An Association between Acne And Vitamin D Level: A Systematic Review

Yusuf Hasamoh and Premjit Juntongjin*

Division of Dermatology, Chulabhorn International College of Medicine, Thammasat University, Pathum Thani, Thailand.
*Corresponding author, E-mail: premjitvp@yahoo.com

Abstract

Acne vulgaris is a self-limited disorder of the pilosebaceous unit that is seen primarily in adolescents. Most cases of acne present with comedones, papules, pustules, and nodules with varying extent and severity. There were some reviews about an association between Vitamin D deficiency and acne vulgaris. However, Vitamin D levels in association with acne have not properly summarized yet. This study aims to determine to the relationship between vitamin D level and acne. *Methodology*: A systematic review was conducted by using the Pubmed, EMBASE, and Cochrane Library, Scopus, CINAHL, and Google Scholar databases up to 31 December 2019 by using the following keywords: (acne OR acne vulgaris) AND (vitamin D OR vitamin D2 OR vitamin D3 OR 25(OH)D OR Cholecalciferol OR Ergocalciferol) The search terms related to design type would be based on the Cochrane Highly Sensitive Search Strategy. *Result:* Total of ten articles with a total of 741 patients with acne and 652 healthy controls (HCs) were included. Overall, this review shows a significantly lower level of 25(OH)D in the acne group in most studies. *Conclusions*: This systematic review demonstrated that circulating 25(OH)D levels are lower in patients with acne than in HCs. Thus, our systematic review suggests that 25(OH)D may play an important role in the pathogenesis of acne.

Keywords: *vitamin D, acne, acne vulgaris, 25(OH) level, Cholecalciferol, systematic review*

1. Introduction

Acne vulgaris is one of the most common disorders of the pilosebaceous unit. It is more common in adolescents. Normally it can be presented with comedones, papules, pustules, and nodules. The course of acne can be lifelong which effects psychological impairment especially in young adult.

Vitamin D was primarily acknowledged for its importance in bone formation, however; increasing evidence points to its interference with the proper function of nearly every tissue in our bodies including brain, heart, muscles, immune system and skin. Thereby its deficiency has been incriminated in a long panel of diseases including cancers, autoimmune diseases, cardiovascular and neurological disorders (Armas et al, 2011; Heaney et al, 2008; Lehmann, et al,. 2010; Reddy et al, 2010; Tsiaras et al, 2011).

The skin is unique in being not only the source of vitamin D for the body but also in being capable of responding to the active metabolite of vitamin D, 1,25(OH)2D. Both 1, 25(OH)2D and its receptor (VDR) play essential roles in the skin, such as; Skin proliferation and differentiation (Hawker et al, 2007), innate immunity in the skin(Wang et al, 2004), adaptive immunity in the skin(Romagnani et al.,2006), antimicrobial effects in the skin (Oda et al, 2009), wound healing (Gombart et al, 2005), and sebaceous gland (Reichrath et al, 2006).

Deficiency of vitamin D might as well causes many skin diseases include; skin cancer(Tang et al.,2012), psoriasis (Gisondi et al.,2012), autoimmune skin disorders such as vitiligo(Silverberg et al, 2010), blistering disorders (El-Komy et al, 2014), as well as atopic dermatitis (Mutgi et al, 2013), acne (Lee et al, 2013), and hair loss (Bolland et al, 2008).

There were some reviews about an association between vitamin D deficiency and acne vulgaris. However, vitamin D levels in association with acne have not properly summarized yet. Therefore, the main objective of this study is to analyze the relationship between vitamin D level and acne.

2. Objectives

To determine the relationship between vitamin D level and acne.

