DOI: https://doi.org/10.61841/7sa3eh95 Publication URL: https://nnpub.org/index.php/MHS/article/view/2027

VITAMIN D DEFICIENCY IN PATIENTS WITH ALOPECIA AERATA, AND RESPONSIVENESS TO VITAMIN D ANALOGUES: A SYSTEMATIC REVIEW

[1*]Maylia Lie, [1,2]Cut Bueleun Maulida Buket
[1]*Faculty of Medicine, Indonesian Prima University, Indonesia*
[2]*General Practitioner, BSH General Hospital, Indonesia*

Correspondence Author:
maylialee7@gmail.com

ABSTRACT

Background: *Alopecia areata (AA) is a type of T cell-mediated autoimmune disease involving hair follicles (HF), which is manifested as round or oval non-cicatricial alopecia on the head, but also can occur anywhere in the body. The global morbidity of AA ranges from 0.1% to 0.2%, affecting the population of all ages without significant difference between genders. Vitamin D deficiency is common in alopecia aerata, but there is limited evidence to determine whether vitamin D supplementation improves alopecia aerata currently.*

The aim: *This study aims to show vitamin D deficiency in patients with alopecia aerata, and responsiveness to vitamin D analogues.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 46 articles, whereas the results of our search on SagePub brought up 74 articles. The results of the search conducted for the last year of 2013 yielded a total 43 articles for PubMed and 20 articles for SagePub. The result from title screening, a total 20 articles for PubMed and 3 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *Vitamin D deficiency in alopecia aerata correlates inversely with disease severity and duration. Vitamin D receptor expression is reduced in alopecia aerata and inversely correlate with inflammation histologically but does not correlates with serum vitamin D levels, severity, pattern, or duration of illness.*

Keyword: *Vitamin D, Alopecia aerate, autoimmune.*

INTRODUCTION

Alopecia areata (AA) is a common autoimmune skin disease characterized by loss of the hair on the scalp and elsewhere on the body, affecting approximately 2% of the general population at some point during their lifetime. AA may cause anxiety on patients and increases the risks of developing psychological and psychiatric complications. The hair loss in AA is believed to result from an autoimmune-mediated hair follicle (HF) destruction consequent to a loss of immune privilege (IP) in the HF. Autoreactive effector T cells and mast cells, CD8-positive nature killer group 2 member D (NKG2D)-positive cytotoxic T cells ($CD8^+NKG2D^+$ cytotoxic T cells), Janus kinase/signal transducers and activators of transcriptional signaling (JAK/STAT) pathways, regulatory T cells (Tregs) and immune checkpoints and oxidative stress (OS) are involved in AA. However, the pathogenesis of AA remains incompletely understood and AA remains incurable.[1]

AA is mainly treated topically, including intralesional hormone injections, contact immunotherapy, JAK inhibitors, minoxidil, the excimer laser/light and so on. Intralesional or local corticosteroid is the most effective treatment for AA, Intralesional or topical corticosteroids are the most effective treatments for AA, but they often cause adverse effects such as folliculitis, skin atrophy, and osteoporosis. Moreover, the adverse events of other treatment methods have also been reported. For example, sensitization after diphenyl prone immunotherapy may lead to severe head and face edema. JAK inhibitors are prone to cause complications such as upper respiratory tract infection, elevating transaminase, and headache. Long-term phototherapy can cause pigmentation, photoaging, and even canceration. Pain is common occurred in patients receiving platelet rich plasma. Each treatment has its advantages and disadvantages and consequently providing a more safe, effective, and economic treatment for AA patients is a hard issue in current research.[2]

The association between vitamin D and several autoimmune-mediated diseases has been reported, including vitiligo, systemic lupus erythematosus, type I diabetes mellitus, rheumatoid arthritis, psoriasis, multiple sclerosis, and inflammatory bowel disease. Although associations are not causative factors, that might imply that vitamin D deficiency is an environmental trigger for the induction of abnormal autoimmunity. Therefore, 1,25(OH)D3 modulates both innate and adaptive immune responses by targeting various immune cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, and dendritic cells, among others. In addition, vitamin D synthesis decreases with age. Vitamin D deficiency is common in both men and women, and can affect pregnancy outcomes in women and increase the risk of osteoporosis, especially in menopausal women. Although the relationship between vitamin D deficiency and AA in patients was reported in two previous meta-analyses, this relationship has not been comprehensively evaluated since five subsequent studies were not considered.[3]

