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Serum 25-hydroxy vitamin d deficiency against IL 17 acne vulgaris

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ARTICLE INFO

Article history:

Received Jan 30, 2023
Revised Feb 16, 2023
Accepted Feb 28, 2023

Keywords:

Acne vulgaris
Deficiency
IL-17
Vitamin

ABSTRACT

Vitamin D is essential to immune system function and influences many dermatological diseases, such as psoriasis and atopic dermatitis, a fat-soluble steroid hormone derivative sourced from food intake and synthesized in the skin through exposure to sunlight. Vitamin D deficiency is recognized as a global problem, with high cases in South and Southeast Asia. Acne vulgaris is a chronic inflammatory disease of the skin, specifically the pilosebaceous unit. Inflammation is a critical factor in the development of acne vulgaris. IL-17 is a proinflammatory cytokine that plays a central role in acne vulgaris inflammation. This study aims to obtain information regarding serum 25(OH)D deficiency for IL -17 acne vulgaris. The data collection method was through collecting data from articles related to serum 25-(OH)D deficiency against IL-17 acne vulgaris. The inclusion criteria involved original articles, case-control studies, and review papers on 25(OH)D, IL-17, and acne vulgaris. Vitamin D deficiency can lead to cosmogenesis and inflammatory exacerbations that characterize the acne vulgaris nodulocystic phenotype. The immune response in acne vulgaris is stimulated by the innate immune system via toll-like receptor 2 (TLR2) and adaptive immunity via Th1 lymphocytes. There is evidence that vitamin D inhibits TLR2 expression in monocytes and reduces proinflammatory cytokine production. The most common biomarker in inflammation is IL-17 which was significantly higher in acne vulgaris patients with vitamin D deficiency than in patients with normal vitamin D levels.

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INTRODUCTION

Vitamin D is a fat-soluble steroid hormone derivative from food intake and is synthesized in the skin through exposure to sunlight (Alhetheli et al., 2020). Vitamin D is essential for the development and maintenance of bone tissue (Bostanci et al., 2018). In addition, vitamin D has important roles in the skin, such as differentiation and proliferation of sebocytes and keratinocytes, antimicrobial effects, adaptive and innate immune functions, regulation of sebaceous glands, protection against light, and participation in wound healing (Saptarini et al., 2020). Vitamin D is primarily metabolized in the epidermis with UVB activity through 7-dehydroxycholesterol, which is finally converted to 25-hydroxy vitamin D [25(OH)D] in the liver (Wang et al., 2021) . The 25(OH)D is the precursor of the active form of vitamin D, an indicator of vitamin D levels (Jassil et al., 2017; Sukmawati, 2016).

Vitamin D deficiency is recognized as a global problem, with high cases occurring in South and Southeast Asia (Querfeld, 2013; Saptarini et al., 2020). Vitamin D deficiency is a risk factor in the development of acne vulgaris. Insufficient levels of 25(OH)D promote the increase of inflammatory lesions in acne vulgaris (Navarro-Triviño et al., 2019; Sharaf et al., 2022). Acne vulgaris is a chronic inflammatory disease of the skin, specifically the pilosebaceous unit (hair follicles in the skin associated with oil glands), that occurs in both women and men (Alhetheli et al., 2020; Mohamed et al., 2021; Williams et al., 2012). Acne is a chronic inflammatory dermatosis consisting of open comedones (blackheads), closed comedones (whiteheads), and inflammatory lesions, such as nodules, pustules, and papules (Fox et al., 2016). Acne vulgaris is the most common skin disease, affecting up to 95% of adolescents (Zouboulis & Bettoli, 2014). A predilection for acne vulgaris is in areas of the skin with the densest population of sebaceous follicles, namely the face (99% of cases), upper chest (15%), and back (60%). Acne vulgaris is commonly found in adolescents, affecting nearly 85%, and its prevalence decreases with age (Murlistyarini et al., 2018).

