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ORIGINAL ARTICLE

The association between low serum vitamin-B12 levels and hyperpigmentation in patients who use isotretinonin

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Abstract

Oral isotretinoin is the most effective agent in the treatment of acne vulgaris. The risk of pigmentation due to the systemic isotretinoin may be associated with decrease in serum levels of vitamin B12. The study aims to contribute to the literature by defining the association between the increase in pigmentation caused by oral isotretinoin (O-ISO) use and low vitamin B12 level (vit-B12). In our study we evaluated 144 patients who have facial acnes at medium degree according to FDA Acne Score and take O-ISO treatment with the dose 0.5 mg/ kg/ day for six months. The mean vit-B12 levels of the patients at the admission and 6th month and the existence of pigmentation at 6th month, the skin type and the skin layer at which the pigmentation occurs were evaluated. Association of vit-B12 level on admission and six months post drug use with the presence of pigmentation at six months, the type of skin and the skin layer in which pigmentation occurs were evaluated. In the patient group with pigmentation, the mean vit-B12 level after six months of drug use was statistically lower than the mean vit-B12 level on admission ($p<0.001$). In patients without pigmentation, difference between the mean levels of vit-B12 levels was not statistically significant ($p = 0,255$). As a result, it was determined that the mean vit-B12 level decreased due to O-ISO use and the association of hyperpigmentation and low vit-B12 level was statistically significant. Vit-B12 monitoring and supplementation, if necessary, can help us to prevent hyperpigmentation that may occur during the treatment.

Keywords: *Isotretinonin, hyperpigmentation, vitamin-B12, side effect*

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Introduction

Acne vulgaris is one of the most common skin disorders in the world, especially in the adolescence period, affecting 85-100% of individuals during any period of life. Prevalence of acne vulgaris is around 9.4%. The major pathogenic factors in the pathogenesis of acne vulgaris are increased sebum secretion, androgen stimulation, abnormal keratinization, and inflammation due to microbial colonization [1,2].

Many topical and systemic drugs can be used in the treatment of acne vulgaris. As topical treatments, antibiotics, azelaic acid, salicylic acid, benzoyl peroxide, retinoic acids, and combinations are commonly used. Antibiotics, hormonal agents and vitamin A derivatives (retinoids) are used as systemic treatment of acne vulgaris. Oral isotretinoin (O-ISO), a vitamin A derivative, is the most effective agent in the treatment of acne vulgaris [3]. O-ISO has been considered as the gold standard in the treatment of moderate to severe acne vulgaris [4,5].

Beside the local and cutaneous side effects such as hyper/hypopigmentation, excess sebum production, thinning of stratum corneum, inflammation of the skin and nasal hemorrhage, xerophthalmia, blepharoconjunctivitis, itching, photosensitivity, skin infections with Staphylococcus aureus; there have been rare but important systemic side effects of O-ISO such as hematological, musculoskeletal, endocrinologic, gastrointestinal, urinary and central nervous systems side effects [6,7]. Although the mechanism has not been fully understood, it has been documented that O-ISO may lead to decrease in vit-B12 and folic acid levels [8]. In this study, we aimed to contribute to the literature by defining a possible association between the increase of pigmentation and the low serum levels of vit-B12 caused by O-ISO.

Materials and Methods

This study was carried out as a prospective observational study between February 2016 and February 2017 in the Dermatology Clinic of Ağrı State Hospital after approval of the ethics committee of Van Regional Education & Research Hospital. This study was conducted according to the Declaration of Helsinki and all subjects provided informed consent.

The study included 144 patients who have topical and oral antibiotic-resistant moderate or severe facial acne vulgaris lesions and have been taking O-ISO (min 0,1- max 0,5 mg/kg/day) regularly for 6 months. Patients were selected from the group of patients who did not have any pigmentation disorder at the time of admission. The Fitzpatrick scale was used to evaluate the skin type before the treatment. The skin layer where the pigmentation occurred (dermis, epidermis, or both) was evaluated at the end of six months. Wood's lamp was used to determine the presence of pigmentation and the skin layer of pigmentation. The difference in serum vit-B12 levels at the time of referral and at six months after drug use, the presence and the depth of pigmentation and skin type were assessed.

