studies with larger samples with more control on possible confounding factors, and involving more the adult population, are needed to confirm these data[30]. Furthermore, despite incongruent results, some studies suggest a positive influence of higher prenatal values of maternal vitamin D on the onset of AD during childhood and the benefit of vitamin D supplementation during pregnancy or breastfeeding in the prevention of AD in childhood.

With the present data, it is possible to conclude that there is a probable benefit of vitamin D supplementation in improving the symptoms and clinical signs of AD and that this might be an adjuvant treatment for AD. For this, studies with the same methodology, with larger samples and longer duration are needed to obtain more concrete conclusions.

As discussed in a Cochrane analysis (2012) (Dietary supplements for established atopic eczema. Cochrane Database Syst Rev. 2012 Feb 15;2012(2):CD005205) which continues to be very actual, the available studies about vitamin D supplementation in AD are small, with low numbers of participants to even exclude moderate treatment effects, besides the poor quality in terms of the way these studies were run. It is possible that some supplements may have, or may not, an impact on the severity of AD but until we have an appropriate-powered trial with a publicly, transparent registered protocol we are left with poor quality data and a number of meta-analysis and narrative reviews that have to explore that same poor quality data.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appears in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

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