Inflammation is a critical factor in the development of acne vulgaris. The production of proinflammatory cytokines is caused by follicular disruption, which ultimately leads to changes in sebum production (Dreno et al., 2015). This follicular disorder is caused by the activity of Propionibacterium acnes, which can trigger an inflammatory response in acne vulgaris which activates the T helper 17 (Th17) pathway and is considered a significant contributor to the inflammatory response of P. Acnes stimulates the production of interleukin 17 (IL-17) and interferon γ (IFN -γ) as well as increasing the expression of other inflammatory cytokines (Ebrahim et al., 2019). Therefore, this study aims to obtain information on the deficiency of serum 25-hydroxy vitamin D against IL -17 acne vulgaris.

RESEARCH METHOD

A literature review was conducted to gather as much information as possible regarding serum 25(OH)D deficiency against IL-17 acne vulgaris. This study was a type of review article that aims to get information about acne based on a biomarker. The data source used a secondary source (Lee et al., 2019). Methods of data collection were through collecting data from articles related to serum 25-hydroxy vitamin D deficiency against IL-17 acne vulgaris. Inclusion criteria were original articles, case-control studies (human, animal, and cell studies), and review papers on 25(OH)D, IL-17, and also acne vulgaris within the last ten years (Lenis et al., 2020).

RESULTS AND DISCUSSIONS

Acne vulgaris

Acne vulgaris is a common inflammatory skin condition. Although often considered a disease of youth, its prevalence remains high into adulthood. Nearly 90% of adolescents have acne vulgaris, and half continue to have symptoms as adults (Dawson & Dellavalle, 2013). The prevalence of acne

vulgaris after adolescence decreases with age (Knutsen-Larson et al., 2012). At the age of 40 years, 1% of men and 5% of women still have lesions (Dawson & Dellavalle, 2013). The Global Burden of Disease Study 2010 found that acne vulgaris was the eighth most common skin disease, with an estimated global prevalence of 9.38%. In different countries and age groups, acne vulgaris varied, with estimates ranging from 35% to almost 100% in adolescents (Heng & Chew, 2020).

Acne vulgaris lesions develop in the pilosebaceous units, which are mainly spread on the cheeks, chin, forehead, and back (Wang et al., 2021). Acne vulgaris does not affect the general health status and poses no vital danger, but this disease can become a problem in social life (Aydemir, 2014). The psychosocial impact of acne vulgaris includes adverse effects on various dimensions of quality of life. These include effects on self-perception, socialization, emotional health, and employment opportunities. Besides, it may be associated with symptoms of anxiety and depression and loss of self-esteem (Tan & Bhate, 2015).

Pathogenesis of Acne Vulgaris

Acne vulgaris is a multifactorial skin disorder (Kemeriz et al., 2020). The pathogenesis of acne vulgaris is related to many factors, such as increased follicular hyperkeratinization, sebum and hormone production, proliferation, and inflammatory processes (Karadag et al., 2012). Abnormal hyperkeratinization of the central infundibulum of the pilosebaceous duerict with comedo formation caused by increased androgens (Aydemir, 2014; Tan & Bhate, 2015), iincreased sebum production from enlarged sebaceous glands caused by increased androgens (Mohiuddin, 2019), colonization and proliferation of the ducts with bacteria (mostly P. acnes) (Mohiuddin, 2019), inflammatory response induced by the immunological activity of P. acnes (Mohiuddin, 2019).

Other factors that exacerbate acne vulgaris are diet, menstruation, sweat, stress, ultraviolet radiation, and the use of pomade. The use of drugs, such as lithium, steroids, and anticonvulsants, excessive sun exposure, use of clothing, endocrine disorders due to polycystic ovary syndrome, and even pregnancy also trigger acne vulgaris factors. Foods with a high glycemic index stimulate increased insulin signaling, which stimulates androgen secretion and causes increased sebum production, sebaceous gland growth, and hyper-keratinization, which results in acne (Mohiuddin, 2019). In addition, genetics and oxidative stress also contribute to the pathogenesis of acne vulgaris. Recent studies have revealed that new factors that may contribute to the pathogenesis of acne vulgaris include inflammation and T helper (Th) cell immunology17 (Suh & Kwon, 2015).

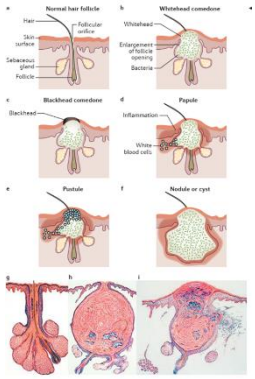

Figure 1 Formation of Acne Vulgaris.

