The Open Dermatology Journal

Content list available at: https://opendermatologyjournal.com

RESEARCH ARTICLE

Serum Vitamin D Levels at Different Stages of Acne Vulgaris Patients Treated with Isotretinoin: A Prospective Study

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Abstract:

Background:

Acne vulgaris is a common chronic inflammatory skin disorder of pilosebaceous units. Isotretinoin (13-cis retinoic acid) is the most effective multifunctional treatment for moderate-to-severe and nodulocystic acne. Vitamin D plays a role in the immune system, and its deficiency might contribute to the pathogenesis of acne.

Objective:

To investigate whether isotretinoin improves serum 25-hydroxyvitamin D levels in acne vulgaris patients.

Methods:

This prospective cohort study included 68 patients with acne vulgaris. Lipid profiles, liver function tests, and serum 25-hydroxyvitamin D [25 (OH) D] levels were measured at baseline and three months after starting isotretinoin treatment.

Results:

There was a significant increase in serum vitamin D levels three months after starting isotretinoin treatment in mild acne patients (P=0.0003).

Conclusion:

Vitamin D levels are altered in acne vulgaris. Isotretinoin therapy is associated with an increase in vitamin D levels, which was statistically significant in mild acne patients. Considering the role of vitamin D in acne, effective treatment with isotretinoin might highlight vitamin D as a possible target for acne therapy or as a biomarker for disease activity and remission.

Keywords: Acne vulgaris, Vitamin D, Vitamin D deficiency, Isotretinoin, Acne therapy, Isotretinoin therapy.

Article History	Received: December 16, 2020	Revised: February 11, 2021	Accepted: February 15, 2021

1. INTRODUCTION

Acne Vulgaris (AV) is a common primary inflammatory skin disorder of pilosebaceous units. Clinically, AV is characterized by open-and-closed comedones, papules, pustules, and nodules [1, 2]. AV affects both genders equally, and it usually starts in adolescence between 14 and 17 years of age in females and 16 and 19 years of age in males; however, its emergence may be delayed until 25 to 30 years of age. The time at which AV fades varies [3]. The pathogenesis of acne involves four primary factors: increased sebum production, increased follicular hyperkeratinization, colonization with cutibacterium acnes (formerly known as propionibacterium acnes), and inflammatory process [4].

Several treatment modalities have been used to treat AV. Topical therapies include antibiotics, azelaic acid, benzoyl peroxide, and retinoids. Systemic treatments include antibiotics, hormonal therapy, and isotretinoin [5].

Isotretinoin (13-cis-retinoic acid) is a systemic non-aromatic retinoid that is highly effective in the treatment of nodulocystic and moderate-to-severe acne, and it affects all four underlying factors of AV pathogenesis. Therefore,

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isotretinoin is regarded as the most effective medication currently available for acne, and it is also an effective treatment for many other dermatological conditions [6]. Isotretinoin is indicated mainly for severe cases of acne but can be used in moderate cases to minimize scarring. The recommended dose for isotretinoin treatment is 0.5–1 mg/kg daily, with a cumulative dose between 120 and 150 mg/kg [7, 8]. Isotretinoin has many side effects, the most important of which are its hepatotoxicity, psychological effects, social effects, teratogenicity, and xerosis [9].

Vitamin D is a fat-soluble steroid hormone derived from dietary intake and synthesized through the skin via exposure to sunlight. Vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) are manufactured through solar ultraviolet B radiation (UVB). Absorption of UVB radiation in the skin leads to the conversion of provitamin D to pre-vitamin D, followed by the production of vitamin D3 [10].

Vitamin D has both anticomedogenic and antioxidant properties; it demonstrates a regulatory effect on the immune system, proliferation, differentiation of sebocytes and keratinocytes. Therefore, its deficiency may contribute to the pathogenesis of acne [11, 12].

In this study, the effect of isotretinoin in the improvement of serum vitamin D levels in AV patients is explored. It is known that this is the first study in the Kingdom of Saudi Arabia to address this issue.