3. Materials and Methods

A systematic review was conducted by using the Pubmed, EMBASE, and Cochrane Library, Scopus, CINAHL, and Google Scholar databases up to 31 December 2019 by using the following keywords: (acne or acne vulgaris) AND (vitamin D OR vitamin D2 OR vitamin D3 OR 25(OH)D OR Cholecalciferol or Ergocalciferol) The search terms related to design type would be based on the Cochrane Highly Sensitive Search Strategy. The presence of Acne and data available for serum vitamin D or 25(OH) D level was included for the systematic review. However, patients with hirsutism, polycystic ovary syndrome (PCOS), and premenstrual acne were excluded for analysis. The study characteristics, patient's details, the mean level of 25(OH)D and standard deviations (SD) were extracted for analysis. Data analysis was performed using the RevMan 5 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, from https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman)

4. Results and Discussion

The initial search yielded 155 articles; of which 15 were selected for full-text review based on the title and abstract; 5 of these were excluded.

The studies Stratified into regions, comprising of, 2 studies from the West, 5 studies from the Middle East, 1 study from North America, 1 Study from Asia, and 1 study from the West and the North. Of which, 2 were RCTs, 3 were cross sectionals, 3 were case controls, 1 was observational retrospective, and 1 was an observational cohort. A total of 741 patients with acne and 652 HCs, were reviewed. The diseases were ranged from acne vulgaris, acne conglobata, nodulocystic acne and acne tarda, see Figure 1.

In the West region, Yildizgoren et al (Yildizgoren et al, 2014) conducted a cross-sectional study of 43 acne patients and 46 HCs to assess vitamin D level in nodulocystic acne patients. The result was vitamin D level significantly lower in acne group compared to HCs (Mean (SD) = 11.2(5.9) ng/ml and 19.7(8.1) ng/ml, p<0.005, respectively). However, Karabay et al (Karabay et al, 2019) evaluated the vitamin D level in 65 acne patients and 41 HCs, classified acne based on the International Consensus Conference on Acne Classification (Pochi et al, 1991). There were no significantly lower vitamin D levels in acne patients compared to HCs (Mean (SD) = 10.22(6.11) ng/ml and 10.37(7.41) ng/ml, p=0.692, respectively), see Table 1 and Table 2.

On the other hand, in the Middle East region, Abd-Elmaged et al (Abd-Elmaged et al, 2018) assessed vitamin D level in 135 acne patients and 150 HCs based on GAGs score(Zohra et al, 2017). The result was vitamin D level significantly lower in acne group (Mean (SD) = 33.3(9.7) ng/ml and 51.7(2.7) ng/ml, p=<0.005, respectively). While, El-Hamd et al (El-Hamd et al, 2019) evaluated the vitamin D level in 90 acne patients and 60 HCs. The level of vitamin D in acne patients was significantly lower compared to HCs (Mean (SD) = 17.34(7.58) ng/ml and 44.83(11.91) ng/ml, p=0.001, respectively). In 2016, El-Ramly et al (El-Ramly et al, 2016) measured vitamin D level in 60 acne patients and 60 HCs based on Lehmann classification (Lehmann et al.,2002). The result was not significantly lower in vitamin D level in acne group (Mean (SD) = 28.7(10.65) ng/ml and 32(18.15) ng/mlp, p=0.226, respectively). Mohamed et al (Mohamed et al, 2019) evaluated the vitamin D level in 100 acne patients and 100 HCs, the level of vitamin D in acne patients were significantly lower compared to HCs(Mean (SD) = 21.48(5.46) ng/ml and 31.48(15.04) ng/ml, p<0.001, respectively). Lastly, Swelam et al (Swelam et al, 2019) conducted a pilot study of vitamin D level in 30 acne patients and 30 HCs, the level of vitamin D in acne patients were significantly lower compared to HCs(Mean (SD) = 0.14(0.031) ng/ml and 2.21(0.567) ng/ml, p=<0.001, respectively), see Table 1 and Table 2.