Vitamin D is also a secosteroid hormone, primarily synthesized in epidermal keratinocytes or acquired from the diet, and plays an important role in calcium homeostasis and bone health. Two studies revealed no difference in serum calcium levels between patients with AA and controls despite a statistically significant difference in vitamin D levels. The presence of 25-hydroxyvitamin D [25(OH)D] deficiency in patients with AA correlated with increased parathyroid hormone (PTH), suggesting a compensatory effect of increased PTH to maintain normal serum calcium in a state of vitamin D deficiency. Darwish et al. showed lower levels of calcium but comparable PTH level, while Yilmaz et al. showed comparable levels of both calcium and PTH in patients with AA compared to controls.[3]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast vitamin D deficiency in patients with alopecia aerata, and responsiveness to vitamin D analogues. It is possible to accomplish this by researching or investigating vitamin D deficiency in patients with alopecia aerata, and responsiveness to vitamin D analogues. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about vitamin D deficiency in patients with alopecia aerata, and responsiveness to vitamin D analogues. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " vitamin D deficiency in patients with alopecia aerata, and responsiveness to vitamin D analogues." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases

by inputting the words: *(("*Vitamin D deficiency*"[MeSH Subheading] OR "*Alopecia aerata*"[All Fields] OR "*Effects of vitamin D analogues in alopecia aerate*" [All Fields]) AND ("*Vitamin D deficiency in patients with alopecia aerata*"[All Fields] OR "* effects of deficiency of vitamin D *"[All Fields]) AND ("*Mechanism of alopecia aerata*"[All Fields]) OR ("*Alopecia aerate and vitamin D analogues" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

