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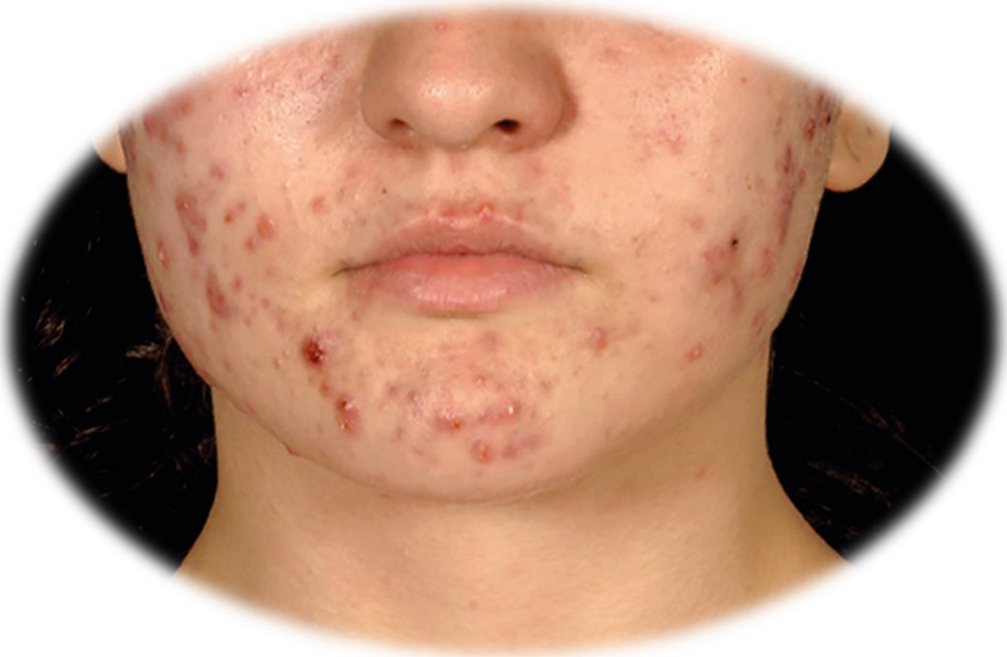
Collage of medicine

The role of vitamine D level in acne vulgaris patient



Supervised by

د. انتصار احمد حسن

Prepared By

يوسف غالب ادريس

Introduction

Acne vulgaris (AV) is a chronic inflammatory disease of the hair stracture units. It is one of the most mutual skin illnesses happening in 80-100% of people aged 11-30 years old

There are many recognized pathological issues that control the occurrence of acne vulgaris. Amongst of these issues are the illness of hair follicle keratosis, colonization by Propionibacterium acnes (P. acnes), overproduction and fluctuations in a composition of sebum. All these issues lead to the creation of microcomedones – a arrangement of collected un-exfoliated corneocytes blocking the follicle ostium, next leading to bacterial colonization and inflammation , Furthermore, new studies emphasized the part of inflammation as one of the earliest and the most critical pathophysiological phenomena in acne, In subclinical lesions, lymphocytes and macrophages begin to gather and create many proinflammatory cytokines – interleukins: IL-1, IL-6, IL-8, IL-10, IL-12 and tumor necrosis factor – TNF-α. These molecules, furthermore to start of inflammation, arouse keratinocytes proliferation and rebuilding of a surrounding connective tissue

Vitamin D is a fat-soluble vitamin, its chief basis is the de novo synthesis in the skin by UV B rays of sunshine. The early vitamin D compound is not active and is hydroxylated in the liver to produce 25-hydroxy-vitamin D which is also an inactive compound, but it is the most reliable measurement of vitamin D levels. It is rehabilitated in the kidney to the active form 1, 25-dihydroxyvitamin D by 1-αhydroxylase (CYP27B1), an enzyme that is enthused by the parathyroid hormone. 1, 25-dihydroxyvitamin D may be further absorbed to the inactive 1, 24, 25 vitamin Accepted ManuscriptD by 24-hydroxylase (CYP24). 1, 25-dihydroxyvitamin D is a regulator of bone and calcium metabolism. It uses immunomodulation by the nuclear vitamin D receptor (VDR) articulated in antigen-presenting cells (APC) and activated T/B cells

