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

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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^{-12}M [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 hetero-dimerize 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 1,25VD3, 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.

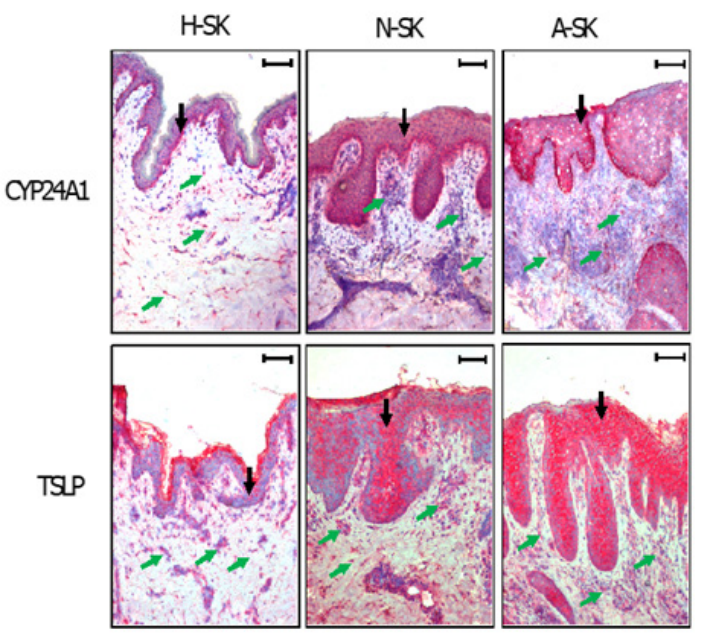

Figure 1: Expression of CYP24A1 and TSLP in the skin from healthy controls (n=3, 52 year, 66% female) and patients with atopic dermatitis (n=3, 29 years, 66% female, 32 SCORAD). Representative immunohistochemical images of CYP24A1 and TSLP staining of healthy (H-SK), non-affected (N-SK) and affected 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 25VD3 serum values present in AD-patients and the potential connection of reduced vitamin D intake, represented by reduced 25VD3 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.

References

1. Albert PJ, Proal AD, Marshall TG (2009) Vitamin D: the alternative hypothesis. Autoimmun Rev 8(8): 639-644.
2. Wjst M (2006) The vitamin D slant on allergy. Pediatr Allergy Immunol 17(7): 477-83.
3. Wjst M (2012) Is vitamin D supplementation responsible for the allergy pandemic? Curr Opin Allergy Clin Immunol 12(3): 257-62.
4. Lucas R, Mihaly J, Gericke J, Torocsik D, Rühl R (2020) Vitamin D signaling in a mouse allergic sensitization model. Int J Vitam Nutr Res 90(5-6): 385-8.
5. Lyra EC, Silva IA, Katayama ML, Brentani MM, Nonogaki S, et al. (2006) 25(OH)D3 and 1,25(OH)2D3 serum concentration and breast tissue expression of 1alpha-hydroxylase, 24-hydroxylase and Vitamin D receptor in women with and without breast cancer. J Steroid Biochem Mol Biol 100(4-5): 184-192.