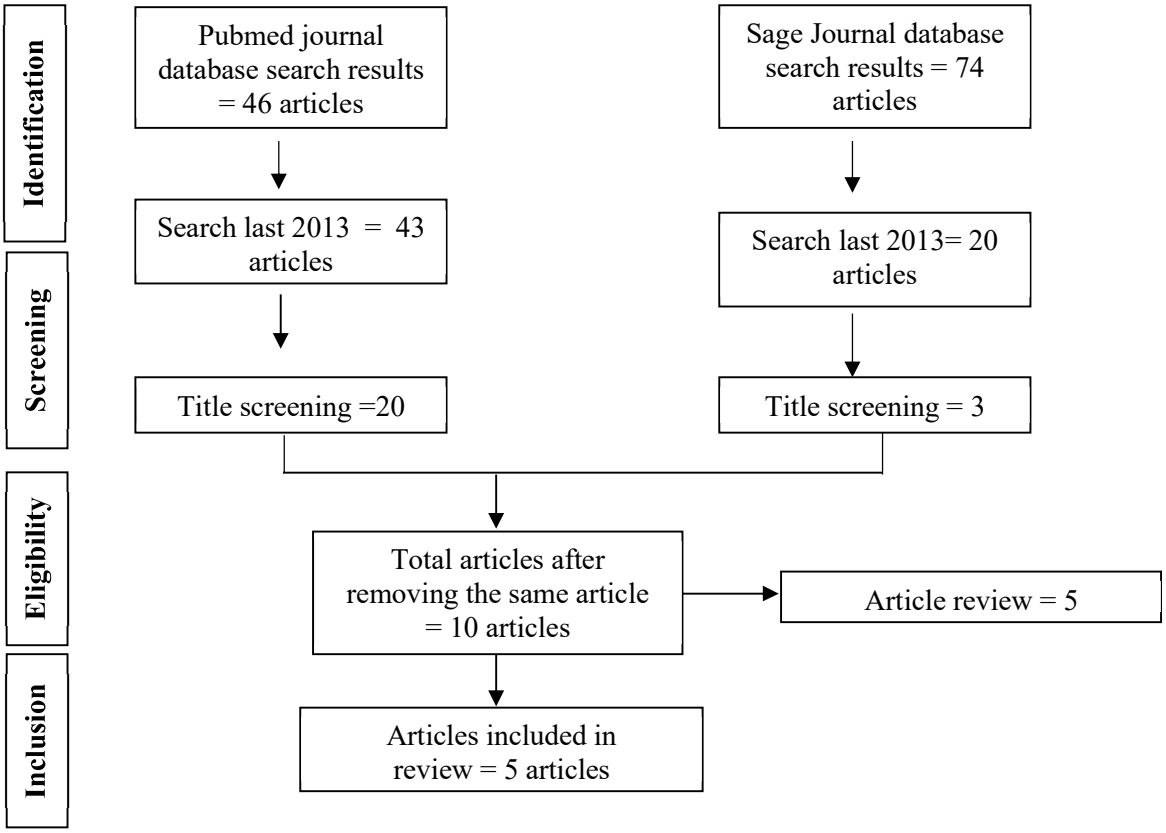

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 46 articles, whereas the results of our search on SagePub brought up 74 articles. The results of the search conducted for the last year of 2013 yielded a total 43 articles for PubMed and 20 articles for SagePub. The result from title screening, a total 20 articles for PubMed and 3 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Bhat, YJ *et al* (2017)[4] showed the levels of 25(OH)D were low in patients of AA when compared to healthy controls. Furthermore, there was a negative correlation between the levels and severity of AA assessed by SALT score. Thus, the study suggests the role of Vitamin D in pathogenesis of AA and hence a possible role of Vitamin D supplementation in the treatment of same.

Rehman, F *et al* (2019)[5] showed Vitamin D is deficient in more number of patients as compared to controls. Furthermore, Vitamin D levels inversely correlated with the severity, extent, and pattern of the disease. Hence, Vitamin D deficiency may be one of the factors involved in etiopathogenesis of AA or may be one of the exacerbating factors.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Bhat, YJ *et al*., 2017[4]	India	Cross-sectional study	50 patients	The mean body mass index in cases was 20.96 ± 1.91, whereas in controls, it was 21.37 ± 1.70 (P = 0.31). The mean serum 25(OH)D levels of AA patients was 16.6 ± 5.9 ng/ml, whereas in control group, the mean level was 40.5 ± 5.7, the difference being statistically significant (P < 0.001). A significant negative correlation was found between severity of alopecia tool score and Vitamin D level (P < 0.001; r = −0.730) and also between the number of patches and Vitamin D level (P < 0.001, r = −0.670).
Rehman, F *et al*., 2019[5]	India	Case control study	270 participants	The more number of patients from the case group had deficient and insufficient levels of Vitamin D as compared to controls, the difference being statistically significant (*P* = 0.01). A highly significant difference was found in mean Vitamin D levels between cases and controls (*P* = 0.0004). A negative correlation was found between Vitamin D levels and severity of AA as accessed by SALT score. A negative correlation was also found between Vitamin D levels with pattern and extent of the disease.
Erpolat, S *et al*., 2017[6]	Turkey	Case control study	73 participants	The study was based on 41 patients aged between 20 and 50 (mean: 32.8 ±7.5). The control group included 32 healthy persons aged between 20 and 51 (mean: 32.7 ±7.5). Serum 25(OH)D levels in patients with AA ranged from 5.0 to 38.6 ng/ml with a mean of 8.1 ng/ml. Serum 25(OH)D levels in healthy controls ranged from 3.6 to 38.5 ng/ml with a mean of 9.8 ng/ml. There was no statistically significant difference in the serum vitamin D level between

				AA patients and healthy controls ($p > 0.05$).
Siddappa, H *et al*., 2019[7]	India	Case control study	100 patients	The cases were further divided into new and old cases – 66 new cases and 34 old cases. The mean serum vitamin D level in old cases was significantly lower than that of new cases (15.11 ± 4.75 vs 20.85 ± 9.09 ng/mL; $P < 0.001$). The number of patients with vitamin D deficiency was significantly higher among old cases ascompared to new cases (29/34 old cases vs 35/66 new cases; $P < 0.05$). A total of 76 cases presented with alopecia involving scalp and they were further subclassified from S1 to S5 based on their SALT scores. Almost all the scalp alopecia cases, that is, 75 cases, belonged to subclass 1 (S1). Only one case belonged to subclass 3 (S3). When the serum vitamin D levels were plotted against their SALT score, there was a significant inverse correlation between the two. ($r = -0.298$; $P < 0.05$)
Fahim, M *et al*., 2023[8]				There were 100 cases of AA in total. The mean age was30.5 ±8.4 with 42% male and 58%females. The mean SALT score at baseline was20.7±5.4 and at the end of six months it decreased to 9.4±3.5s. Out of 100 patients 69 had low serum vit.D levels. Topical calcipotriol was effective in overall 71% patients using SALT50as a measure of efficacy.

Erpolat, S *et al* (2017)[6] showed decreased serum 25(OH)D levels in patients with AA, but there was no statistically significant difference in the serum vitamin D level between AA patients and healthy controls. Further studies are needed to clarify the association between a deficiency of 25(OH)D and AA. But still in our opinion, we recommend screening blood vitamin D levels in AA patients and if deficient, adding oral vitamin D to the AA treatment protocol.