2. MATERIALS AND METHODS

2.1. Subjects

This prospective cohort study was conducted in the outpatient dermatology clinic at Qassim University, Saudi Arabia, between October 2016 and March 2017. The Medical Research Ethics Committee in the College of Medicine at Qassim University approved the study with the approval number 15/18/13. The study was conducted in the cold weather seasons to minimize the effect of seasonal variation on vitamin D levels. Of the enrolled AV patients (n=68), 30.88%, 38.24%, and 30.88% had mild, moderate, and severe acne, respectively.

Before initiating the study, a written informed consent was received from the participants after explaining the aim, value, and necessary steps in a simplified manner and the potential side effects of isotretinoin drugs.

Acne was graded and classified as mild, moderate, or severe. Mild acne was marked by <20 comedones, <15 inflammatory lesions, or a total lesion count <30. Moderate acne was characterized by 20–100 comedones, 15–50 inflammatory lesions, or a total lesion count of 30–125. Severe acne required >5 pseudocysts, a total comedones count >100, a total inflammatory count >50, or a total lesion count >125 [13].

All 68 subjects completed a data collection form to provide their demographics, family history of acne, sun exposure >2 hours/day, age of onset, duration of disease, site of acne (face, chest, or back), past medical history, and other relevant variables.

Inclusion Criteria: Patients from 15 to 35 years of age with AV, irrespective of sex, and who did not opt for acne treatments for at least the previous four weeks and patients who were unresponsive to conventional topical therapies or systemic antibiotics (other than systemic isotretinoin) were included in this study.

Exclusion Criteria: Pregnant and breastfeeding, patients taking vitamin D supplements for any reason, and patients who were on a concurrent treatment for acne were excluded.

2.2. Treatment

All patients were treated with isotretinoin (0.5–1 mg/kg/d) adjusted to 30–40 mg/day for three months. Serum beta HCG tests were performed for all female patients before starting the treatment.

2.3. Biochemical and Laboratory Analysis

2.3.1. Serum Vitamin D Concentration Measurements

Patients had their baseline serum 25-hydroxyvitamin D (25(OH)D) concentrations measured. Blood samples were collected from veins and analyzed within 24 h of sampling using the Roche Cobas e411 (Roche Diagnostics System, Switzerland). Based on the guidelines of the Food and Nutrition Board of the Institute of Medicine, 25(OH)D serum levels were categorized into adequate (>20 ng/ml), inadequate (12–20 ng/ml), or deficient (<12 ng/ml) categories [14].

2.3.2. Lipid Profile Measurements

Estimation of lipid profile: Plasma levels for triglycerides (TG) and Total Cholesterol (TC) were measured by standardized enzymatic procedures, using kits supplied by Roche Diagnostics (Mannheim, Germany) on the Olympus AU 400 automated clinical chemistry analyzer.

2.3.3. Liver Function Test measurements.

Serum AST was estimated using the Aspartate Aminotransferase (AST) Activity Assay Kit Catalog Number MAK055 (Sigma-Aldrich, USA). Serum ALT was evaluated using the Alanine Aminotransferase Activity Assay Kit Catalog Number MAK052 (Sigma-Aldrich, USA).

2.3.4. Statistical Analysis

Recorded data were analyzed using the Statistical Package for Social Sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). An analysis of variance (ANOVA) test was performed between more than two means t-tests and chi-squares to analyze the mean and percentage differences. A significance level of $P \leq 0.001$ was considered highly significant, and $P \geq 0.05$ was deemed to be insignificant. Furthermore, the quantitative data were expressed as a mean ± Standard Deviation (SD), while the qualitative data were expressed as frequency and percentage.

3. RESULTS

The study included 68 patients with AV (41 females and 27 males). Table **1** presents the participants' baseline demographics and clinical characteristics [15].

Table 1. Baseline demographic and clinical characteristics of acne vulgaris patients [15].

