DOI: https://doi.org/10.25121/PNM.2018.31.1A.55 Post N Med 2018; XXXI(1A): 55-60

*Monika Bilewicz-Stebel[1], Beata Bergler-Czop[2], Katarzyna Sierant[3], Dominika Wcisło-Dziadecka[4]

Vitamin D in dermatology

Witamina D w dermatologii

[1]Department of Internal Medicine, Dermatology and Allergology, Specialized Hospital in Zabrze
Head of Department: Professor Jerzy Jarząb, MD, PhD
[2]Department of Dermatology, School of Medicine in Katowice, Medical University of Silesia in Katowice
Head of Department: Professor Ligia Brzezińska-Wcisło, MD, PhD
[3]Chair and Department of Dermatology, Andrzej Mielęcki Silesian Independent Public Hospital in Katowice
Head of Department: Professor Ligia Brzezińska-Wcisło, MD, PhD
[4]Department of Skin Structural Studies, School of Pharmacy with the Division of Laboratory Medicine in Sosnowiec, Medical University of Silesia in Katowice
Head of Department: Krzysztof Jasik, assistant professor

Keywords
vitamin D, diseases, dermatology, psoriasis, skin cancer

Słowa kluczowe
witamina D, choroby, dermatologia, łuszczyca, rak skóry

Summary

Vitamin D was primarily acknowledged for its role in bones formation by regulating parathyroid hormone (PTH), calcium and phosphorous metabolism leading to maintain the integrity of the skeletal system. Over the past decades, once more the vitamin D attracted a great attention because of its implication in a numerous medical disorders. Researches confirmed its interference in the proper functioning of the most tissues in human body including brain, heart, muscles, immune system and also the skin. Pointing multiple new roles of the vitamin was possible because of discovery of vitamin D receptors (VDRs) in most cells of the body and the presence of enzymes that synthesize the active form of vitamin D in other than renal tissue, especially in the skin. It led to an interest in its role in decreasing the risk of chronic, highly morbid conditions such as carcinomas, autoimmune diseases, infectious diseases and cardiovascular diseases. Basically, its importance for dermatologists focused on its significance in psoriasis but further researches broadens its therapeutic effects in skin diseases such as skin cancers or atopic dermatitis.

Streszczenie

Witamina D pierwotnie znana była ze swej roli w utrzymaniu prawidłowej gospodarki kostnej poprzez regulację metabolizmu parathormonu (PTH), wapnia i fosforu, zapewniając integralność układu kostnego. W ostatnich dziesięcioleciach witamina D ponownie wzbudziła uwagę badaczy z powodu swojego wpływu na wiele zaburzeń zdrowotnych. Badania potwierdziły jej ingerencję w prawidłowe funkcjonowanie większości tkanek w organizmie człowieka, m.in. mózgu, sercu, mięśniach, układzie odpornościowym, a także w skórze. Wskazanie wielu nowych aktywności witaminy D było możliwe dzięki odkryciu obecności receptora witaminy D (VDR) w większości komórek organizmu i enzymów, które syntetyzują aktywną formę witaminy w innych niż nerkowe tkankach, zwłaszcza w skórze. Doprowadziło to do poszukiwania, jaką rolę odgrywa witamina D w zmniejszaniu ryzyka przewlekłych i śmiertelnych stanów chorobowych, takich jak: nowotwory, choroby autoimmunologiczne i zakaźne czy choroby układu krążenia. Zasadniczo uwaga dermatologów skupiała się na znaczeniu witaminy D w łuszczycy, ale prowadzone badania poszerzają jej terapeutyczne wskazania w chorobach skórnych, takich jak nowotwory czy atopowe zapalenie skóry.