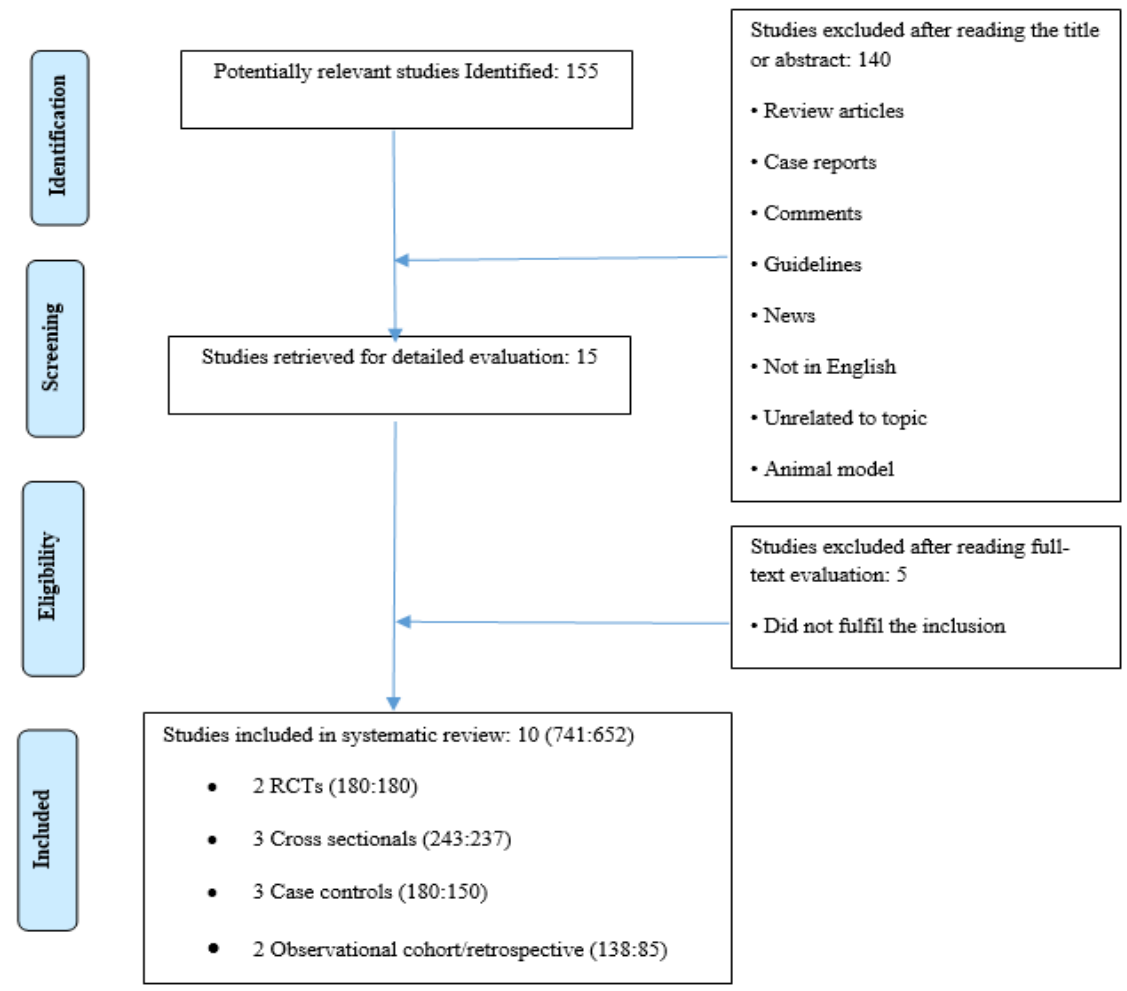

Figure 1 Data selection

In the North America region, Leachman et al (Leachman et al, 1999) measured vitamin D level in 18 nodulocystic acne patients and 14 HCs. The result was not significantly lower of vitamin D level in acne group (Mean (SD) = 16.79(3.67) ng/ml and 18.77(2.42) ng/ml, p<0.45, respectively), see Table 1 and Table 2.