Characteristic	Patients with Acne Vulgaris N (68)
Gender **Male N (%)** **Female N (%)**	 27 (39.7%) 41 (60.3%)
Age, year N **Male N (mean±SD)** **Female N (mean±SD)**	 (20.7±3.8) (21.3±3.6)
Sun–exposure >2 hours per day N (%)	14 (20.5%)
Positive family history of acne N (%)	29 (42.65%)
Age at onset of disease, years	16.55±4.99
Duration of the disease, years (mean±SD)	4.8±0.8
Site of acne **Face N (%)** **Chest N (%)** **Back N (%)**	 68 (100%) 24 (35.3%) 40 (54.41)
The severity of the disease **Mild N (%)** **Moderate N (%)** **Severe N (%)**	 21 (30.88%) 26 (38.24%) 21 (30.88%)

N=Number, SD=Stander deviation, % =percentage.

The study reveals an overall non-significant increase in vitamin D levels, lipid profiles, and liver enzymes in all patients regardless of disease severity three months after starting isotretinoin treatment (Table **2**).

Table 2. Comparison between means ± SD of serum concentration of vitamin D [25 (OH) D], lipid profiles, and liver enzymes before and 3 months after isotretinoin treatment in patients with acne vulgaris.

Parameters	Before treatment	After 3 months of treatment	T-Test P-value
Serum vitamin D level (ng/ml) (mean±SD)	28.8±7.9	33.4±6.8	0.327
Serum AST (u/l) (mean±SD)	29.69±8.4	36.46±11	0.305
Serum ALT (u/l) (mean±SD)	26.6±7	32.5±9.09	0.132
Triglyceride (mg/dl) (mean±SD)	102.23±12.3	106.46±16.6	0.838
Cholesterol (mg/dl) (mean±SD)	170.5±13.9	236.8±18.4	0.412

SD=Standard deviation, AST=Aspartate Aminotransferase, and ALT=Alanine Aminotransferase.

At baseline, the vitamin D level was 26±9.4ng/ml for patients in the mild acne group and 31.4±6.9ng/ml for patients in the moderate acne group, while in patients with severe acne, it was 28.4±6.7 ng/ml. There were no significant variations in serum vitamin D levels between the mild, moderate, and severe acne groups (P=0.067), as levels were maintained post-treatment with isotretinoin (P=0.773). Three months after starting isotretinoin treatment, an increase in the mean value of serum vitamin D levels in mild, moderate, and severe acne was reported (35.6±6.5, 32.14±7.1, and 32.9±4.9, respectively). However, this was only significant in the mild acne group (P=0.003; Tables **3** and **4**).

Table 3. The relationship between acne vulgaris severity patients and serum concentration of vitamin D [25 (OH) D] before and 3 months after isotretinoin treatment.

Parameters	Mild Acne Vulgaris Patients (N=21)	Moderate Acne Vulgaris Patients (N=26)	Severe Acne Vulgaris Patients (N=21)	ANOVA - Test P-value
Serum vitamin D level (ng/ml) before isotretinoin treatment. (mean±SD)	26±9.4	31.4±6.9	28.4±6.7	0.067
Serum vitamin D level (ng/ml) 3 months after isotretinoin treatment. (mean±SD)	35.6±6.5	32.14±7.1	32.9±4.9	0.773

N=Number and SD=Standard deviation.

Table 4. Comparison between means ± SD of serum concentration of vitamin D [25 (OH) D] before and 3 months after isotretinoin treatment in patients with mild, moderate, and severe acne vulgaris.

Parameters	Serum vitamin D level (ng/ml) (mean±SD) Before Treatment	Serum vitamin D level (ng/ml) (mean±SD) After Treatment	T-test P-value
Mild Acne vulgaris (N=21)	26±9.4	35.6±6.5	0.003**
Moderate Acne vulgaris (N=26)	31.4±6.9	32.14±7.1	0.990
Severe Acne vulgaris (N=21)	28.4±6.7	32.9±4.9	0.081

N = Number, SD = Standard deviation.

No significant change in lipid profile mean values were detected in all subgroups mild, moderate, and severe acne throughout the study while in liver enzymes, only serum AST were significant in severe acne vulgaris after treatment with P-value 0.011 (Table **5**).