Conflict of interest
Konflikt interesów
None
Brak konfliktu interesów

Address/adres:
*Monika Bilewicz-Stebel
Katedra i Oddział Kliniczny Chorób Wewnętrznych, Dermatologii i Alergologii
Szpital Specjalistyczny w Zabrzu
ul. Marii Curie-Skłodowskiej 10, 41-800 Zabrze
tel. +48 (32) 373-23-00
bil.ste@hotmail.com

INTRODUCTION

Vitamin D_3 – chemically 1α,25-dihydroxycholecalciferol – is an organic steroid substance, historically classified as a vitamin, in fact being a hormonal compound. Its precursor – cholesterol – is a steroid lipid compound supplied to the human organism with food (exogenous cholesterol) or produced in a process of biosynthesis (endogenous cholesterol) (1, 2). At the basal layer of epidermis, the cholesterol is converted to provitamin D_3 (7-dehydrocholesterol), which undergoes

a photochemical transformation due to ultraviolet B radiation (UVB) into the intermediate compound previtamin D_3. Then a slow isomerization process under the influence of temperature results in a production of cholecalciferol (traditionally called vitamin D_3), lumisterol and tachysterol. This process takes place at UVB range between 290-320 nm, with the pick reaction at 297 nm. The process is presented at the figure 1. It is estimated that cholecalciferol biosynthesis in the skin covers 80-100% of the vitamin D demand. In the vitamin D metabolic pathway exists the reaction which protects against the formation of toxic amounts of this substance during a prolonged UVB exposure. It is a mechanism of increased production and accumulation of lumisterol, at the expense of vitamin D and tachysterol. But beyond skin biosynthesis, vitamin D is also delivered by absorption in the intestines from food and dietary supplements or medical products (3).

Vitamin D_3 is a form of prohormone – a chemical compound with a very low activity. It can be converted into a fully active hormone by enzymatic and non-enzymatic photochemical processes. Cholecalciferol synthesized in the skin is transferred to a circulatory system. The first activation is made in hepatic cells into 25-hydroxycholecalciferol – calcidiol [25(OH)D], which is the main form of vitamin circulating in the blood. The second stage occurs in the kidney cells with production of 1α,25-dihydroxycholecalciferol – calcitriol [1,25(OH)D], which is the main active form of the vitamin and a specific ligand for a nuclear vitamin D receptor (VDR). The receptor was initially found in intestinal epithelial cells, renal cells and bone tissue. For this reason, vitamin D was perceived by its activity in the calcium-phosphate and bone mineral metabolism (1). Researches which discovered the presence of VDR in most tissues of the human body made an increased interest in vitamin D action and underlined its importance in numerous diseases (3, 4). Vitamin D deficiency is a proved risk factor for such affection as cancers, skin diseases, autoimmune diseases, type 1 and type 2 diabetes mellitus, cardiovascular disease, hypertension, metabolic or infectious diseases, neurological syndromes and mental disorders (4, 5).

1,25(OH)D induces its endocrine effects on target tissues by intracrine, autocrine and paracrine routes in two ways – by modifying transcription of genes (genomic mechanism) and non-transcription (non-genomic mechanism) (1, 3).

Gene transcription is effected via binding calcitriol to VDR in the target cell cytoplasm what initiates the intracellular heterodimerization of VDR and the retinoic X receptor (RXR) leading to form a complex able to penetrate into the cell nucleus. Formed VDR-RXR heterodimer is capable to recognize specific DNA sequences – the VDRE (vitamin D response element) and along with multiple regulatory proteins, impacts the gene transcription, mainly by chromatin acetylation (4, 6). This process may result in the activation or inhibition of gene expression. The inhibition is probably responsible for anti-inflammatory and anti-proliferative features of the vitamin (3, 7).