Also, in Asia region, a RCT from Lim et al (Lim et al, 2016) examined vitamin D level in 80 acne patients and 80 HCs. The result was not significantly lower of vitamin D level in acne group (Mean (SD) = 13.1(9.8) ng/ml and 15.2(7.2) ng/ml, p<0.112, respectively), see Table 1 and Table 2**.**

Lastly, in the West & North America region, an observational retrospective from Amon et al (Amon et al, 2018) was conducted in UK, US and Germany to assess vitamin D level in 86 acne vulgaris (AV) patients, 11 acne conglobate(AC) patients and 23 acne tarda (AT) patients in comparison with 71 HCs, There were significantly lower of vitamin D level in these acne groups compared to HCs group (Mean (SD) = 27.4(14.5) ng/ml, 21.0(5.3) ng/ml, 26.8(14.7) ng/ml and 44.1(10.7) ng/ml, p<0.0001(p value in AC and AD were not given), respectively), see Table 1 and Table 2.

The cut point of vitamin D deficiency in all studies was < 20 ng/ml, except in Lim et al (Lim et al, 2016) used < 12 ng/ml as vitamin D deficiency. And the cut point of vitamin D deficiency was not given in El-Hamd et al (El-Hamd et al, 2019), see Table 2.

Acne vulgaris is the most common skin disorder affecting millions of people worldwide. Inflammation resulting from the immune response targeting *Cutibacterium acnes* (*P. acne*) has a significant role in acne pathogenesis.

The prevalence of acne is estimated at 85% (ages 12–25 years) (Lynn et al, 2016) and has no predilection for ethnicity. It can occur at any age and may persist from adolescence to adulthood. The global incidence of acne vulgaris is rising, the causes are unclear. Although several studies supported that genetic and environmental factors might play important roles.

Vitamin D is important in bone formation, brain, heart, muscles, immune system and skin. Therefore, vitamin D deficiency can cause; cancers, autoimmune diseases, cardiovascular and neurological disorders (Armas et al, 2011; Heaney et al, 2008; Lehmann, et al, 2010; Reddy et al, 2010; Tsiaras et al, 2011).

The skin is not only the source of vitamin D production, but also play very important roles in the skin, such as; Skin proliferation and differentiation (Hawker et al, 2007), innate immunity in the skin (Wang et al, 2004), adaptive immunity in the skin (Romagnani et al, 2006), antimicrobial effects in the skin (Oda et al, 2009), wound healing (Gombart et al, 2005), and sebaceous gland (Reichrath et al, 2006).

Vitamin D deficiency might cause many skin diseases such as; skin cancer, psoriasis, ichthyosis, autoimmune skin disorders such as vitiligo, blistering disorders, scleroderma and systemic lupus erythematosus, atopic dermatitis, acne, hair loss, infections and photodermatoses (Wedad et al, 2015).

Table 1 Characteristic of studies

Author, Year	Country Region	Study type	Sample size (n)		Age Mean (SD) (year)	Match
			Acne	HCs		
Yildizgoren, 2014	Turkey West	Cross sectional	43	46	23.13 (5.78)	Age, sex
Karabay, 2019	Turkey West	Cross sectional	65	41	NA	Age, sex
El-Ramly, 2016	Egypt Middle East	Case control	60	60	20 (4.636)	Age, sex
Abd-Elmaged, 2017	Egypt Middle East	Cross sectional	135	150	21.04 (2.8)	Age, sex
Swelam, 2018	Egypt Middle East	Case control	30	30	23.67 (3.294)	Age, sex
El-Hamd, 2019	Egypt Middle East	Case control	90	60	20.73 (3.32)	Age, sex, BMI
Mohamed, 2019	Egypt Middle East	Case control/RCT	100	100	24.67 (6.137)	Age, sex, BMI
Leachman, 1999	USA North America	Observational cohort	18	14	19.7 (2.3)	Age, sex
Lim , 2016	Korea Asia	Case control/RCT	80	80	20.9 (4.1)	Age, sex, BMI
Amon , 2018	Germany, UK, USA West & North America	Observational retrospective	86, 11, 23	71	21.2	Age, sex