4. DISCUSSION

The role of vitamin D in acne pathogenesis has been reported in different studies. Vitamin D regulates the immune system and the growth of various cell types, including proliferation, differentiation of sebocytes, and keratinocytes. Vitamin D demonstrates both anticomedogenic and antioxidant effects, and it exerts its influence by binding to intranuclear vitamin D receptor (VDR), which is part of the trans-acting transcriptional regulatory factors superfamily that also includes a steroid receptor, thyroid hormone receptors, both Retinoic Acid Receptors (RAR), and Retinoid-X Receptor (RXR) [12, 16].

Table 5. Comparison between means ± SD of lipid profiles, and liver enzymes at baseline and 3 months after isotretinoin treatment in patients with mild, moderate, and severe acne vulgaris.

Parameters	At baseline	3 Months	T-test P-value
	Mild Acne (N=21)		
Serum AST (u/l) (mean±SD)	24±1.14	24±2.3	0.353
Serum ALT (u/l) (mean±SD)	29±5.7	28±2.3	0.987
Triglyceride (mg/dl) (mean±SD)	60±2.8	66.5±1.5	0.759
Cholesterol (mg/dl) (mean±SD)	132±12.1	143±13.5	0.432
	Moderate Acne (N=26)		
Serum AST (u/l) (mean±SD)	23.2±4.8	25±4.6	0.484
Serum ALT (u/l) (mean±SD)	22±7.6	29±6.2	0.247
Triglyceride (mg/dl) (mean±SD)	111±12.8	140±11.6	0.392
Cholesterol (mg/dl) (mean±SD)	165±13.2	171±12.7	0.368
-	**Severe Acne (N=21)**		
Serum AST (u/l) (mean±SD)	28.5±8.3	41±2.3	0.011**
Serum ALT (u/l) (mean±SD)	30±2.3	41.5±5.6	0.222
Triglyceride (mg/dl) (mean±SD)	132±18.5	104±15.3	0.479
Cholesterol (mg/dl) (mean±SD)	180±9.7	197±1.3	0.463

N = Number, SD = Standard deviation, AST =Aspartate Aminotransferase and ALT =Alanine Aminotransferase.
** mild significant differences $P \leq 0.005$

There is an established interaction between these receptors. RXR exerts a dimerizing effect on VDR receptors, and heterodimers can also be formed between them (VDR/RXR) [17]. In addition to the impact on RXR responsive genes, RXR selective retinoids could also influence vitamin D responsive genes. Furthermore, vitamin D could also regulate RXR responsive genes [18]. Although isotretinoin has a low affinity to retinoid receptors, it is converted intracellularly, demonstrating an agonist effect on RAR and RXR receptors [19].

Systemic isotretinoin is a potent acne treatment that affects all four pathogenic factors of the disease, suppressing sebum production and the abnormal desquamation of the sebaceous follicle epithelium and decreasing cutibacterium acne and inflammation [20]. Systemic isotretinoin also demonstrates an inhibitory effect on Th17 development and IL-17 [21].

The results of this study revealed that there was an increase in vitamin D levels after three months of isotretinoin treatment, with a significant difference in the mild acne group only (P=0.0003). What is interesting, no existed theoretical explanation by authors behind this which could be further investigated by future studies. Our results were nearly similar to El-Hamd *et al*. study [22]. On the other hand, a study by Moravvej H *et al*. showed no effect on serum vitamin D levels after recommended dose of oral isotretinoin [23], while the result of another study of Ertugrul *et al*. showed increased 1,25-dihydroxyvitamin D levels and decreased 25-hydroxyvitamin D levels after isotretinoin treatment [24]. The possible rationale behind the contradicting results of these studies is that there might be differences in inclusions and exclusions criteria or in other methodologies' sittings of those studies that had affected the results.

The results of our study and other studies focus on the active role of vitamin D deficiency and its effect on the development of AV, which can be illustrated by the role of cutibacterium acnes in increasing the gene expression of immunological factors to block vitamin D production [25, 26].

This highlights the promising role of vitamin D in AV treatment. In our results, the absence of statistically significant differences between vitamin D and AV severity is mostly due to the small sample size.