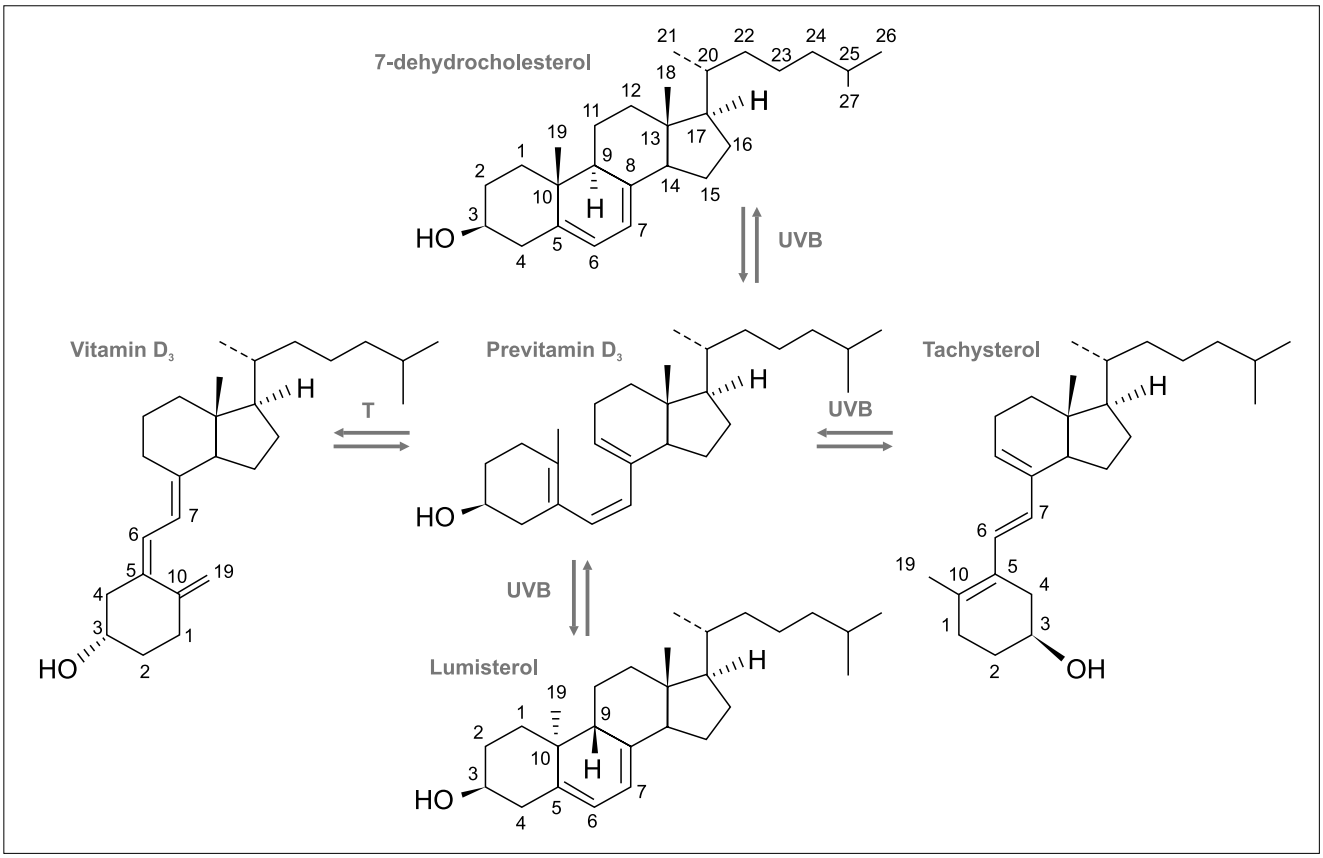

Fig. 1. Cycle of skin conversion 7-dehydrocholesterol to cholecalciferol – vitamin D_3 (3)

As a non-transcriptional pathway the literature describes the ability of 1,25-dihydroxycholecalciferol to affect intracellular calcium levels, as well as intracellular signaling kinases and phosphatases. The facility of activation different pathways in different types of cells confirmed the pleiotropic features of vitamin D (7-9).

Vitamin D within the skin exerts control of cell proliferation, differentiation and maturation, control of angiogenesis, regulation of cellular apoptosis, induction of tumor cell differentiation, participation in the process of epidermal barrier renewal. The most recent literature reports highlight the immunomodulating effect of this compound, including stimulating immune system cell differentiation and inhibiting the production of proinflammatory cytokines that contribute to the development and progression of inflammatory process in skin diseases (10, 11).

Because of the proven impact of vitamin D on numerous disorders and its multiple activities, it is important to sick for its role in skin diseases.