Patients and methods

This Study was prospective, randomized, controlled and open label trial. It was directed on 100 patients with AV diagnosis employed from Outpatient Dermatology Clinic of National Hepatology and Tropical Medicine Research Institute (NHTMRI), Cairo, Egypt, after 6 months from November 2016 to April 2017. And 100 age- and sex-matched healthy controls also employed to comparison serum 25- hydroxy- vitamin D as an index of vitamin D content between patients with acne on one part and healthy people on the other part.

The sample size was designed based on a self-assurance interval of 95%, an alpha worth of 5%, and a worldwide occurrence of vitamin D deficiency in about 2%. This caused in a obligatory sample size of 100 cases and 100 controls. Then the 100 AV patients were just randomized into 2 groups:

Group 1 (Study group): 50 patients received 0.25ug alfacalcidol daily for 3 months.
Group 2 (Placebo group): 50 patients received an oral placebo taken with the exact same routine, for a 3 months' duration

The following occurrence standards remained useful for the cases: patients aged ≥ 18 years with AV, no oral or topical vitamin D or its byproducts occupied in the prior three months, no anti-inflammatory administration for acne. The standards for healthy control group were as follows: patients without AV; no previously diagnosed vitamin D deficiency, regardless of whether it was treated. The following prohibiting standards were practical to both cases and controls: a diagnosis of vitamin D deficiency; not agreeable to participate; or suffering from multiple sclerosis, , sarcoidosis, , rheumatoid arthritis, renal failure, any type of liver disease, diabetes mellitus , celiac disease, systemic lupus erythema or inflammatory bowel disease.

Alfacalcidol (One Alpha®) soft gelatin capsule was produced by LEO Company for pharmaceutical and chemical industries, Denmark. The placebo was produced and provided by Memphis Company for pharmaceutical and chemical industries, Cairo, Egypt

The next data was collected: Demographic data, counting:-

- Age
- Sex
- smoking history
- family history
- and signs of polycystic ovary syndrome (PCOS)
- daily sun exposure rate, and sunscreen use were drawn before to enrollment.

History of AV

- age of onset of acne
- duration
- history of previous therapy was documented.

Body mass index (BMI) was considered. Dermatological inspection to assess acne type, sites involved, counts of non –inflammatory lesions (comedones) and inflammatory lesions (papules, pustules, and nodules), and severity of acne score was achieved at baseline and upon following visits every 2 weeks till the end of the study.

The severity of acne was measured according to the global acne grading system (GAGS) ,where each type of lesion is given a value: no lesion=0, comedones=1, papules=2, pustules=3, and nodules=4. Acne-prone parts are separated into 6 areas each having a score (forehead=2, each cheek= 2, nose=1, chin=1, chest and back=3). The score for every area (local score) is considered using the method: local score= Area score x Grade (0-4). The universal score is the sum of local scores. A score of 1-18 is considered mild; 19-30, moderate; 31-38, severe; and greater than 39, very severe. Both groups were followed up for any opposing or side effects by the principal investigator every 2 weeks till the end of the study.

Laboratory measurements

A 3 ml blood example was reserved from all acne patients (at starting point and at the end of the study) and the healthy parts for biochemical valuation of serum 25(OH) D, Accepted Manuscript Interleukin 6 (IL6), Tumor necrosis factor alpha (TNFα). Sera then were centrifuged at 3000 rpm, for about 10 minutes at 4°c, and then saved frozen at -80 C, at the Central Labs of NHTMRI, Cairo, Egypt.