The results in this study for lipid profiles and liver function showed an insignificant increase after three months of oral isotretinoin treatment which is similar to other studies [22].

CONCLUSION

Vitamin D plays a role in acne pathogenesis and its level are altered in acne vulgaris. Serum 25-hydroxyvitamin D levels increased after three months of oral isotretinoin therapy, and the effect was significant in mild acne patients. Oral isotretinoin and its influence on vitamin D serum levels in acne patients might highlight vitamin D as a possible target for acne therapy. Furthermore, vitamin D might be considered a biomarker for disease activity and remission.

Further studies on a larger scale are needed to address the effect of isotretinoin in improving vitamin D levels and the exact role of vitamin D deficiency in the pathogenesis of acne, as well as the possible therapeutic effect of vitamin D preparations in acne vulgaris.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Medical Research Ethics Committee in the College of Medicine at Qassim University approved the study with the approval number 15/18/13.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical

standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all the participants.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author (G.A) upon reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Thanks for Clinical, Cosmetic and Investigational Dermatology Journal and Dove press Ltd and authors of the article titled “Vitamin D Levels in Patients with and without Acne and Its Relation to Acne Severity: A Case-Control Study” for the permission to use their data in Table **1** as a reference in our research article.

REFERENCES

[1] Zaenglein AL. Acne Vulgaris. N Engl J Med 2018; 379(14): 1343-52. [http://dx.doi.org/10.1056/NEJMcp1702493] [PMID: 30281982]

[2] Aydemir EH. Acne vulgaris. Turk Pediatri Ars 2014; 49(1): 13-6. [http://dx.doi.org/10.5152/tpa.2014.1943] [PMID: 26078626]

[3] Lone AH, Habib S, Ahmad T, Anwar M. Effect of a Polyherbal Unani formulation in acne vulgaris: A preliminary study. J Ayurveda Integr Med 2012; 3(4): 180-3. [http://dx.doi.org/10.4103/0975-9476.104430] [PMID: 23326087]

[4] Platsidaki E, Dessinioti C. Recent advances in understanding Propionibacterium acnes (Cutibacterium acnes) in acne. F1000Res. 2018;7: F1000 Faculty Rev. Published 1953; 2018(Dec): 19.

[5] Fox L, Csongradi C, Aucamp M, du Plessis J, Gerber M. Treatment modalities for acne. Molecules 2016; 21(8): 1063. [http://dx.doi.org/10.3390/molecules21081063] [PMID: 27529209]

[6] Ganceviciene R, Zouboulis CC. Isotretinoin: state of the art treatment for acne vulgaris. J Dtsch Dermatol Ges 2010; 8(Suppl. 1): S47-59. [http://dx.doi.org/10.1111/j.1610-0387.2009.07238.x] [PMID: 20482692]

[7] Leyden JJ, Del Rosso JQ, Baum EW. The use of isotretinoin in the treatment of acne vulgaris: clinical considerations and future directions. J Clin Aesthet Dermatol 2014; 7(2)(Suppl.): S3-S21. [PMID: 24688620]

[8] Zaenglein AL, Pathy AL, Schlosser BJ, *et al.* Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol 2016; 74(5): 945-73. e33

[9] Yesilova Y, Bez Y, Ari M, Turan E. Effects of isotretinoin on social anxiety and quality of life in patients with acne vulgaris: A prospective trial. Acta Dermatovenerol Croat 2012; 20(2): 80-3. [PMID: 22726279]

[10] Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. Dermatoendocrinol 2013; 5(1): 51-108. [http://dx.doi.org/10.4161/derm.24494] [PMID: 24494042]

[11] Yildizgören MT, Togral AK. Preliminary evidence for vitamin D deficiency in nodulocystic acne. Dermatoendocrinol 2015; 6(1)e983687 [http://dx.doi.org/10.4161/derm.29799] [PMID: 26413187]

[12] Kemeriz F, Tuncer SÇ, Acar EM, Tuğrul B. Evaluation of 25-hydroxy vitamin D levels and disease severity in patients with acne vulgaris. Dermatol Ther (Heidelb) 2020; 33(3)e13393 [http://dx.doi.org/10.1111/dth.13393] [PMID: 32268447]

