Increased Vitamin D Signalling Markers in the Skin of Atopic Dermatitis Patients

Christin Weise1,2, Margitta Worm1 and Ralph Rühl3,4*

1Department of Dermatology and Allergy, Allergy-Center-Charité, Charité-Universitätsmedizin, Germany
2NBS Scientific GmbH, Weinheim, Germany
3Department of Biochemistry and Molecular Biology, University of Debrecen, Hungary
4Paprika Bioanalytics BT, Debrecen, Hungary

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*Corresponding author: Dr. Ralph Rühl, Paprika Bioanalytics BT, Debrecen, Hungary

Abstract

Vitamin D-mediated signalling is discussed controversial in regard of allergic sensitization and atopic dermatitis (AD). In this study we determined that in AD patients two main target genes of vitamin D-mediated signalling CYP24A1 (vitamin D 24-hydroxylase) and TSLP (thymic stromal lymphopoietin) are strongly upregulated in both affected as well as non-affected skin of AD patients vs healthy volunteers skin. We conclude that this increased local vitamin D-mediated signalling resulting is in a strong local pro-inflammatory and pro-allergic conditions present in the skin of AD patients with an impact on the systemic vitamin D-signalling and systemic allergic sensitization.

Keywords: Atopic Dermatitis; Skin; Vitamin D; Thymic Stromal Lymphopoietin; Allergic Sensitization; 24-Hydroxylase

Introduction

Serum vitamin D levels have been described to be positively or negatively affected in atopic dermatitis [1-4]. Endogenous serum as well as skin concentrations of the endogenous bioactive vitamin D receptor (VDR) ligand 1,25-dihydroxy-vitamin D3 (1,25VD3) are hard to determine using analytical techniques due to the low endogenous levels in the range of 10^-12M [5]. Just ELISA / RIA techniques in combination with prior chromatography enable a reliable determination of this derivative in serum. Levels of the 1,25VD3-precursor 25-hydroxy-vitamin D3 (25VD3), which is present in higher levels in serum, can routinely be determined in serum samples. Polymorphisms of the VDR are present in patients with severe AD indicating a strong association of vitamin D-mediated signaling and AD [6]. In addition the VDR can heterodimerize with the retinoid X receptor (RXR) which ligands [7-9] were associated with positively influencing VDR-RXR-mediated signalling [10,11].

In various studies reduced serum levels of 25VD3 are found in serum of adult and young AD patients and were even partly inversely correlating with the disease status [12-14]. Unfortunately it is not clear if this phenomenon is due to reduced dietary vitamin D intakes, reduced UV skin exposure and/or targeted down-regulation of serum vitamin D homeostasis via vitamin D binding proteins [15,16], comparable to fatty acids and retinoids under inflammatory conditions, reviewed in Rühl [17,18]. Positive effects of vitamin D supplementation or administration of more stable and less calcemic synthetic VDR agonists are found on clinical markers of AD [19,20], while other studies determined negative effects [21,22]. Various studies postulate that due to reduced 25VD3 levels targeted vitamin D supplementation may be an optimal treatment strategy for improving AD conditions [23,24]. Unfortunately, just limited AD-relevant target organs like the skin and the immune system were examined for vitamin D-mediated signaling during allergic sensitization, chronic manifested atopic dermatitis and after vitamin D-supplementation studies [12-14]. These lacks of knowledge make it difficult to judge the potential positive and negative impact of vitamin D signaling and supplementation in AD.

Case Presentation

In this study we determined based on immunohistological studies the semi-quantitative occurrence of the two VDR-signaling markers TSLP and CYP24A1 [22,25] in normal skin from healthy volunteers compared to affected and non-affected
skin of AD-patients. CYP24A1, the 24-hydroxylase responsible for inactivation of 1,25-D3, is the most common and sensitive marker of VDR-mediated signaling [25], while TSLP is a well-known vitamin D target and trigger of TH2-signalling and thereby a major initiator of allergic sensitization [22,26,27]. For both proteins an increased presence was observed in the epidermis and infiltrating cells in dermis of affected and non-affected skin of AD-patients compared to skin of healthy volunteers (Figure 1). AD-skin possesses remarkably more CYP24A1 protein in epidermis, especially in the stratum basale. CYP24A1 expressing cells were broadly distributed throughout the dermis of healthy and AD-skin. Interestingly, the number of CYP24A1 expressing infiltrating cells seems to be smaller in both affected and non-affected AD-skin than in healthy skin. In contrast to CYP24A1, TSLP presence is scattered in the epidermis of healthy skin and strongly increased in differentiating epidermal keratinocytes over the stratum basale of AD-skin. Furthermore, the proportion of infiltrating cells with TSLP presence is further increased in affected skin, thereby increasing TSLP levels in AD-lesions.

Figure 1: Expression of CYP24A1 and TSLP in the skin from healthy controls (n=3, 52 year, 66% female) and patients with atopic dermatitis (n=3, 29 years, 66% female, 32 SCORAD). Representative immunohistochemical images of CYP24A1 and TSLP staining of healthy (H-SK), non-affected (N-SK) and affected skin (A-SK). Bars, 100 μm. [Tissue cryo-sections were stained with anti-human CYP24A1 (Sigma-Aldrich, Taufkirchen, Germany) or TSLP (Bioss Inc., Woburn, USA) and goat anti-rabbit IgG (DAKO Diagnostika, Hamburg, Germany). Images were taken at the Axioplan light microscope (Carl Zeiss, Jena, Germany)]. Ethical approval for the study was obtained from the local ethics committee (EA1/168/06).

Discussion

Our data describe a strongly induced vitamin D signaling and thereby pro-allergic conditions in the affected and non-affected skin of AD-patients. These data are partly in contrast with the described reduced 25D3 serum values present in AD-patients and the potential connection of reduced vitamin D intake, represented by reduced 25D3 serum levels, and AD [1,14,28,29]. We suggest that serum vitamin D levels may be reduced by our organisms in a feedback mechanism to dampen local vitamin D-mediated pro-allergic and pro-inflammatory conditions, comparable to feedback mechanisms of serum vitamin A levels during local inflammation [17,18,30].

Conclusion

These results prove that vitamin D mediated signaling is strongly increased in affected and non-affected skin of AD-patients and thereby resulting in strong pro-inflammatory and pro-allergic conditions present in the skin of atopic dermatitis.

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