VITAMIN D AND PSORIASIS

Psoriasis is a chronic immune-mediated inflammatory skin disease that affects about 2-3% of the general population (12). Although the countless researches, the pathogenesis of psoriasis is still not fully known. Evidences suggest the dysregulation of the immune cells in the skin, especially lymphocyte T cells (2). Characteristic histopathological image shows hyperproliferation associated with incomplete differentiation of keratinocytes and decreased keratinocyte apoptosis, skin infiltration by activated inflammatory cells and impaired epidermal barrier function at the sites of skin lesions (2, 12).

Studies which focused on the possible role of vitamin D in psoriasis show several pathways of possible mechanism (13-15). It involves the anti-proliferative function of vitamin D – human keratinocytes exposed to an active form of the vitamin showed inhibition of growth and faster maturation (16). Moreover, the anti-inflammatory and anti-angiogenic activity of calcitriol counteract with inflammation and angiogenesis present in psoriatic lesions. It suppresses the proinflammatory Th1 and Th17 cell proliferation, as well as induce the regulatory T cells.

Topically used vitamin D analogues significantly decreases cutaneous levels of proinflammatory IL-17 and IL-8 (2, 17). In addition, dendritic cells differentiation, maturation and antigen presentation seem to be reduced by active 1,25(OH)D (12).

Anti-inflammatory effects exhibit a role of systemic vitamin D deficiency in the pathogenesis of psoriasis. Recent studies have shown that its level is significantly lower in psoriatic patients than in control groups (14, 18). Aside these reports, some review researches point that the significance of low serum vitamin D level in psoriasis is unknown and the legitimacy of vitamin supplementation is unclear. It states a question if a low level of cholecalciferol is a cause or a result of the underlying illness, citing the fact that low serum vitamin levels are also widely observed in the general population (19). Probable supplementation benefits are expected in patients with additional comorbidities such as risk of reduced bone mineral density (20).

VITAMIN D AND SKIN CANCER

UV radiation is indispensable in the process of formation approximately 80-90% of all required vitamin D. Simultaneously, UV radiation is the most important environmental carcinogen associated with increased risk of photocarcinogenesis of skin cancer. The risk applies to melanomas and two non-melanomas types: basal-cell carcinomas (BCC) and squamous-cell carcinomas (SCC) (21, 22). Calcitriol would be beneficial as it stimulates the differentiation of epidermal keratinocytes leading to prevent form developing malignancies in affected cells (23). Moreover, studies on cell cultures *in vitro* and mouse studies with topically applied vitamin D to the skin revealed that vitamin D shows photoprotective effects by decreasing DNA damage, reducing apoptosis, increasing cell survival and decreasing erythema (24-26). On the other hand, researches revealed that malignantly transformed cells may be resistant to active form of vitamin D and e.g. SCC failed to respond to calcitriol in prodifferentiating effect. Surprisingly, these cells had normal expression of VDR and appropriate binding to response elements (23). Besides, Caini et al. did not find that vitamin D intaken from diet or supplements has any protective effect against skin cancer development (27).

Summarizing, there is no direct evidence to show for a protective effect of vitamin D in melanoma and non-melanoma skin cancer formation and development. Up to date question is where is the balance between favourable and harmful effects of UV radiation on skin and health and what is the amount of UVB radiation to bring health benefits of vitamin D production without increasing the risk of cancer (27).

VITAMIN D AND VITILIGO

Vitiligo is an acquired disorder with presence of hypopigmented macules which formation is caused by the loss of melanocyte activity for melanin pigment generation and destruction of epidermal melanocytes. It affects 0.1-2% of individuals of different populations (28, 29).

Possible clinical effect of vitamin D in autoimmune diseases suggests that a deficiency in 25(OH)D may be a co-factor in the development of vitiligo – as autoimmunity lies at the base of pathogenesis of vitiligo (2). Many studies revealed decreased levels of 25(OH)D in patients with vitiligo along or with concomitant autoimmune diseases. But it is still not evident if vitamin D deficiency plays a role in causing vitiligo (30, 31). However, it is confirmed that the vitamin via its anti-apoptotic effect protects the epidermal melanin and melanocyte through a control over the activation, proliferation, migration of melanocytes and melanogenesis by modu-

lating T cell activation. The exact mechanism of these effects is not fully understood. Vitamin D probably exerts melanocyte physiology through melanogenic cytokines (such as endothelin-3) and regulatory factors of melanocyte life and maturation process (32). Vitamin D could also protect the skin cells because of its antioxidant properties and regulatory function toward the reactive oxygen species (33). In addition, vitamin D by inhibiting IL-6, IL-8, TNF-a, and TNF-c, modulates dendritic cell maturation and functioning, immunomoduling the autoimmune pathway of vitiligo (34).