Examination was achieved by enzyme linked immunosorbent assay technique (ELISA) and (Quantikine, USA). Levels of 25(OH)D < 20 ng/ml were vitamin D deficient, 21-29 ng/ml were inadequate, and 30ng/ml or more were adequate or normal.

Ethical consideration

The study was directed in agreement with Good Clinical Practice guidelines, and the ethical principals in 1964 Helsinki Declaration. This study also done with CONSORT guidelines and ICMJE recommendations. The procedure was studied and accepted by NHTMRI Institution Review Board (IRB no 2387). Preceding to contribution all patients and healthy controls were informed about the study protocol and asked to sign a written informed consent

Statistical analysis

Statistical analysis was achieved using the SPSS statistical program. Data were articulated as the middle and interquartile range for quantitative non- parametric measures, as the mean and standard deviation (SD) for parametric data, and as numbers and percentage for categorical data. The Balancing Student t test, , Mann–Whitney test, Wilcoxon test, Unpaired Student t test, and Chisquare test were used for data analysis. The association between the acne severity (GAGS score) and the other limits were measured with Spearman's Correlation test. The probability of error of 0.05 was considered to be significant, and 0.001 to be highly significant.

Results

At baseline, there was no significant difference between acne patient group and healthy control in terms of demographics and clinical characteristics. However, there was a important difference ($p< 0.001$) in the mean serum 25(OH) D level which is lower in the acne group. The prevalence of 25(OH) D deficiency was significantly higher in patients with acne compared to healthy controls (34% vs. 12%; $P = 0.0019$), Moreover, the acne group showed significantly higher levels in the median serum TNFα ($P= 0.03$) as compared to the healthy group, but there was no significant difference in median serum IL6.

Using the GAGS score to assess the acne severity, 10 patients showed mild cases, 53 were moderate, 32 were severe and 5 were very severe.

We also determined whether vitamin D deficiency was influenced by any factor. No significant correlation was shown between deficient 25(OD) D levels and age, sex, disease duration, BMI, family history, smoking. The only factor affecting 25 (OH) D deficiency was disease severity. In total, 4 of the 5 patients (80%) in the very severe group were 25(OH) D-deficient, 18 out of 32 in the severe group were deficient whereas only 1 of the 10 (10%) patients in the mild group were deficient. In addition, the mean 25(OH) D concentration was inversely correlated with the severity of acne (figure 1)

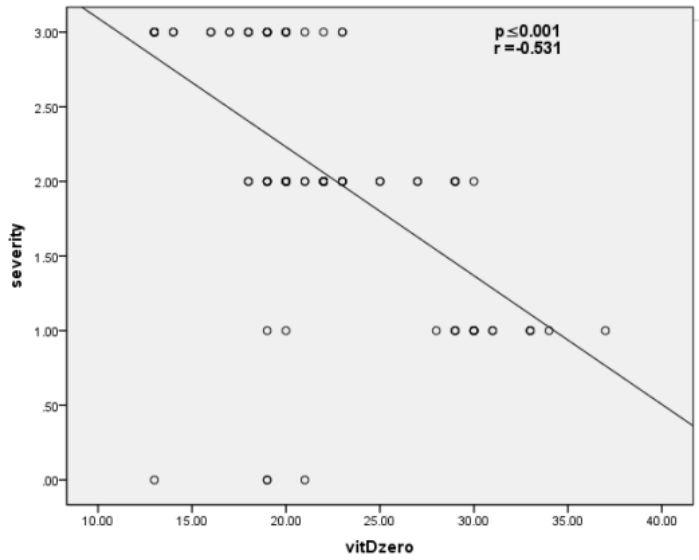


Fig 1 Correlation between acne severity and serum 25(OD) D level

Moreover, at starting point there was no important difference between the study and placebo group in demographics, clinical characteristics and laboratory limits (mean serum 25(OH) D level, IL6, TNFα), also there were no important differences ($p>0.05$) in the mean serum 25(OH) D level amongst patients in both groups with mild, moderate, severe and very severe acne

Administration of 0.25ug alfacalcidol daily for 3 months caused in a momentous increase in 25(OH)D levels ($P< 0.05$) in the study group as comparison to placebo group, furthermore, median serum level of IL6 and TNFα meaningfully decreased ($p< 0.05$) in the study group in contrast to placebo group and as likened to their starting point results.

