The Effect of Isotretinoin on Oxidative Stress in Severe Acne Vulgaris Patients

Şiddetli Akne Vulgarisli Hastalarda İzotretinoinin Oksidatif Stres Üzerine Etkisi

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ABSTRACT Objective: Oxidative stress (OS) has been implicated in the pathogenesis of a variety of diseases including acne vulgaris. Isotretinoin (Iso), which is accepted to be the most effective medication in the treatment of nodulocystic acne, has a number of adverse effects related to OS. The aim of this study was to enlighten the disputed role of OS in the pathogenesis of acne and the effects of Iso on OS. **Material and Methods:** Fifty patients with nodulocystic acne who were receiving Iso and fifty healthy controls were included in the study. Blood samples were obtained from patients before and on the 45th day of treatment and once from the controls. Serum total oxidant status (TOS), total antioxidant capacity (TAC) levels were measured spectrophotometrically and oxidative stress index (OSI) was calculated as a ratio of TOS to TAC. **Results:** Before Iso, serum TOS levels and OSI values were significantly lower in the patients compared to the controls (p=0.004 and p=0.006, respectively). On the other hand, there was no statistically significant difference between the groups for TAC levels (p=0.285). When the values of patients before and after the treatment were compared, it was revealed that serum TOS levels and OSI values had significantly increased (p=0.035 and p=0.043, respectively), yet, TAC levels were not statistically different (p=0.308). **Conclusion:** These results suggest that OS is decreased in patients with acne. Besides, Iso's exact mechanism of action on OS remains somewhat obscure. Further studies are required to clarify the relationship between acne, Iso and OS.

Key Words: Acne vulgaris; isotretinoin; oxidative stress

ÖZET Amaç: Oksidatif stres (OS) akne vulgaris de dahil olmak üzere birçok hastalığın patogenezinde suçlanmıştır. Nodülokistik akne tedavisinde en etkili ilaç olarak kabul edilen izotretinoin (İzo), OS ile ilişki çok sayıda yan etkiye sahiptir. Bu çalışmanın amacı akne patogenezinde OS'nin rolünü ve İzo'nun OS üzerindeki etkilerini ortaya koymaktır. **Gereç ve Yöntemler:** Bu çalışmaya İzo tedavisi alan 50 nodülokistik akne hastası ve 50 sağlıklı kontrol dahil edildi. Kan örnekleri hastalardan tedavinin öncesinde ve 45. gününde; kontrollerden ise bir kez alındı. Serum total oksidan seviye (TOS) ve total antioksidan kapasite (TAK) spektrofotometrik yöntemle ölçüldü; TOS'un TAK'a oranı kullanılarak da oksidatif stres indeksi (OSİ) hesaplandı. **Bulgular:** Kontrol grubu ile karşılaştırıldığında, İzo öncesinde hastaların serum TOS seviyeleri ve OSİ değerleri anlamlı derecede düşük tespit edildi (sırasıyla p=0,004 ve p=0,006). Bunun aksine, TAK düzeyleri göz önünde bulundurulduğunda iki grup arasında istatistiksel olarak anlamlı bir fark yoktu (p=0,285). Tedavi öncesine göre sonrasında ise, serum TOS düzeylerinin ve OSİ değerlerinin anlamlı derecede arttığı (sırasıyla p=0,035 ve p=0,043), ancak TAK seviyelerinin istatistiksel açısından farklı olmadığı görüldü (p=0,308). **Sonuç:** Bu bulgular, normal popülasyona göre akne hastalarında OS'nin azaldığını göstermektedir. Bununla birlikte, İzo'nun OS üzerindeki etki mekanizması tam olarak aydınlatılabilmiş değildir. Akne, İzo ve OS arasındaki ilişkinin ortaya konabilmesi için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Akne vulgaris; izotretinoin; oksidatif stres

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Acne vulgaris is a multifactorial, chronic inflammatory disease of the pilosebaceous units.[1] Although acne is a self-limited disease, *considering* the *risk of* physical *scarring it* may have a negative psychological impact on an individual's social life.[2,3] More aggressive treatment