Topical vitamin D analogs treatment is widely and effectively used as monotherapy or in a combination with corticosteroids or UV therapy (35, 36). Study of Gargoom et al. indicated better results after application the ointment rather that the cream of calcipotriol (36). There are few reports about a systemic therapy. One interesting researches conducted by Finamor et al. concerned the oral vitamin D treatment. The patients who were administrated high dose of the vitamin for 6 months demonstrated 25-75% repigmentation without metabolic side effects. The researches suppose such therapy may be effective and safe (37).

Overally, the action of vitamin D on autoimmune system is not fully clear, the therapy with vitamin D medicaments may be effective in monotherapy, as well as in combination other forms of therapy (29).

VITAMIN D IN ACNE VULGARIS

Acne vulgaris is a chronic inflammatory disease of the hair-sebaceous units. It is one of the most common skin diseases in a clinical dermatological practice – tt occurs in 80-100% of people aged 11-30 years old (5, 38).

There are many identified etiopathological factors that determine the occurrence of acne vulgaris. Among the traditional causes are disorders of hair follicle keratosis, colonization by *Propionibacterium acnes* (*P. acnes*), overproduction and changes in a composition of sebum. These phenomena lead to the formation of microcomedones – a composition of accumulated unexfoliated corneocytes obstructing the follicle ostium, subsequently leading to bacterial colonization and inflammation. However, recent research focuses on the opposite chronology in etiological steps highlighting the role of inflammation as one of the earliest and the most important pathophysiological phenomena in acne (39). It has been shown that inflammatory and immune processes are primary to keratosis disorders, changes in the amount and quality of sebum and *P. acnes* colonization. A number of essential immunological events take place during the early stage of inflammation development. In subclinical lesions, lymphocytes and macrophages start to accumulate and produce multiple proinflammatory cytokines – interleukins: IL-1, IL-6, IL-8, IL-10, IL-12 and tumor necrosis factor – TNF-α. These molecules, in addition to activation of inflammation, stimulate keratinocytes proliferation and reconstruction of a surrounding connective tissue (34, 39, 40).

Actions demonstrated by vitamin D are in opposition to the etiological factors responsible for the occurrence and course of acne vulgaris (21). Vitamin D counteracts the development and maintenance of inflammation observed at the base of lesion formation. In addition, the functions of 1,25(OH)D, which are not directly related to the inhibition of inflammation, may also be useful in limiting the onset of eruption as they affect other traditional pathophysiological mechanisms of acne. Abnormal keratosis in hair follicles is caused by excessive production and accumulation in the follicle ostium of corneocytes, which do not exfoliate enough but obstruct the duct and form comedones. Vitamin D inhibits excessive cell proliferation and regulates keratinocytes apoptosis, thus it can reduce the number of cells that transform into primary efflorescences. Most patient with acne vulgaris manifest abnormalities in the composition and amount of sebum – lipid secretion of sebaceous glands. The pathogenesis of it involves the growth of sebaceous glands, and increased secretion of sebum, stimulated principally by androgens. Researches proved that sebocytes are capable to synthesis the endogenous active form of vitamin D and metabolize its exogenous analogs. The vitamin regulates local sebocytes' proliferation and life cycle, also lipid composition, and secretion of inflammatory IL-6 and IL-8 *in vitro*. Moreover, sebocytes do express the vitamin D receptor (VDR) on their cell membranes (2, 41).

There are few researches linking vitamin D with acne disease. In Yildizgören and Togral study, the investigated patients with nodulocystic acne had lower vitamin D levels in sera compared with the control group (42). It's too little to estimate 1,25(OH)D role in acne. Currently, the research of efficacy of topical calcipotriene as a therapy of acne is being conducted (43).