Recently, it has been demonstrated that P. acnes is a potent inducer of Th17, and that 1,25OH2D inhibits *Cutibacterium acnes* (*P. acne*) induced Th17 differentiation (Agak et al, 2014; Joshi et al, 2011; Lee et al, 2013). Also, sebocytes were identified as 1,25OH2D responsive target cells, indicating that vitamin D analogs may be effective in the treatment of acne. This systematic review shows that circulating 25(OH)D levels were significantly lower among patients with acne than among HCs. Furthermore, a RCT from Lim et al observed the improvement in inflammatory lesions after supplementation with vitamin D in

39 acne patients with 25(OH)D deficiency with no adverse effect (Lim et al, 2016). Therefore, this review suggests that vitamin D may involve in the pathogenesis of acne and vitamin D supplement may be a potential treatment for acne. A further study with larger sample size is needed to confirm the result of vitamin D supplements in acne patients.

Table 2 Studies on vitamin D level in acne patients in comparison with healthy controls

Author, Year	Country Region	Sample size (n)		Vit D level Mean (SD) (ng/ml)		Vitamin D level cut point	*p*-value
		Acne	HCs	Acne	HCs		
Yildizgoren, 2014	Turkey West	43	46	11.2 (5.9)	19.7 (8.1)	<20 ng/ml	<0.005
Karabay, 2019	Turkey West	65	41	10.22 (6.11)	10.37 (7.41)	<20 ng/ml	0.692
El-Ramly, 2016	Egypt Middle East	60	60	28.7 (10.65)	32 (18.15)	<20 ng/ml	0.226
Abd-Elmaged, 2017	Egypt Middle East	135	150	33.3 (9.7)	51.7 (2.7)	<20 ng/ml	<0.005
Swelam, 2018	Egypt Middle East	30	30	0.14 (0.031)	2.21 (0.567)	<20 ng/ml	<0.001
El-Hamd, 2019	Egypt Middle East	90	60	17.34 (7.58)	44.83 (11.91)	NA	0.001
Mohamed, 2019	Egypt Middle East	100	100	21.48 (5.46)	31.48 (15.04)	<20 ng/ml	<0.001
Leachman, 1999	USA North America	18	14	16.79 (3.67)	18.77 (2.42)	<20 ng/ml	0.45
Lim , 2016	Korea Asia	80	80	13.1 (9.8)	15.2 (7.2)	<12 ng/ml	0.112
Amon , 2018	Germany, UK, USA West & North America	86, 11, 23	71	27.4 (14.5) 21.0 (5.3) 26.8 (14.7)	44.1 (10.7)	<20 ng/ml	<0.0001 NA NA

5. Conclusion

It was demonstrated that circulating 25(OH)D levels are lower in patients with acne. Thus, our systematic review suggests that 25(OH) D may play an important role in the pathogenesis of acne.

6. Acknowledgements

I would like to express my appreciation to everyone who provided generous support and contributed to the effort in my thesis, including my advisor and the committee.

7. References

Armas, L. G., Heaney R. P. (2011). Vitamin D: the iceberg nutrient. *Journal of Renal Nutrition, 21*, 134-139.

Agak, G. W., Qin, M., Nobe, J., Kim, M. H., Krutzik, S. R., Tristan, G. R., et al. (2014). Propionibacterium acnes induces an IL-17 response in acne vulgaris that is regulated by vitamin A and vitamin D. *Journal of Investigative Dermatology*, *134*(2), 366–373.

Abd-Elmaged, W., Hassan, M., Nada, E., Elsadek, B., Abdelrahim, E., Ahmed, N., et al. (2018). Lesional and circulating levels of interleukin-17 and 25-hydroxycholecalciferol in active acne vulgaris: Correlation to disease severity. *Journal of Cosmetic Dermatology, 18*(2), 671-676.