Siddappa, H *et al* (2019)[7] showed Decreased vitamin D levels were observed in patients with alopecia areata and significant inverse correlation exists between vitamin D levels and duration/severity of the disease. These findings may suggest a causal role of vitamin D deficiency in the pathogenesis and therapeutic role of vitamin D supplementation in the management of alopecia areata.

Fahim, M *et al* (2023)[8] showed an associationbetween AA and vit.D deficiency, and its severity being inversely correlated with serum vit.D levels. Similarlyin achieving hair regrowth vit.D Analogues are more effective in vit.D deficient patients.

DISCUSSION

Vitamin D plays an important role in human health. Its main source is photosynthesis in the skin, whereas lower amounts are derived from nutrition and diet supplements. The role of vitamin D in regulation of calcium homeostasis is well established. It stimulates the intestinal absorption of calcium and phosphate, reduces their renal clearance, and promotes bone mineralization. Apart from calcium homeostasis, vitamin D has also been shown to modulate both innate and

adaptive immunity. It stimulates differentiation of monocytes into classical macrophages and enhances the chemotactic and phagocytic capacity of macrophages. Wang et al. demonstrated that 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) activates the transcription of antimicrobial peptides such as cathelicidin antimicrobial peptide in isolated human keratinocytes, monocytes, and neutrophils and enhances expression of defensin β2 in primary cultures of adult keratinocytes. Moreover, they observed that $1,25(OH)_2D$ alone or in conjunction with lipopolysaccharide (LPS) induced cathelicidin antimicrobial peptide expression and release of antimicrobial activity in neutrophils. It has been proposed that induction of antimicrobial peptide expression by $1,25(OH)_2D$ could be involved in the suppressive effects of ultraviolet B (UVB) radiation on innate immunity and suggested the potential of its analogues in treatment of opportunistic infections.[9,10]

Alopecia areata (AA) is one of the most common skin diseases, leading to chronic and relapsing hair loss. The onset may be at any age and there is no known race or gender preponderance. It usually presents as patches of hair loss on the scalp but any hair-bearing skin may also be involved. The etiology of AA is not exactly known; however, genetic predisposition, autoimmunity, and environmental factors have been suggested to play a role. Autoimmune etiology has been proposed on the basis of its association with various autoimmune diseases, the presence of autoantibodies, the presence of inflammatory lymphocytes around and within the affected hair follicles, and the ability to promote hair regrowth with the use of immunosuppressive agents. Vitamin D is a secosteroid hormone that plays an important role in calcium homeostasis and bone health. It has three sources: endogenous synthesis in the skin, which is induced by UVB radiation, dietary intake, and vitamin D supplementation.[11]

Vitamin D is a modulator of both the innate and adaptive immune systems through its varied effects on T and B lymphocytes, dendritic cells (DCs), and macrophages. The connection between vitamin D deficiency and some autoimmune diseases, including type I diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosis, vitiligo, psoriasis, multiple sclerosis, and inflammatory bowel disease has been reported. This suggests that vitamin D deficiency might be an environmental trigger for the induction of autoimmunity. On the other hand, it has been demonstrated that vitamin D receptors (VDRs) are strongly expressed in the key structures of hair follicles. Expression of VDRs on keratinocytes is necessary for maintenance of the normal hair cycle. It has also been shown that a lack of VDRs reduces epidermal differentiation and hair follicle growth.[11,12]

Vitamin D is produced in the skin and is an important factor in keratinocyte proliferation and differentiation, as well as regulation of the hair follicle cycle. It is implicated in the pathogenesis of various diseases, including hair loss. In our clinic, serum vitamin D levels are collected routinely during evaluation of hair loss, allowing us to address this controversial issue. We aim to evaluate the prevalence of vitamin D deficiency in patients with alopecia areata (AA), androgenic alopecia (AGA), central centrifugal scarring alopecia (CCCA), lichen planopilaris (LPP), and telogen effluvium (TE).[13,14]

Patients diagnosed with AA, AGA, CCCA, LPP and TE between May 2009 and April 2010 were identified (n=358). Data on age, gender, race, hair loss type, onset, and serum 25-hydroxyvitamin D values within 3 months of a visit for new or recurrent hair loss were extracted from the electronic health record. Patients taking vitamin D supplements at the time of their visit were excluded. Vitamin D deficiency was defined as vitamin D levels < 30ng/ml, and this was further categorized into mild (21–30ng/ml), moderate (12–21ng/ml), or severe (<12ng/ml). Kruskall-Wallis test, χ^2 test and Fisher exact were used to compare demographic variables and vitamin D levels. The association between Vitamin D and hair loss type, gender, age, and race was assessed with logistic regression.[13,15]

CONCLUSION

Vitamin D deficiency in alopecia aerata correlates inversely with disease severity and duration. Vitamin D receptor expression is reduced in alopecia aerata and inversely correlate with inflammation histologically but does not correlates with serum vitamin D levels, severity, pattern, or duration of illness.