[13] Tan J, Wolfe B, Weiss J, *et al.* Acne severity grading: Determining essential clinical components and features using a Delphi consensus. J Am Acad Dermatol 2012; 67(2): 187-93. [http://dx.doi.org/10.1016/j.jaad.2011.09.005] [PMID: 22036609]

[14] 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(8)e0161162 [http://dx.doi.org/10.1371/journal.pone.0161162] [PMID: 27560161]

[15] Alhetheli G, Elneam AIA, Alsenaid A, Al-Dhubaibi M. Vitamin D Levels in Patients with and without Acne and Its Relation to Acne Severity: A Case-Control Study. Clin Cosmet Investig Dermatol 2020; 13: 759-65. [http://dx.doi.org/10.2147/CCID.S271500] [PMID: 33116739]

[16] Krämer C, Seltmann H, Seifert M, Tilgen W, Zouboulis CC, Reichrath J. Characterization of the vitamin D endocrine system in human sebocytes in vitro. J Steroid Biochem Mol Biol 2009; 113(1-2): 9-16. [http://dx.doi.org/10.1016/j.jsbmb.2008.10.010] [PMID: 19027855]

[17] Barsony J, Prufer K. Vitamin D receptor and retinoid X receptor interactions in motion. Vitam Horm 2002; 65: 345-76. [http://dx.doi.org/10.1016/S0083-6729(02)65071-X] [PMID: 12481554]

[18] Zouboulis CC. Retinoids which dermatological indications will benefit in the near future? Skin Pharmacol Appl Skin Physiol 2001; 14(5): 303-15. [http://dx.doi.org/10.1159/000056361] [PMID: 11586072]

[19] Layton A. The use of isotretinoin in acne. Dermatoendocrinol 2009; 1(3): 162-9. [http://dx.doi.org/10.4161/derm.1.3.9364] [PMID: 20436884]

[20] Moradi Tuchayi S, Makrantonaki E, Ganceviciene R, Dessinioti C, Feldman SR, Zouboulis CC. Acne vulgaris. Nat Rev Dis Primers 2015; 1: 15029. [http://dx.doi.org/10.1038/nrdp.2015.29] [PMID: 27189872]

[21] Lee WJ, Choi YH, Sohn MY, Lee SJ, Kim DW. Expression of inflammatory biomarkers from cultured sebocytes was influenced by treatment with vitamin D. Indian J Dermatol 2013; 58(4): 327. [http://dx.doi.org/10.4103/0019-5154.113959] [PMID: 23919024]

[22] El-Hamd MA, El Taieb MA, Ibrahim HM, Aly SS. Vitamin D levels in acne vulgaris patients treated with oral isotretinoin. J Cosmet Dermatol 2019; 18(1): 16-20. [http://dx.doi.org/10.1111/jocd.12503] [PMID: 29460332]

[23] Moravvej H, Yousefi M, Mohtasham N, Saadat N, Haghighatkhah H. Effects of oral isotretinoin on serum vitamin D metabolites and other biochemical markers of bone turnover and calcium homeostasis in severe acne. Iran J Dermatol 2008; 11(3): 108-12.

[24] Ertugrul DT, Karadag AS, Tutal E, Akin KO. Therapeutic hotline. Does isotretinoin have effect on vitamin D physiology and bone metabolism in acne patients? Dermatol Ther (Heidelb) 2011; 24(2): 291-5. [http://dx.doi.org/10.1111/j.1529-8019.2011.01406.x] [PMID: 21410620]

[25] 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 Invest Dermatol 2014; 134(2): 366-73. [http://dx.doi.org/10.1038/jid.2013.334] [PMID: 23924903]

[26] Thiboutot DM, Layton AM, Anne Eady E. IL-17: A key player in the P. acnes inflammatory cascade? J Invest Dermatol 2014; 134(2): 307-10. [http://dx.doi.org/10.1038/jid.2013.400] [PMID: 24424453]