Amon, U., Baier, L., Yaguboglu, R., Ennis, M., Holick, MF., Amon, J. (2018). Serum 25-hydroxyvitamin D levels in patients with skin diseases including psoriasis, infections, and atopic dermatitis. *Dermato-endocrinology*, *10*(1), e1442159. doi: 10.1080/19381980.2018.1442159

Ahmed, Mohamed. A., Salah, Ahmed. E. M., Abdel-Aziz, R. T., Eldeeb, Abdallah. H. H., El-Hanafi, H., Hussein, G. (2019). Informative title:"The Impact of Active Vitamin D Administration on the Clinical outcomes of Acne Vulgaris". *Journal of Dermatological Treatmant*, *3*, 1-6.

Bolland, M. J., Ames, R. W., Grey, A. B., Horne, A. M., Mason, B. H., Gamble, G. D. (2008). Does degree of baldness influence vitamin D status? *Medical Journal of Australia*. *189*, 674–675.

El-Komy, M. H., Samir, N., Shaker, O. G. (2014). Estimation of vitamin D levels in patients with pemphigus vulgaris. *Journal of the European Academy of Dermatology and Venereology*, *28*(7), 859–863.

El-Ramly, A. Z., Fawzi, M. M., Mahmoud, S. B., Abdel-Ghaffar, M. M., Shaker, O. G. (2016). Assessment of serum levels of cathelicidin and vitamin D in acne vulgaris. *Journal of Egypt Women's Dermatologic Society*, *13*(2), 99-105.

El-Hamd, M. A., El, Taieb. M. A., Ibrahim, H. M., Aly, S. S. (2019). Vitamin D levels in acne vulgaris patients treated with oral isotretinoin. *Journal of Cosmetic Dermatology*, *18*(1), 16-20.

Gombart, A. F., Borregaard, N., Koeffler, H. P. (2005). Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is stronglyup-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. *The FASEB Journal*, *19*, 1067–1077.

Gisondi, P., Rossini, M., Di, Cesare. A., Idolazzi. L., Farina, S., Beltrami, G. (2012). Vitamin D status in patients with chronic plaque psoriasis. *British Journal of Dermatology*, *166*, 505–510.

Hawker, N. P., Pennypacker, S. D., Chang, SM., Bikle, D. D. (2007). Regulation of human epidermal keratinocyte differentiation by the vitamin D receptor and its coactivators DRIP205, SRC2, and SRC3. *Journal of Investigative Dermatology*, *127*, 874.

Heaney, R. P. (2008). Vitamin D in health and disease. *Clinical Journal of the American Society of Nephrology*, *3*, 1535–1541.

Joshi, S., Pantalena, L. C., Liu, X. K., Gaffen, S. L., Liu, H., Rohowsky- Kochan, C., et al. (2011). 1,25-Dihydroxyvitamin D(3) ameliorates Th17 autoimmunity via transcriptional modulation of interleukin-17A. *Molecular and Cellular Biology*, *31*, 3653–3669.

Karabay, E., Cerman, A. (2019). Serum Levels of 25-Hyroxyvitamin-D and C-Reactive Protein in Acne Vulgaris Patients. *Turkiye Klinikleri Journal Dermatology*, *29*(1), 1-6.

Leachman, S. A., Insogna, K. L., Katz, L., Ellison, A., Milstone, L. M. (1999). Bone densities in patients receiving isotretinoin for cystic acne. *Archieves of Dermatology*, *135*(8), 961-965.

Lehmann, H. P., Robinson, K. A., Andrews, J. S., Holloway, V., Goodman, S. N. (2002). Acne therapy: a methodologic review. *Journal of American Academy of Dermatology*, *47*(2), 231-240.

Lehmann, B., Meurer, M. (2010). Vitamin D metabolism. *Dermatologic Therapy*, *23*, 2–12.