Furthermore, study group presented improvement ($p< 0.05$) in the acne severity (GAGS scale) at the end of the study as likened their baseline results (figure 2)

None of the patients stated cessation of the intervention, and there were no side effects

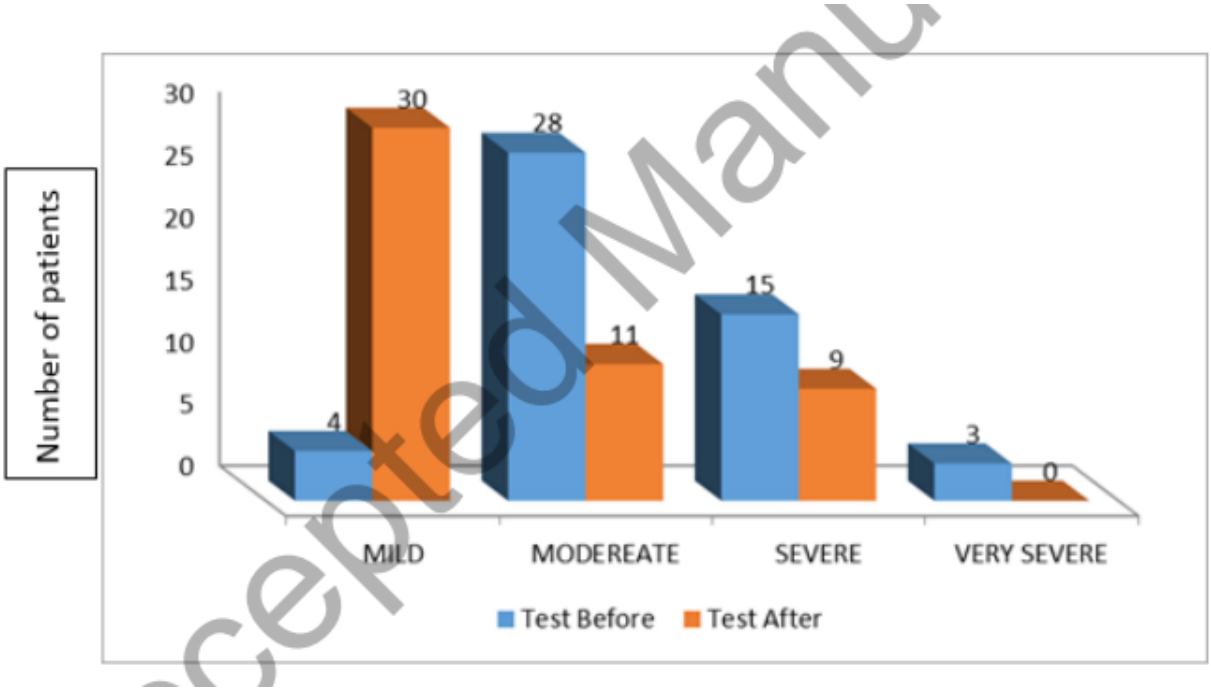


Fig 2 GAGS scale in the Study group before and after Vitamin D supplementation

Discussion

Vitamin D was mostly recognized for its boundless role in bone homeostasis by modifiable Parathyroid hormone (PTH), calcium and phosphorous metabolism result to preserve the integrity of the skeletal system. But over the previous periods there was a great care given to the developing role of vitamin D in many medical disorders. This was because of the detection of vitamin D receptors (VDRs) in most cells of the body and the attendance of enzymes that create the active form of vitamin D in other than renal tissue, particularly in the skin