VITAMIN D AND ATOPIC DERMATITIS

It is a recurrent chronic inflammatory disease with pruritus and eczema. It's frequently accompanied by hypersensitivity to allergens – mostly in immunoglobulin E-dependent reaction – and other allergic diseases such as allergic rhinitis or asthma (1, 44).

The most significant pathological lesions demonstrate destruction of antibacterial stratum corneum barrier (mainly defect of filaggrin) and inappropriate amount and function of antimicrobacterial proteins (cathelicidin and defensins) (1).

Vitamin D can regulate the keratinocyte differentiation (stimulates or inhibits) according to vitamin concentration and stimulate the synthesis of filaggrin, essential for formation of stratum corneum barrier. These two actions favour the integrity of antibacterial protection barrier (45). As a second mechanism, 1,25(OH)D intensifies antimicrobial peptide activity in order to prevented skin infections. The studies indicate a connection between activation of toll-like receptors and the production of cathelicidin by vitamin D and diminishing sensitivity to bacterial infections (46, 47). The her-

pes simplex virus (HSV) superinfection, common in atopic skin, in observed with significantly lower level of cathelicidin in patient sera. Increased cathelicidin production, mediated by vitamin D, may help in HSV infection because of its activity against the virus (48). Some researches points the effectiveness of vitamin D analogues in suppression of immunoglobulin E (IgE) production *in vitro* and IgE-mediated cutaneous reactions (49).

Beside above, meta-analysis summarizes that 25(OH)D level is lower in atopic dermatitis patients serum than in the controls, especially in pediatric patients. Researches with placebo groups, exhibit that vitamin D supplementation decreased symptoms and improve the clinical course of atopic dermatitis. However, the specific mechanisms of vitamin D role is not clear. Moreover, some studies indicate no connection between vitamin D and clinical disease severity (44). Interestingly, it is possible that to high intake of vitamin D during infancy may results in increased prevalence of atopic manifestations and earlier development of atopic allergy later in childhood (50).

CONCLUSIONS

Vitamin D is attracting a great attention in a numerous medical disorders with confirmed interference in the proper functioning of the most tissues in human body including the skin. Pointing multiple new roles of the vitamin was possible because of discovery of vitamin D receptors (VDRs) in most cells of the body. Wide range of diseases exhibits improvement after topical or oral administration of vitamin D. Explanation of underlying mechanism of vitamin theoretical and clinical effects are still under investigation. The significance of vitamin D role in a human organism is indisputable, although the fully established treatment in skin diseases include psoriasis with topical calcitriol. Nevertheless, researches findings are encouraging for numerous cutaneous disorders and worth exploring.