Schematic represents the skin containing the sebaceous unit (section a) consisting of a hair follicle and a sebaceous gland responsible for sebum production. The formation of acne vulgaris begins when sebum and keratinous material exuded from the skin clogs pores and triggers bacterial colonization, which causes closed comedones or whiteheads (part b). As whitehead

comedones grow due to more sebum and keratin material accumulation, the follicular orifice opens and forms an open comedo or blackhead (section c). The black color results from the oxidation of lipids and the skin pigment melanin. More significant distension of the comedo results in follicular rupture and inflammatory lesions, such as papules (section d), pustules (section e), and nodules or cysts (section f). Acne vulgaris cysts are not true cysts because true cysts are covered by epithelium. Histological images of pilosebaceous units (section g), comedones (section h), and inflammatory lesions with rupture of the follicular wall (section i) are presented (Moradi Tuchayi et al., 2015).

Clinical Symptoms of Acne Vulgaris

Acne vulgaris patient exhibits skin condition with comedones, papules, and pustules. Therefore, blackheads can be divided into two types: open comedones (blackheads), clogged follicles with openings exposing their contents to air, and closed comedones (whiteheads), clogged follicles without holes. Papules are raised lesions on the skin smaller than 1 cm in diameter, whereas pustules are similar to papules but are inflamed and filled with pus (Heng & Chew, 2020). Lesions may be on the face, neck, chest, or back (Dawson & Dellavalle, 2013). In patients with severe acne vulgaris, nodules and cysts are inflamed and swollen with a minimum size of 5 mm. Other symptoms, such as scarring, erythema, and hyperpigmentation, can be observed in acne vulgaris patients (Heng & Chew, 2020).

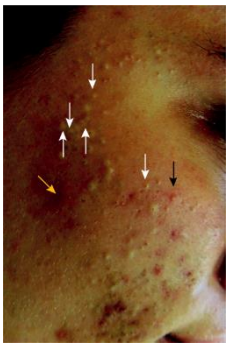

Figure 2. Clinical Presentation of Acne Vulgaris. Acne vulgaris lesions include comedones (white arrows), papules (yellow arrows), and pustules (black arrows) on the facial skin (Moradi Tuchayi et al., 2015).

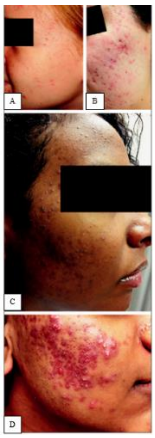

Figure 3. An Example of the Severity of Acne Vulgaris; Mild, Moderate, and Severe.

Panel A shows a patient with mild acne vulgaris (papules, pustules, and some closed comedones). Panel B shows a patient with moderate acne vulgaris, numerous post-inflammatory papules, erythema, and scars. Panel C shows a patient with moderate inflammation and

comedonal acne vulgaris, with postinflammatory hyperpigmentation of the forehead, cheeks, and chin. Panel D shows a patient with severe acne vulgaris, with confluent papules, pustules, and deep nodules (Zaenglein, 2018).

Impact of Acne Vulgaris

Acne vulgaris produces physical symptoms, such as aches, itching, and pain, but the main effect is on quality of life (Williams et al., 2012). Acne vulgaris has been found to harm an individual's social life, self-esteem, and body image, resulting in psychological disorders, including depression and anxiety (Heng & Chew, 2020).

Depression is 2-3 times more common in patients with acne vulgaris than in the general population. At the same time, rates of depression are two times higher in women with acne vulgaris than in men (Moradi Tuchayi et al., 2015). Facial appearance has an essential role in self-perception and interaction with others. Psychiatric symptoms, such as somatization, obsession, sensitivity, hostility, phobias, paranoia, and psychoticism, are associated with acne vulgaris. The rate of decline in quality of life increases significantly with increasing clinical severity of acne vulgaris (Mohiuddin, 2019). Patients with mild to moderate acne vulgaris show higher depression scores than patients with alopecia areata, atopic dermatitis, or psoriasis (Moradi Tuchayi et al., 2015).