Before only few lessons have examined the connotation between vitamin D and AV. The first study was directed by Toossi et al. in Iran and included 35 patients with AV and 40 healthy parts, and showed no change in the medians levels of vitamin D between cases of AV and controls

The second study was in Turkey, where patients with nodulocystic AV (n = 43) had meaningfully lower mean levels of vitamin D than the subjects in the control group (n = 46).The third study was in South Korea; and stated significantly higher

occurrence of vitamin D deficiency (<12 ng/mL) in AV patients (n = 80) in comparison to healthy controls (n = 80) (48.8% vs. 22.5%; p = 0.019)

The last study was directed by Al-Taiar et al in kuawit he saw that the serum 25- OH-VitD levels were not meaningfully (p = 0.07) different between those with (median 30.0; IQR 20.9–44.1 nmol/L) and without (median 32.5; IQR 22.5-47.7 nmol/L) AV identified by clinical exam

In the current study, we found that the mean serum 25(OH) D level is significantly lower (p= 0.001) in the acne group as compared to the healthy control.

Moreover, the present study showed that there was opposite correlation ($p \leq 0.001$) between the mean 25(OH) D concentration and the cruelty of acne disease, this finding is in agreement with Lim et al. who stated a link between the degree of vitamin D deficiency and the degree of acne inflammation ($r = -0.512$; $P < 0.001$). This can be qualified to patients with severe acne may be exposed to more psychological stress, and may have a habit of spending extended periods outdoors, recommending a possible explanation for low vitamin D levels in patients with severe acne.

Likewise, earlier results stated that disease severity of atopic dermatitis, Psoriasis, and vitiligo was related with lower levels of vitamin D. Furthermore this study has produced positive outcomes with the management of oral active vitamin D (0.25ug daily) for 3 months, where the mean 25(OH) D concentration in the study group meaningfully augmented from 20.38 ± 3.26 to 38.24 ± 2.16. Also the study group presented very important increase in the mean 25(OH) D concentration as comparison to the placebo group at the end of the study. Similarly, in the present study the study group presented meaningfully ($p< 0.005$) clinical enhancement in the severity of acne using the GAGS gage as comparison to their starting point results where no patient

Lim et al. stated that not active Vitamin D (1000IU/day) supplementation for 2 months lead to in a statistically important increase in 25(OH) D levels ($P < 0.001$) and produced a clinical enhancement compared to placebo, the inflammatory lesions exhibited a statistically important enhancement in the vitamin D group compared with the control group ($P < 0.05$). Inflammatory lesions in the vitamin D group reduced by 34.6% after 8 weeks of treatment, while those in the control group reduced by 5.8%

An earlier study saw no effect of vitamin D supplementation on acne lesions, The inconsistency between recent results and the previous study maybe due to the fact that patients with acne had polycystic ovary syndrome in the previous trial. There were earlier studies that backing the theory that vitamin D has an immune regulatory purpose in sebocytes, through decrease of expression of inflammatory biomarkers, such as interleukin (IL)-6, IL-8, and matrix metalloproteinase 9, is reduced in cultured sebocytes . also there was also printed suggestion that vitamin D inhibits P. acnes-induced Th17 differentiation with reduced expression of IL-17 and TNFα that is increased in acne patients

As far we know this is the first study to assess the effect of vitamin D supplementation on inflammatory markers in acne patients. The test group stated meaningfully lower median serum IL6 and TNFα (1±0.21, 2.3±0.25 respectively) at the end of the study as compared to the placebo group (1.9±0.18, 4.2±0.1 respectively). This supported the possible anti-inflammatory effects of vitamin D in acne patients.

Extra large scale, multicenter, randomized, double blinded for longer duration are warranted for further evaluation of the potential role of vitamin D in acne vulgaris.