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6. Heine G, Hoefer N, Franke A, Nothling U, Schumann RR, et al. (2013) Association of vitamin D receptor gene polymorphisms with severe atopic dermatitis in adults. Br J Dermatol 168(4): 855-888.
7. Krezel W, Rühl R, Lera AR (2019) Alternative retinoid X receptor (RXR) ligands. Mol Cell Endocrinol 491: 110436.
8. Rühl R, Krzyzosiak A, Niewiadomska CA, Rochel N, Szeles L, et al. (2015) 9-cis-13,14-dihydroretinoic acid is an endogenous retinoid acting as RXR ligand in mice. PLoS Genet 11(6): e1005213.
9. Rühl R, Krezel W, Lera AR (2018) 9-Cis-13,14-dihydroretinoic acid, a new endogenous mammalian ligand of retinoid X receptor and the active ligand of a potential new vitamin A category: vitamin A5. Nutr Rev 76(12): 929-41.
10. Treptow S, Grun J, Scholz J, Radbruch A, Heine G, et al. (2020) 9-cis retinoic acid and 1.25-dihydroxyvitamin D3 drive differentiation into IgA(+) secreting plasmablasts in human naive B cells. Eur J Immunol.
11. Li XY, Xiao JH, Feng X, Qin L, Voorhees JJ (1997) Retinoid X receptor-specific ligands synergistically upregulate 1, 25-dihydroxyvitamin D3-dependent transcription in epidermal keratinocytes in vitro and in vivo. J Invest Dermatol 108(4): 506-512.
12. Brehm JM, Celedon JC, Soto QME, Avila L, Hunninghake GM, et al. (2009) Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med 179(9): 765-771.
13. Peroni DG, Piacentini GL, Cametti E, Chinellato I, Boner AL (2011) Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. Br J Dermatol 164: 1078-1082.
14. Weisse K, Winkler S, Hirche F, Herberth G, Hinz D, et al. (2013) Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. Allergy 68(2): 220-228.
15. Touvier M, Deschasaux M, Montourcy M, Sutton A, Charnaux N, et al. (2014) Determinants of Vitamin D Status in Caucasian Adults: Influence of Sun Exposure, Dietary Intake, Sociodemographic, Lifestyle, Anthropometric, and Genetic Factors. J Invest Dermatol 135(2): 378-388.
16. Bratke K, Wendt A, Garbe K, Kuepper M, Julius P, et al. (2014) Vitamin D binding protein and vitamin D in human allergen-induced endobronchial inflammation. Clin Exp Immunol 177(1): 366-372.
17. Rühl R (2013) Non-pro-vitamin A and pro-vitamin A carotenoids in atopy development. Int Arch Allergy Appl Immunol 161: 99-115.
18. Rühl R (2007) Effects of dietary retinoids and carotenoids on immune development. Proc Nutr Soc 66(3): 458-69.
19. Hartmann B, Riedel R, Jorss K, Loddenkemper C, Steinmeyer A, et al. (2012) Vitamin D receptor activation improves allergen-triggered eczema in mice. J Invest Dermatol 132(2): 330-336.
20. Hartmann B, Heine G, Babina M, Steinmeyer A, Zugel U, et al. (2011) Targeting the vitamin D receptor inhibits the B cell-dependent allergic immune response. Allergy 66(4): 540-548.
21. Back O, Blomquist HK, Hernell O, Stenberg B (2009) Does vitamin D intake during infancy promote the development of atopic allergy? Acta Derm Venereol 89(1): 28-32.
22. Li M, Hener P, Zhang Z, Kato S, Metzger D, et al. (2006) Topical vitamin D3 and low-calcemic analogs induce thymic stromal lymphopoietin in mouse keratinocytes and trigger an atopic dermatitis. Proc Natl Acad Sci U S A 103(31): 11736-41.
23. Peroni DG, Boner AL (2013) Food allergy: the perspectives of prevention using vitamin D. Curr Opin Allergy Clin Immunol 13(3): 287-292.
24. Devereux G, Macdonald H, Hawrylowicz C (2009) Vitamin D and asthma: time for intervention? Am J Respir Crit Care Med 179(9): 739-740.
25. Prosser DE, Jones G (2004) Enzymes involved in the activation and inactivation of vitamin D. Trends Biochem Sci 29(12): 664-673.
26. Jessup HK, Brewer AW, Omori M, Rickel EA, Budelsky AL, et al. (2008) Intradermal administration of thymic stromal lymphopoietin induces a T cell- and eosinophil-dependent systemic Th2 inflammatory response. J Immunol 181(6): 4311-4319.
27. Soumelis V, Liu YJ (2004) Human thymic stromal lymphopoietin: a novel epithelial cell-derived cytokine and a potential key player in the induction of allergic inflammation. Springer Semin Immunopathol 25(3-4): 325-333.
28. Searing DA, Leung DY (2010) Vitamin D in atopic dermatitis, asthma and allergic diseases. Immunol Allergy Clin North Am 30(3): 397-409.
29. Muehleisen B, Gallo RL (2013) Vitamin D in allergic disease: shedding light on a complex problem. J Allergy Clin Immunol 131(2): 324-329.
30. Gieng SH, Raila J, Rosales FJ (2005) Accumulation of retinol in the liver after prolonged hyporetinolemia in the vitamin A-sufficient rat. J Lipid Res 46(4): 641-649.

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