Vitamin D is a fat-soluble steroid prohormone with endocrine, paracrine, and autocrine functions. The paracrine and autocrine effects of vitamin D depend on genetic transcription that triggers inhibition of cell proliferation, promotion of cell differentiation, and apoptosis which have a role in cancer metabolism, immunity, and many organ systems (Mostafa & Hegazy, 2013). Vitamin D has been known to play an essential role in maintaining bone and calcium homeostasis (Rasti et al., 2022). Vitamin D is also known as an antioxidant agent (Toossi et al., 2015). Vitamin D can regulate the immune system and the proliferation and differentiation of keratinocytes and sebocytes, which have anti-comedogenic and antioxidant properties that facilitate the synthesis of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) (Singh et al., 2021; Toossi et al., 2015).

The main circulating form of vitamin D is 25(OH)D (Abd-Elmaged et al., 2019). Serum 25(OH)D level results from skin exposure to sunlight and total vitamin D intake from diet and supplements (Autier et al., 2012). The 25(OH)D is the result of the process of hydrolyzing vitamin D, which takes place in the liver, which was previously synthesized in the skin with the primary source of ultraviolet B rays from sunlight (Autier et al., 2012; Mohamed et al., 2021). Age, skin pigmentation, smoking, and adiposity are other determinants of 25(OH)D levels (Autier et al., 2012; Mohamed et al., 2021).

Besides its well-known role as a modulator of calcium metabolism, vitamin D also plays a role in influencing the innate and adaptive immune systems through its effects on T and B lymphocytes, dendritic cells, and macrophages, and is associated with systemic inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory intestinal and dermatological diseases (Lim et al., 2016). In dermatological diseases, vitamin D regulates the immune system by influencing the proliferation and differentiation of keratinocytes and sebocytes, as well as anti-comedogenic and anti-oxidative functions (El-Hamd et al., 2019; Wang et al., 2021). On the other hand, vitamin D, with its anti-apoptotic effect, can protect melanin and epidermal melanocytes through activation, proliferation, melanocyte migration, and melanogenesis by modulating T-cell activation. Vitamin D provides melanocyte physiology through melanogenic cytokines (such as endothelin-3) (Haydar et al., 2019). Vitamin D deficiency may contribute to the pathogenesis of acne vulgaris (El-Hamd et al., 2019).

Correlation Vitamin D With Acne

There are only three sources of vitamin D: sunlight, diet, and vitamin D supplements. UVB radiation on the body induces light pink erythema for at least 15-20 minutes and can produce up to

250 µg of vitamin D (10,000 IU) (Mostafa & Hegazy, 2013). UV-B radiation converts 7-dehydrocholesterol (synthesized in the skin) to pre-vitamin D3, which is then inactive vitamin D. This inactive vitamin D is then converted in the liver to 25(OH)D via hepatic hydroxylation. In the second step, 25(OH)D is metabolized in the kidney to the active metabonavalite 1,25(OH)D or calcitriol via the action of renal alpha-1-hydroxylase (Navarro-Triviño et al., 2019). Calcitriol synthesized in keratinocytes regulates growth, differentiation, apoptosis, and other biological processes through the effects of intracrine, autocrine, and paracrine on the epidermal cell population (Wadhwa et al., 2015). This mechanism is regulated by serum levels of inorganic calcium and phosphorus, detected by glands that secrete parathyroid hormone (PTH) and stimulate alpha-1-hydroxylase activity. Calcitriol concentration regulates PTH secretion. The 1,25(OH)D acts via the vitamin D receptor (VDR) in cells, which activates transcription and translation of messenger RNA, leading to vitamin D-dependent protein synthesis and its activity depending on target cell function (Navarro-Triviño et al., 2019). Peak serum vitamin D concentrates 24-48 hours after exposure to UV radiation. After that, vitamin D levels decrease exponentially, with serum half-lives ranging from 36 to 78 hours. As a fat-soluble molecule, adipocytes can take vitamin D and store it in subcutaneous fat (Mostafa & Hegazy, 2013).