Lee, W. J., Choi, Y. H., Sohn, M. Y., Lee, S. J., Kim, D. W. (2013). Expression of inflammatory biomarkers from cultured sebocytes was influenced by treatment with vitamin D. *Indian Journal of Dermatology*, *58*, 327.

Lim, S-K., Ha, J-M., Lee, Y-H., Lee, Y., Seo, Y-J., Kim, C-D., et al. (2016). Comparison of vitamin D levels in patients with and without acne: a case-control study combined with a randomized controlled trial. *PloS one*, *11*(8), e0161162. doi: 10.1371/journal.pone.0161162

Lynn, D. D., Umari, T., Dunnick, CA., Dellavalle, R. P. (2016). The epidemiology of acne vulgaris in late adolescence. *Adolescent Health, Medicine and Therapeutics, 7*, 13-25.

Mutgi, K., Koo, J. (2013). Update on the role of systemic vitamin D in atopic dermatitis. *Pediatric Dermatology*, *0*, 303–307.

Oda, Y., Uchida, Y., Moradian, S., Crumrine, D., Elias, P. M., Bikle, D. D. (2009). Vitamin D receptor and coactivators SRC 2 and 3 regulate epidermis-specific sphingolipid production and permeability barrier formation. *Journal of Investigative Dermatology*, *129*, 1367–1378.

Pochi, P. E., Shalita, A. R., Strauss, J. S., Webster, S. B., Cunliffe, W. J., Katz, H. I., et al. (1991). Report of the Consensus Conference on Acne Classification. *Journal of American Academy of Dermatology*, *24*(3), 495-500.

Reichrath, J., Schuler, Ch., Seifert, M., Zouboulis, C. H., Tilgen, W. (2006). The vitamin D endocrine system of human sebocytes. *Experimental Dermatology*, *15,* 643.

Romagnani, S. (2006). Regulation of the T cell response. *Clinical & Experimental Allergy. 36*, 1357–1366.

Reddy, K. K., Gilchrest, B. A. (2010). What is all this commotion about vitamin D? *Journal of Investigative Dermatology*, *130*, 321–326.

Silverberg, J., Silverberg, A. (2010). A pilot study assessing the role of 25 hydroxyvitamin D levels in patients with vitiligo vulgaris. *Journal of the American Academy of Dermatology*, *626*, 938–941.

Swelam, M. M., El-Barbary, R. A., Saudi, W. M., Fathi, M. S., Soliman, D. A., Abd-Elrehem, H. H. (2019). Associations among two vitamin D receptor (VDR) gene polymorphisms (ApaI and TaqI) in acne vulgaris: A pilot susceptibility study. *Journal of Cosmetic Dermatology*, *18*(4), 1113-1120.

Tsiaras, W. G., Weinstock, M. A. (2011). Factors influencing vitamin D status. *Acta Dermato-Venereologica*, *91*, 115–124.

Tang, J. Y., Fu, T., Lau, C., Oh, D. H., Bikle, D. D., Asgari, M. M. (2012). Vitamin D in cutaneous carcinogenesis: Part II. *Journal of the American Academy of Dermatology*, *67*, 817.e1–11; quiz 827–828. doi: 10.1016/j.jaad.2012.07.022

Wang, T. T., Nestel, F. P., Bourdeau, V., Nagai, Y., Wang, Q., Liao, J., et al. (2004). Cutting edge: 1,25dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *Journal of Immunology*, *173*, 2909–2912.

Yildizgoren, M. T., Togral, A. K. (2015). Preliminary evidence for vitamin D deficiency in nodulocystic acne. *Dermato-endocrinology*, *6*(1), e983687. doi: 10.4161/derm.29799

Zohra, F., Sultana, T., Islam, S., Nasreen, T. (2017). Evaluation of severity in patients of acne vulgaris by global acne grading system in Bangladesh. *Clinical Pathology*, *1*(1), 1-3.