Patients with any history of liver and/or renal failure, hyperlipidemia, malignity, dermatological or systemic diseases which cause pigmentation such as diabetes mellitus, atopic dermatitis etc. were excluded from the study. Furthermore, pregnant or planning to be pregnant, younger than 18 were not included either. Descriptive values of the quantitative measurements obtained in the study are given as mean, standard deviation, median, minimum and maximum levels and categorical measurements as frequency and percentage. Shapiro Wilk test was used as the preferred test of normality. Differences in the median of the quantitative variables between the groups were examined by the Mann Whitney-U test. The paired t test was used to compare the mean of the 6th month vit-B12 levels and B12 levels on admission and the Wilcoxon Signed Rank Test was used to compare the medians. Alpha level is accepted as 0.05 and $p < 0.05$ was considered as statistically significant. SPSS (ver. 21) program was used for statistical analysis.

Results

One hundred forty-four patients with acne vulgaris were included in this study. 60.4% (n=87) of the patients were female and 39.6% (n=35) of the patients were male. The mean age of the patients was 25.95±4.8. Other features of the patients such as skin type, the presence of pigmentation after the treatment and distribution of this pigmentation (epidermal, dermal or both) are presented in Table 1. The mean vit-B12 level at time of admission was similar in individuals with and without pigmentation ($p > 0.05$). Six months after the start of treatment, the mean vit-B12 level in the group without pigmentation was significantly higher than the group with pigmentation ($p = 0.013$)

(Table 2). In the group with pigmentation, the mean vit-B12 levels at six months after drug use was found to be significantly lower than the mean of vit-B12 measured at time of admission (p <0.001). In the group without pigmentation, there was no significant difference between the two mean vit-B12 levels (p> 0.05) (Table 3). Moreover, among the pigmented group patients, the mean vit-B12 values was not statistically significant according to the pigmentation layer (epidermal, dermal, both) (p=0,454).

Table 1. Sociodemographic characteristics and clinical and laboratory findings

		n	%
Sex	Female	87	60.4
	Male	57	39.6
Skin Type	II	9	6.3
	III	80	55.6
	IV	55	38.2
Pigmentation after the treatment	Yes	20	13.9
	No	124	86.1
Epidermal	Yes	16	11.1
	No	128	88.9
Epidermal-Dermal	Yes	13	9
	No	131	91
Dermal	Yes	17	12.5
	No	127	(87.5)

Table 2. Vitamin-B12 levels before and after treatment of pigmented and non-pigmented group

	Pigmentation	n	Mean	Median	Standard Deviation	Minimum	Maximum	p
Vit-B12 at time of admission	Yes	20	294.70	295.00	67.624	185	412	0.534
	No	124	307.38	300.00	73.865	170	456	
Vit-B12 after 6 months of O-ISO use	Yes	20	253.45	250.00	64.191	170	406	0.013
	No	124	299.75	300.00	79.043	130	470	

Table 3. Comparison of pre- and post-treatment vitamin-B12 levels between pigmented and non-pigmented group

Pigmentation		n	Mean	Median	Standard Deviation	Minimum	Maximum	p
Yes	Vit-B12 at time of admission	20	294.70	295.00	67.624	185	412	<0.001
	Vit-B12 after 6 months of O-ISO use	20	253.45	250.00	64.191	170	406	
No	Vit-B12 at time of admission	124	307.38	300.00	73.865	170	456	0.255
	Vit-B12 after 6 months of O-ISO use	124	299.75	300.00	79.043	130	470	

Discussion

In the study, the increase of pigmentation due to O-ISO treatment was found to be associated with a decrease in vit-B12 levels. This pigmentation increase could occur in all layers of the skin and the association was more evident in Type-IV skin type.

The amount of pigmentation in the skin may differ due to hereditary and/or acquired causes. Increase in hormones and enzymes leading to deterioration in melanocyte distribution and increase in melanin synthesis can lead to hyperpigmentation [9]. Drug-induced hyperpigmentation accounts for 10-20% of acquired hyperpigmentation. This hyperpigmentation may develop due to melanin storage, nonspecific cutaneous inflammation, post-inflammatory reaction, accumulation of specific pigment fragments of the drug or deposition of the triggering agent [6].