BIBLIOGRAPHY

1. Wadhwa B, Relhan V, Goel K et al.: Vitamin D and skin diseases: A review. Indian J Dermatol Venereol Leprol 2015; 81(4): 344-355.
2. Mostafa WZ, Hegazy RA: Vitamin D and the skin: Focus on a complex relationship: A review. J Adv Res 2015; 6(6): 793-804.
3. Piotrowska A: Modulacyjny wpływ witaminy D na działanie reaktywnych form tlenu w keratynocytach. Rozprawa doktorska. Gdański Uniwersytet Medyczny 2014.
4. Sintov AC, Yarmolinsky L, Dahan A et al.: Pharmacological effects of vitamin D and its analogs: recent developments. Drug Discov Today 2014; 19(11): 1769-1774.
5. Williams HC, Dellavalle RP, Garner S: Acne vulgaris Lancet 2012; 379(9813): 361-372.
6. Tukaj C: Właściwy poziom witaminy D warunkiem zachowania zdrowia. Postepy Hig Med Dosw 2008; 62: 502-510.
7. Ryan JW, Anderson PH, Morris HA: Pleiotropic Activities of Vitamin D Receptors – Adequate Activation for Multiple Health Outcomes. Clin Biochem Rev 2015; 36(2): 53-61.
8. Abelha-Aleixo J, Fonseca R, Bernardo A et al.: Vitamin D – immunomodulatory actions and new potentialities. Acta Reumatol Port 2014; 39(4): 355-356.
9. Maestro MA, Molnar F, Mourino A et al.: Vitamin D receptor 2016: novel ligands and structural insights. Expert Opin Ther Pat 2016; 26(11): 1291-1306.
10. Schlager JG, Rosumeck S, Werner RN et al.: Topical treatments for scalp psoriasis: summary of a Cochrane Systematic Review. Br J Dermatol 2017; 176(3): 604-614.
11. Cannell JJ, Hollis BW: Use of Vitamin D in Clinical Practice. Altern Med Rev 2008; 13(1): 6-20.
12. Barrea L, Savanelli MC, Di Somma C et al.: Vitamin D and its role in psoriasis: An overview of the dermatologist and nutritionist. Rev Endocr Metab Disord 2017; 18(2): 195-205.
13. Gisondi P, Rossini M, Di Cesare A et al.: Vitamin D status in patients with chronic plaque psoriasis. Br J Dermatol 2012; 166: 505-510.
14. Orgaz-Molina J, Buendía-Eisman A, Arrabal-Polo MA et al.: Deficiency of serum concentration of 25-hydroxyvitamin D in psoriatic patients: a case-control study. J Am Acad Dermatol 2012; 67: 931-938.
15. El-Moaty Zaher HA, El-Komy MH, Hegazy RA et al.: Assessment of interleukin-17 and vitamin D serum levels in psoriatic patients. J Am Acad Dermatol 2013; 69: 840-842.
16. Holick MF: Vitamin D: a millenium perspective. J Cell Biochem 2003; 88: 296-307.
17. Sugiyama H, Gyulai R, Toichi E et al.: Dysfunctional blood and target tissue CD4+ CD25 high regulatory T cells in psoriasis: mechanism underlying unrestrained pathogenic effector T cell proliferation. J Immunol 2005; 174: 164-173.
18. Soleymani T, Hung T, Soung J: The role of vitamin D in psoriasis: a review. Int J Dermatol 2015; 54(4): 383-392.
19. Autier P, Boniol M, Pizot C, Mullie P: Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol 2014; 2(1): 76-89.
20. Hambly R, Kirby B: The relevance of serum vitamin D in psoriasis: a review. Arch Dermatol Res 2017. DOI: 10.1007/s00403-017-1751-2.
21. Lehmann B: Role of the vitamin D_3 pathway in healthy and diseased skinfacts, contradictions and hypotheses. Exp Dermatol 2009; 18(2): 97-108.
22. Reichrath J, Saternus R, Vogt T: Endocrine actions of vitamin D in skin: Relevance for photocarcinogenesis of non-melanoma skin cancer, and beyond. Mol Cell Endocrinol 2017; 453: 96-102.
23. Bikle D: Vitamin D and skin cancer. J Nutr 2004; 12: 3472S-3478S.
24. Wong G, Gupta R, Dixon KM et al.: 1,25-Dihydroxyvitamin D and three low-calcemic analogs decrease UV-induced DNA damage via the rapid response pathway. J Steroid Biochem Mol Biol 2004; 89-90: 567-570.
25. Dixon KM, Deo SS, Norman AW et al.: *In vivo* relevance for photoprotection by the vitamin D rapid response pathway. J Steroid Biochem Mol Biol 2007; 103: 451-456.
26. Gupta R, Dixon KM, Deo SS et al.: Photoprotection by 1,25 dihydroxyvitamin D_3 is associated with an increase in p53 and a decrease in nitric oxideproducts. J Invest Dermatol 2007; 127: 707-715.
27. Caini S, Boniol M, Tosti G: Vitamin D and melanoma and non-melanoma skin cancer risk and prognosis: a comprehensive review and meta-analysis. J Cancer 2014; 50(15): 2649-2658.
28. Sharma CK, Sharma M, Aggarwal B, Sharma V: Different Advanced Therapeutic Approaches to Treat Vitiligo. J Environ Pathol Toxicol Oncol 2015; 34(4): 321-334.
29. Grimes PE, Nashawati R: The Role of Diet and Supplements in Vitiligo Management. Dermatol Clin 2017; 35(2): 235-243.
30. Silverberg JI, Silverberg AI, Malka E, Silverberg NB: A pilot study assessing the role of 25 hydroxy vitamin D levels in patients with vitiligo vulgaris. J Am Acad Dermatol 2010; 62: 937-941.
31. Li K, Shi Q, Yang L et al.: The association of vitamin D receptor gene polymorphisms and serum 25-hydroxyvitamin D levels with generalized vitiligo. Br J Dermatol 2012; 167: 815-821.
32. Birlea SA, Costin GE, Norris DA: Cellular and molecular mechanisms involved in the action of vitamin D analogs targeting vitiligo depigmentation. Curr Drug Targets 2008; 9: 345-359.
33. Alghamdi K, Kumar A, Moussa N: The role of vitamin D in melanogenesis with an emphasis on vitiligo. Indian J Dermatol Venereol Leprol 2013; 79: 750-758.
34. Tanghetti EA: The role of inflammation in the pathology of acne. J Clin Aesthet Dermatol 2013; 6(9): 27-35.
35. de Menezes AF, Oliveira de Carvalho F, Barreto RS et al.: Pharmacologic Treatment of Vitiligo in Children and Adolescents: A Systematic Review. Pediatr Dermatol 2017; 34(1): 13-24.
36. Gargoom AM, Duweb GA, Elzorghany AH et al.: Calcipotriol in the treatment of childhood vitiligo. Int J Clin Pharmacol Res 2004; 24: 11-14.
37. Finamor DC, Sinigaglia-Coimbra R, Neves LC et al.: A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis. Dermatoendocrinol 2013; 5: 222-234.