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with more effective medications is needed to prevent scar formation and *psychological* sequelae that often *follows.*[4] Decreasing the size, shape and lipid content of sebaceous glands, *oral isotretinoin (Iso) is the drug* of *choice* for treatment of *severe forms of acne* vulgaris.[4-9-13]

Iso is the only drug that affects *all* the *factors* involved in the *pathogenesis of acne.*[9,10,14] Increased sebum production, ductal hypercornification, Propionibacterium acnes (P. acnes) *colonization and inflammation are thought to be the key factors in acne pathogenesis.*[15,16] *However, there are numerous reports of increased oxidative stress (OS) playing a major role in acne development.*[17-22] *Moreover, recently,* OS is attributed as one of the mechanism involved in the pathogenesis of side effects of Iso.[23-26]

OS represents an imbalance between the production of pro-oxidants and organism's ability to detoxify them and repair the damage that has been developed. An oxidant or oxidizing agent is an electron acceptor and oxidation is a chemical reaction in which an electron loss occurs. As free radicals are atoms or molecules with unpaired electrons in outer orbit, oxidation is the process that produces free radicals. The vast majority of free radicals are derived from molecular oxygen and these are generally known as "reactive oxygen species" (ROS).[27] Either naturally produced or diet-derived, an antioxidant is a compound capable of decreasing the harmful effects of ROS.[27,28] As it has limited capacity, in spite of the b*ody's* antioxidant defence system, oxidative damage products may increase leading to development of many *inflammatory* diseases.[19,29-32]

In consideration of acne vulgaris is an inflammatory disease and OS plays a role in the side effect development process of Iso, we investigated the OS status in patients with acne receiving oral Iso.

MATERIAL AND METHODS

STUDY GROUPS

A total of 50 patients (26 females, 24 males) with nodulocystic acne between 18-30 years of age who had attended the Dermatology Department of Ankara Ataturk *Research and Training Hospital* were included in this study. Fifty healthy individuals *who were age- and sex-matched* pairs of patients were taken as *controls.* Controls were taken from the general population. *The study protocol fulfilled the principles* outlined in the Declaration of Helsinki and was approved by Ethics Committee of our hospital. All participants were informed about the protocol and a written consent was obtained from each one.

A thorough clinical evaluation including a *detailed medical history and complete physical examination was done for each participant.* Those who reported any systemic disease, pregnancy or lactation, t*aking drugs* known or suspected to affect oxidative status such as supplemental vitamins, also alcohol consumption and smoking habit were excluded from the study. *All the patients were weighed* and 0.5 mg/kg per day of oral Iso treatment started. Before and 45 days after treatment with Iso, the following laboratory tests were performed on each patient: Complete blood count, biochemical analyses including serum urea, creatinine, *aspartate aminotransferase* (AST), *alanine aminotransferase* (ALT), *gamma-glutamyl transferase (GGT),* total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides.

BLOOD SAMPLE COLLECTION

After overnight fasting, peripheral venous blood samples were obtained from each participant in the study. Plasma was separated from blood samples by centrifugation at 3500 rpm for 10 minutes and then the samples were stored at -80 °C until further analysis of total antioxidant capacity (TAC) and total oxidant status (TOS).

MEASUREMENT OF TAC OF PLASMA

TAC of serum was determined using a novel automated colorimetric measurement method, developed by Erel.[33] The novel method is based on bleaching of the characteristic color of a more stable 2,2'-azino-bis [3-ethylbenz-thiazoline-6-sulfonic acid (ABTS)] radical cation caused by antioxidants.[33] The results are expressed in mmol Trolox equivalents/L.

MEASUREMENT OF TOS OF PLASMA

Plasma TOS levels were determined using a novel automated colorimetric measurement method, de-

veloped by Erel.[34] The assay is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidant species in acidic medium and the measurement of the ferric ion by xylenol orange. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample.[34] The results are expressed as μmol H2O2 equivalent/l.