The frequency of mucocutaneous side effects during the O-ISO treatment can be seen as high as 95-100% depending on the dose [10-12]. It is established that the frequency of pigmentation due to O-ISO is 2-3.2% [13,14]. The mechanism of O-ISO causing hyper/hypopigmentation is not fully understood [15]. It is believed that initiation of low-dose and regular 3 months O-ISO treatment facilitates improvement of skin color due to the increase in collagen synthesis and dermal vascularization, cell differentiation and extracellular matrix stabilization [16,17]. Though, it is reported that high doses of O-ISO with a longer duration of therapy or an added treatment leads to hyperpigmentation [6,14-17]. O-ISO and glycolic acid combination results in an increased risk of hyperpigmentation, which is also associated with postinflammatory pigmentation [14,15]. Cytokines along with mediators such as leukotrienes, prostaglandins and thromboxanes are responsible for post-inflammatory hyperpigmentation [18,19]. Exposure to sunlight, results in proopiomelanocortin-derived peptides to cause hyperpigmentation by stimulating pigmentation in exposed areas [20]. In the study, 13.9% of participants developed hyperpigmentation after six months of O-ISO use. The reason for a higher percent of hyperpigmentation than what is reported in the literature may be the cumulative effect resulting from the 6-month of O-ISO use, impaired enzyme metabolism and increase in post-inflammatory reactions. The high altitude at the site where the study was conducted and the arrival angle of sunlight may have contributed to the high frequency of hyperpigmentation. In addition, the rate of pigmentation being higher in Type IV skin type, may have contributed to the increase in pigmentation due to postinflammatory processes [21].

Karadağ et al. [13] reported that vit-B12 levels dropped after six months of O-ISO therapy and that liver function was impaired. Gökalp et al. [8] reported similar findings after four months of therapy. Kamal et al. reported that the vit-B12 level after 45 days of O-ISO treatment did not change significantly. They also claimed that the decrease in vit-B12 levels determined in their and other studies in the literature could be a result of the cumulative effect of O-ISO use for a longer period [22]. In our study, we also came to the conclusion that the significant drop in vit-B12 level after treatment is the result of the cumulative effect of O-ISO therapy for six months. This cumulative effect may be due to the degradation of absorption, transport, storage of vit-B12, as well as alteration of dietary habits due to psychological or other organ effects developed in the individual, resulting in an inadequate intake of vit-B12. Melanin is synthesized from tyrosine via tyrosinase enzyme. DNA and RNA molecules responsible for the expression of this enzyme, can be disrupted in vit-B12 deficiencies leading to abnormal pigment responses [20]. The hyperpigmentation in the presence of Vit-B12 deficiency is due to decreased glutathione levels and the over-activation of tyrosinase and/or related proteins caused by defective DNA synthesis. It has also been expressed that hyper-homocysteinemia leads to cysteine accumulation which increases the amount of melanin and leads to erroneous melanin production in keratinocytes from melanocytes [23-25]. In our study, a decrease in vit-B12 levels in the 6-month O-ISO use may lead to abnormal pigment metabolism. And, there was a significant decrease in vit-B12 levels, in the 6th month of O-ISO treatment in the group with pigmentation while no significant difference in vit-B12 level was seen in the group without pigmentation. This suggests that the low vit-B12 level that is observed in patients using O-ISO may lead to an increase in pigmentation along with the Fitzpatrick skin type and the geographical features of the area where patients are present.

To the best of our knowledge, there has been no

study that shows any association of O-ISO-related pigmentation and vit-B12 deficiency with skin type in the literature. It has been shown that post-inflammatory hyperpigmentation was more frequent in dark-skinned individuals during the treatment of acne [18]. Boen et al. reported that hyperpigmentation was more frequent in Fitzpatrick Type 3-4 patients in acne treatment, though this side-effect was temporary [26]. For this reason, some authors suggest that in Fitzpatrick type 3 and 4 patients who undergo acne treatment, more attention should be paid for drug selection and dosing to avoid dyschromia [27-28]. In our study more pigmentation in type IV patients may be related to bigger melanocytes and more pigment secretion despite the same acne severity. The abnormal response to vit B12 changes of these cells may be stronger. To the best of our knowledge, there has been no study that shows the association of pigmentation due to O-ISO and changes due to vit-B12 deficiency with the depth of pigmentation. The melanin accumulation in the dermal macrophages is more common in the basal layer of the epidermis. This has been attributed to melanocyte stimulation, nonspecific cutaneous inflammation, photosensitivity reaction, and faulty melanin excretion from macrophages caused by O-ISO use [6-29]. The rate of dermal hyperpigmentation being higher in our study was in accordance with findings from the literature. The decrease in vit-B12 level was significant in the hyperpigmentation at all depths of the skin. These results can be attributed to the fact that macrophages are more frequently present in the dermis.