38. Szepietowski J, Kapińska-Mrowiecka M, Kaszuba A et al.: Trądzik zwyczajny: patogeneza i leczenie. Konsensus Polskiego Towarzystwa Dermatologicznego. Przegl Dermatol 2012; 99: 649-673.
39. Metiko B, Brooks K, Burkhart CG et al.: Is the current model for acne pathogenesis backwards? J Am Acad Dermatol 2015; 72(6): 167.
40. Reichrath J: Vitamin D and the skin: an ancient friend, revisited. Exp Dermatol 2007; 16(7): 618-625.
41. Kramer C, Seltmann H, Seifert M et al.: Characterization of the vitamin D endocrine system in human sebocytes *in vitro*. J Steroid Biochem Mol Biol 2009; 113(1-2): 9-16.
42. Yildizgören MT, Togral AK: Preliminary evidence for vitamin D deficiency in nodulocystic acne. Dermatoendocrinol 2015; 6(1): e983687.
43. Bhat YJ, Latief I, Hassan I: Update on etiopathogenesis and treatment of Acne. Indian J Dermatol Venereol Leprol 2017; 83(3): 298-306.
44. Kim MJ, Kim SN, Lee YW et al.: Vitamin D Status and Efficacy of Vitamin D Supplementation in Atopic Dermatitis: A systematic Review and Meta-Analysis. Nutrients 2016; 8(12): 789.
45. Van Etten E, Decallone B, Verlinden L et al.: Analogs of 1α,25-dihydroxyvitamin D_3 as pluripotent immunomodulators. J Cell Biochem 2003; 88: 223-226.
46. Liu PT, Stenger S, Li H et al.: Toll-like receptor triggering of vitamin D mediated human antimicrobial response. Science 2006; 311: 1770-1773.
47. Schauber J, Dorschner RA, Coda AB et al.: Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D dependent mechanism. J Clin Invest 2007; 117: 803-811.
48. Howell MD, Wollenberg A, Gallo RL et al.: Cathelicidin deficiency predisposes to eczema herpeticum. J Allergy Clin Immunol 2006; 117: 836-841.
49. Samochocki Z, Bogaczewicz J, Jeziorkowska R et al.: Vitamin D effects in atopic dermatitis. J Am Acad Dermatol 2013; 69: 238-244.
50. Back O, Blomquist HK, Hernell O, Stenberg B: Does Vitamin D intake during infancy promote the development of atopic allergy? Acta Derm Venereol 2009; 89: 28-32.

received/otrzymano: 6.02.2018
accepted/zaakceptowano: 27.02.2018