Conclusion

Vitamin D deficiency was more common in acne patient and was in reverse correlated with disease severity; hereafter vitamin D deficiency might have a possible role in the pathogenesis of acne

Furthermore, this randomized, controlled study established that administration of active vitamin D was effective in enhancement of the clinical status of acne patients in term of decrease the GAGS scale and markers of inflammation

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References

1. Tan J.K.; Bhate K. A global perspective on the epidemiology of acne. Br. J. Dermatol. 2015; 172 (1): 3–12.

2. Metiko B, Brooks K, Burkhart CG et al. Is the current model for acne pathogenesis backwards?. J Am Acad Dermatol. 2015; 72(6): 167.

3. Asai,Y.; Baibergenova A.; Dutil M. et al. Management of acne. Canadian clinical practice guideline. Can. Med. Assoc. J. 2016; 188 (1): 118–126.

4. Agak GW.; Qin M.; Nobe J. et al. Propionibacterium acnes Induces an IL-17 Response in Acne Vulgaris that Is Regulated by Vitamin A and Vitamin D. J. Investig. Dermatol. 2014; 134 (2): 366–373.

5. Bhat YJ, Latief I, Hassan I. Update on etiopathogenesis and treatment of Acne. Indian J Dermatol Venereol Leprol. 2017; 83(3): 298-306.

6. Lee WJ.; Choi YH.; Sohn MY. et al. Expression of Inflammatory Biomarkers from Cultured Sebocytes was Influenced by Treatment with Vitamin D. Indian J. Dermatol. 2013; 58: 327.

7. Sharma R.; Abrol S.; Badgal A. et al. Vitamin D and its role in dermatology: A review of literature. J. Evol. Med. Dent. Sci. 2015; 4: 1689–1693

8. Al-Taiar A.; Rahman A.; Al-Sabah. E et al. Vitamin D Status among Adolescents in Kuwait: A Cross-sectional Study. BMJ Open. 2018; 8: e021401.

9. Yuan KMC.; Lu Y. Immunological Role of Vitamin D in Skin Diseases and Carcinoma. Oncomedicine. 2017; 2: 52–60.

10. Lang PO.; Aspinall R. Can we translate vitamin D immunomodulating effect on innate and adaptive immunity to vaccine response?. Nutrients. 2015; 7: 2044–2060.

11. Toossi P.; Azizian Z.; Yavari H. et al. Serum 25-hydroxy vitamin D levels in patients with acne vulgaris and its association with disease severity. Clin. Cases Miner. Bone Metab. 2015; 12: 238–242.

12. Lim SK.; Ha JM.; Lee YH. et al. Comparison of Vitamin D Levels in Patients with and without Acne: A Case-Control Study Combined with a Randomized Controlled Trial. PLoS ONE. 2016; 11: e0161162.

13. Yildizgören MT, Togral AK. Preliminary evidence for vitamin D deficiency in nodulocystic acne. Dermatoendocrinol. 2015; 6(1): e983687.

14. Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. Int J Dermatol.1997; 36:416–8.

15. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. Lancet. 2012; 379(9813): 361-372.

16. Stewart TJ.; Bazergy C. Hormonal and dietary factors in acne vulgaris versus controls. Derm. Endocrinol. 2018; 10: e1442160.

17. Al-Taiar A.; AlKhabbaz M.; Rahman A. et al. Plasma 25-Hydroxy Vitamin D is not Associated with Acne Vulgaris. Nutrients. 2018; 10(10):1525.

18. Di Filippo P.; Scaparrotta A.; Rapino D. et al. Vitamin D supplementation modulates the immune system and improves atopic dermatitis in children. Int Arch Allergy Immunol.2015; 166:91–6.

19. Cheng HM.; Kim S.; Park GH. Et al. Low vitamin D levels are associated with atopic dermatitis, but not allergic rhinitis, asthma, or IgE sensitization, in the adult Korean population. J Allergy ClinImmunol.2014; 133:1048–55.