Our study has some limitations. It is a cross-sectional study with a relatively small sample size. There should be equal numbers of patients in each types of skin type (especially I and II), but in the present study we included type III and IV skin types more. Therefore, our results should be verified by prospective longitudinal future studies with larger sample sizes.

Conclusion

The study suggests that decreased vit-B12 levels due to O-ISO use for 6-months may be associated with hyperpigmentation development. Therefore, we believe that monitoring and supplementation of vit B12, if necessary, and regular use of sunscreens in the patients under O-ISO treatment will reduce the risk of hyperpigmentation that may occur during treatment.

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Conflict of interest

The authors have no conflicts of interest declared.

References

1. Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ, et al. The global burden of skin disease in 2010: An analysis of the prevalence and impact of skin conditions. J Invest Dermatol. 2014;134(6):1527–34. https://doi.org/10.1038/jid.2013.446.
2. Richter C. Akne vulgaris: Therapie und quantifizierung in klinischen Studien. PhD Thesis. 2017.
3. Terzi E, Tursen B, Tursen U. Comparison of the intermittent and standard isotretinoin treatment in moderate and severe acne vulgaris cases. Rom J Clin Exp Dermatol. 2017;2(4):96–99.
4. Kar BR, Tripathy S, Panda M. Comparative study of oral isotretinoin versus oral isotretinoin +20% salicylic acid peel in the treatment of active acne. J Cutan Aesthet Surg. 2013;6(4):204–8. https://doi.org/10.4103/0974-2077.123403.
5. Kroepfl L, Emer JJ. Combination therapy for acne scarring: Personal experience and clinical suggestions. J Drugs Dermatol. 2016;15(11):1413–9.
6. Demir B, Çiçek D, Bilik L, AydoGdu EG, ArtaS H, Demirpolat N, et al. Oral isotretinoin induced pigmentation disorder: A case report. Firat Med J. 2017;22(3):143–5.
7. Šimić D, Penavić JZ, Babić D, Gunarić A. Psychological status and quality of life in acne patients treated with oral isotretinoin. Psychiatr Danub. 2017;29(2):104–10.
8. Gökalp H, Bulur I, Gürer MA. Decreased vitamin-B12 and folic acid concentrations in acne patients after isotretinoin therapy: A controlled study. Indian J Dermatol. 2014;59(6):630. https://doi.org/10.4103/0019-5154.143533.
9. Evren AlGın Y. Cilt beyazlatıcılara genel bakıS. Marmara Pharm J. 2017;21(1):48–53. https://doi.org/10.12991/marupj.259880.
10. Gökalp H.Isotretinoin yan etkileri: Devlet hastanesinde etkili akne tedavisine engel mi? Turkish Clin J Dermatol. 2012;22(1):1–7.
11. Karadag AS, Çalka Ö, Akdeniz N. Evaluation of side effects of isotretinoin in 150 patients with acne vulgaris. Turkderm Arch Turk D. 2011;45(1):37–42. https://doi.org/10.4274/turkderm.45.09.
12. Rademaker M. Adverse effects of isotretinoin: A retrospective review of 1743 patients started on isotretinoin. Australas J Dermatol. 2010;51(4):248–53. https://doi.org/10.1111/j.1440-0960.2010.00657.x.
13. Karadag AS, Tutal E, Ertugrul DT, Akin KO. Effect of isotretinoin treatment on plasma holotranscobalamin, vitamin-B12, folic acid, and homocysteine levels: Non-controlled study. Int J Dermatol. 2011;50(12):1564–9. https://doi.org/10.1111/j.1365-4632.2011.05027.x.
14. Mahadevappa OH, Mysore V, Viswanath V, Thurakkal S, Majid I, Talwar S, et al. Surgical outcome in patients taking concomitant or recent intake of oral isotretinoin: A multicentric

study-ISO-AIMS study. J Cutan Aesthet Surg. 2016;9(2):106–14. https://doi.org/10.4103/0974-2077.184054.