Interleukin (IL)-17 is a new member of the inflammatory cytokine family produced by Th17 cells (Amatya et al., 2017; Speeckaert et al., 2016). Besides playing a role in inflammatory diseases, IL-17 also plays a role in autoimmune diseases (He et al., 2012). There are six members in the interleukin 17 (IL-17) cytokine family, including IL-17A (commonly called IL-17), IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25) and IL-17F (Jin & Dong, 2013). IL-17 is produced by CD8+(Tc17) cells (McGeachy et al., 2019). Other innate and adaptive immune cells also produce large amounts of IL-17, which include neutrophils, microglia, natural killer cells, mast cells, αβ, and γδ T cells (McGeachy et al., 2019; Speeckaert et al., 2016). IL-17 was first recognized as a cytokine that triggers autoimmune and inflammatory diseases. IL-17 induces proinflammatory mediators and exerts mitogenic effects on tissue progenitor cells, and is capable of reprogramming cellular metabolism (Li et al., 2019). IL-17 increases inflammatory gene expression by inducing gene transcription by stabilizing target mRNA transcripts. The proinflammatory role of IL-17 is demonstrated by its ability to activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) (Amatya et al., 2017). IL-17 is also involved in the pathogenesis of infectious and inflammatory skin diseases, such as Staphylococcal infection, psoriasis, contact hypersensitivity, atopic dermatitis, and acne vulgaris (Agak et al., 2014; Ebrahim et al., 2019).

Deficiency of Serum 25(OH)D Against IL-17 Acne Vulgaris

Vitamin D regulates the immune system and proliferation, as well as the differentiation of keratinocytes and sebocytes (El-Hamd et al., 2019). In addition, vitamin D has antioxidant and anti comedogenic properties. It plays a potential role in acne vulgaris, indicated by vitamin D deficiency that triggers the proliferation and differentiation of keratinocytes and sebocytes, further exacerbated by P.acnes colonization. Vitamin D deficiency can lead to comedogenesis and inflammatory exacerbations that characterize the acne vulgaris nodulocystic phenotype (Yildizgören & Togral, 2014). Th17 is a tissue inflammatory-inducing cell and plays a role in the pathogenesis of many inflammatory and autoimmune diseases, such as psoriasis, rheumatoid arthritis, multiple sclerosis, and Crohn's disease. Inflammation is a significant player in acne vulgaris (Ebrahim et al., 2019). The immune response in acne vulgaris is stimulated by the innate immune system via toll-like receptor 2 (TLR2) and adaptive immunity via activated Th1 lymphocytes. Evidence shows that vitamin D inhibits TLR2 expression in monocytes and reduces proinflammatory cytokine production (Topan et al., 2019).

Acne vulgaris is a primary inflammatory disease, with histological, immunological, and clinical evidence suggesting that inflammation occurs at all stages of acne vulgaris lesion development . The most common biomarker in inflammation is IL-17 which is part of the inflammatory cytokine produced by Th17 cells (Amatya et al., 2017). One study showed that IL-17

levels were significantly higher in acne vulgaris patients with vitamin D deficiency compared to patients with normal vitamin D levels (Singh et al., 2021). Moreover, P. acnes is present in follicles surrounded by an infiltrate containing IL-17 cells (Thiboutot et al., 2014). IL-17 secretion by T cells can be induced by P. acnes, suggesting that acne vulgaris could be a Th-17 cell-mediated disease (Murlistyarini et al., 2018). The adaptive immune response system plays a central role in acne vulgaris inflammation, resulting from the recruitment of activated Th1 lymphocytes to the initial acne vulgaris lesion (Agak et al., 2014). Many studies revealed that serum 25(OH)D levels were significantly lower in acne vulgaris patients (Rasti et al., 2022). Otherwise, inflammation reduces serum 25(OH)D through oxidative stress, which results in oxidative catabolism 25(OH)D. The oxidative environment reduced 25(OH)D by inhibiting the biosynthesis of vitamin D to 25(OH)D in the liver, thereby reducing the concentration of 25(OH)D (Cannell et al., 2014). Low serum 25(OH)D has been demonstrated in the presence of acne vulgaris (Sharaf et al., 2022).

CONCLUSION

Acne vulgaris is closely related to vitamin D deficiency and inflammation. Various sources indicate that inflammation due to IL-17 in acne vulgaris can cause disturbances in the metabolism of vitamin D to 25(OH)D, resulting in a deficit. Otherwise, vitamin D deficiency can cause dermatological disorders that end in acne vulgaris, supported by the proinflammatory cytokine IL-17.

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