REFERENCES

[1] Lin X, Meng X, Song Z. Vitamin D and alopecia areata: Possible roles in pathogenesis and potential implications for therapy. Am J Transl Res. 2019;11(9):5285–300.

[2] Zhu B, Zhang L, Wang J, Tan G. Vitamin D supplementation for patients with alopecia areata: A protocol for systematic review and meta-analysis. Med (United States). 2022;101(42):E31089.

[3] Liu Y, Li J, Liang G, Cheng C, Li Y, Wu X. Association of Alopecia Areata with Vitamin D and Calcium Levels: A Systematic Review and Meta-analysis. Dermatol Ther (Heidelb) [Internet]. 2020;10(5):967–83. Available from: https://doi.org/10.1007/s13555-020-00433-4

[4] Manchanda Y, Das S, Sarda A, Biswas P. Controversies in the Management of Cutaneous Adverse Drug Reactions Systemic Corticosteroids in the Management of SJS / TEN : Is it Still. Indian J Dermatol [Internet]. 2018;63(2):125–30. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85045467996&doi=10.4103%2Fijd.IJD_585_17&partnerID=40&md5=24ac1ecf391acb36c5e83a65633c1c90

[5] Kiszewski AE, Bevilaqua M, Abreu LB De. Alopecia Areata : A New Therapeutic. Int J Trichology. 2018;9(1):50–3.

[6] Erpolat S, Sarifakioglu E, Ayyildiz A. 25-hydroxyvitamin D status in patients with alopecia areata. Postep

Dermatologii i Alergol. 2017;34(3):248–52.
[7] An I, Harman M, Ibiloglu I. Topical Ciclopirox Olamine 1%: Revisiting a Unique Antifungal. Indian Dermatol Online J. 2017;10(4):481–5.
[8] Fahim M, Khoso H, Hussain A, Bakhtiar R. Deficiency in alopecia areata and responsiveness to vitamin D analogues: A prospective trial. J Pakistan Assoc Dermatologists. 2023;33(4):1242–8.
[9] Gerkowicz A, Chyl-Surdacka K, Krasowska D, Chodorowska G. The role of vitamin D in non-scarring alopecia. Int J Mol Sci. 2017;18(12):1–12.
[10] Molinelli E, Campanati A, Brisigotti V, Sapigni C, Paolinelli M, Offidani A. Efficacy and Safety of Topical Calcipotriol 0.005% Versus Topical Clobetasol 0.05% in the Management of Alopecia Areata: An Intrasubject Pilot Study. Dermatol Ther (Heidelb) [Internet]. 2020;10(3):515–21. Available from: https://doi.org/10.1007/s13555-020-00379-7
[11] Bakry O, El Farargy S, El Shafiee M, Soliman A. Serum Vitamin D in patients with alopecia areata. Indian Dermatol Online J. 2016;7(5):371.
[12] Lee S, Kim BJ, Lee CH, Lee WS. Increased prevalence of vitamin D deficiency in patients with alopecia areata: a systematic review and meta-analysis. J Eur Acad Dermatology Venereol. 2018;32(7):1214–21.
[13] Prochaska J, Benowitz N. 乳鼠心肌提取 HHS Public Access. Physiol Behav. 2016;176(1):100–106.
[14] Almohanna HM, Ahmed AA, Tsatalis JP, Tosti A. The Role of Vitamins and Minerals in Hair Loss: A Review. Dermatol Ther (Heidelb) [Internet]. 2019;9(1):51–70. Available from: https://doi.org/10.1007/s13555-018-0278-6
[15] Daroach M, Narang T, Saikia UN, Sachdeva N, Sendhil Kumaran M. Correlation of vitamin D and vitamin D receptor expression in patients with alopecia areata: a clinical paradigm. Int J Dermatol. 2018;57(2):217–22.