15. Gerber PA, Kukova G, Bölke E, Homey B, Diedrichson E. Severe hyperpigmentation and scarring following glycolic acid peel treatment in combination with low-dose isotretinoin. Eur J Med Res. 2014;19(1):60. https://doi.org/10.1186/s40001-014-0060-x.
16. Kalil CLPV, Fachinello FZ, Lamb FM, Comunello LN. Use of oral isotretinoin in photoaging therapy. SkinMed. 2008;7(1):10–14. https://doi.org/10.1111/j.1540-9740.2007.07145.x.
17. Rabello-Fonseca RM, Azulay DR, Luiz RR, Mandarim-De-Lacerda CA, Cuzzi T, Manela-Azulay M. Oral isotretinoin in photoaging: Clinical and histopathological evidence of efficacy of an off-label indication. J Eur Acad Dermatol Venereol. 2009;23(2):115–23. https://doi.org/10.1111/j.1468-3047.x83.2008.029.
18. Cüre K, Kocatürk E, Kızıltaç U. Facial hyperpigmentations and their management. Eur Arch Med Res. 2016;32:211–8. https://doi.org/10.5222/otd.2016.1069.
19. Tomita Y, Maeda K, Tagami H. Melanocyte-stimulating properties of arachidonic acid metabolites: Possible role in postinflammatory pigmentation. Pigment Cell Res. 1992;5(5):357–61. https://doi.org/10.1111/j.1600-0749.1992.tb00562.x.
20. Gillbro JM, Olsson MJ. The melanogenesis and mechanisms of skin-lightening agents–existing and new approaches. Int J Cosmet Sci. 2011;33(3):210–21. https://doi.org/10.1111/j.1468-2494.2010.00616.x.
21. Davis EC, Callender VD. Postinflammatory hyperpigmentation: A review of the epidemiology, clinical features, and treatment options in skin of color. J Clin Aesthet Dermatol. 2010;3(7):20–31.
22. Kamal M, Polat M. Effect of different doses of isotretinoin treatment on the levels of serum homocysteine, vitamin-B12 and folic acid in patients with acne vulgaris: A prospective controlled study. J Pak Med Assoc. 2015;65(9):950–3.
23. Aroni K, Anagnostopoulou K, Tsagroni E, Ioannidis E. Skin hyperpigmentation and increased angiogenesis secondary to vitamin-B12 deficiency in a young vegetarian woman. Acta Derm Venereol. 2008;88(2):191–2. https://doi.org/10.2340/00015555-0377.
24. Padhi S, Sarangi R, Ramdas A, Ravichandran K, Varghese RGB, Alexander T, et al. Cutaneous hyperpigmentation in megaloblastic anemia: A five-year retrospective review. Mediterr J Hematol Infect Dis. 2016;8(1):e2016021. https://doi.org/10.4084/MJHID.2016.021.
25. Speeckaert R, Van Gele M, Speeckaert MM, Lambert J, van Geel N. The biology of hyperpigmentation syndromes. Pigment Cell Melanoma Res. 2014;27(4):512–24. https://doi.org/10.1111/pcmr.12235.
26. Boen M, Brownell J, Patel P, Tsoukas MM. The role of photodynamic therapy in acne: An evidence-based review. Am J Clin Dermatol. 2017;18(3):311–21. https://doi.org/10.1007/s40257-017-0255-3.
27. Hong JS, Jung JY, Yoon JY, Suh DH. Acne treatment by methyl aminolevulinate photodynamic therapy with red light vs. intense pulsed light. Int J Dermatol. 2013;52(5):614–9. https://doi.org/10.1111/j.1365-4632.2012.05673.x.
28. Mei X, Shi W, Piao Y. Effectiveness of photodynamic therapy with topical 5-aminolevulinic acid and intense pulsed light in Chinese acne vulgaris patients. Photodermatol Photoimmunol Photomed. 2013;29(2):90–6. https://doi.org/10.1111/phpp.12031.
29. Dereure O. Drug-induced skin pigmentation. Am J Clin Dermatol. 2001;2(4):253–62. https://doi.org/10.2165/00128071-200102040-00006.