DETERMINATION OF OXIDATIVE STRESS INDEX (OSI)

The percent ratio of TOS to TAC yields the OSI, an indicator of the degree of OS. To perform the calculation, the result unit of TAC, mmol Trolox equivalent/L, was changed to μmol Trolox equivalent/L, and the OSI value was calculated as follows:

OSI= [(TOS, μmol/L)/(TAC, μmol Trolox equivalent/L)/100].

STATISTICAL ANALYSIS

Data were analyzed using the SPSS® for Windows computing program (Version 17; SPSS, Chicago, IL). The values were presented as mean ± standard deviation (SD) or percentages, where appropriate. A paired t-test was used to compare data before and after treatment with Iso. The differences between the different groups of patients and controls were analyzed by Student's *t*-test (two-tailed). All data were tested for normality with *Shapiro-Wilk test* and homogeneity of variances with *Levene's* test. A p-value <0.05 was accepted to be statistically significant.

RESULTS

There was an equal distribution of age and gender among acne patients and controls. Twenty six female (52%) and 24 male (48%) patients, also 26 female (52%) and 24 male (48%) healthy controls were enrolled in the study. The mean ages of both patient and control groups were 22.2±3.4 years. *The values of patients before Iso and controls are delineated in Table 1 whereas of patients after Iso and controls in Table 2.* As can be seen, before treatment there was no significant difference between patients and the control group with respect to serum TAC levels (p=0.285). However, serum TOS levels and OSI values were significantly lower in patients than controls (p=0.004 and p=0.006, respectively). Though serum TOS levels and OSI values considerably increased in patients after treatment when compared to the values before the treatment (p=0.035 and p=0.043 respectively), once again there was no statistically significant difference in serum TAC levels (p=0.308).

TABLE 1: Plasma oxidative and antioxidative parameters of patients with acne vulgaris and controls.

	Patients	Controls	p
TAC (mmol Trolox equiv/L)	2.6±0.31	2.6±0.32	0.285
TOS (μmol H_2O_2 equiv/L)	13.7±3.71	15.1±2.99	0.004
OSI (arbitrary unit)	52.0±12.9	59.1±12.3	0.006

TAC: Total antioxidant capacity; TOS: Total oxidant status; OSI: Oxidative stress index.

TABLE 2: Plasma oxidative and antioxidative parameters of patients with acne vulgaris before and after 45 days on Iso treatment.

	Before Iso	After Iso	p
TAC (mmol Trolox equiv/L)	2.6±0.28	2.6±0.31	0.308
TOS (μmol H_2O_2 equiv/L)	12.4±3.5	13.7±3.71	0.035
OSI (arbitrary unit)	47.7±14.31	52±12.88	0.043

Iso: Isotretnoin; TAC: Total antioxidant capacity; TOS: Total oxidant status; OSI: Oxidative stress index.

DISCUSSION

Acne vulgaris is a distressing skin condition *regardless* of *severity,* even *the mildest forms may induce* significant *psychological and social burden on patients.*[35,36] As further investigations have been carried out to enlighten the *pathogenesis* of acne, newer treatment options in the management of this intricate disease have emerged.[16,37] OS is one of the mechanisms regarded as being responsible for the development of acne vulgaris.[17-20,22] Taking this into consideration, researchers focus on treatment modalities that will lower oxidative status of acne patients.[17,18,21,22] However, the contradiction is inevitable, as existing data suggest that Iso which is accepted to be the most effective drug in acne treatment increases OS.[5,9,13,23,24]

It is known that in acne vulgaris, sebaceous gland size and activity increases thus, sebum excretion rate is magnified.[38-40] Not only quantitative, but

also qualitative variations have been detected in sebum of acne patients. Researches exploring the composition of essential fatty acids in sebum revealed that the proportion of linoleic acid is decreased in acne comedones whereas palmitic acid is increased.[41-44] This altered ratio of fatty acids is approved to induce OS. Normally linoleic acid decreases phagocytosis and generation of ROS by neutrophils.[20,43,44] Additionally, palmitic acid decreases the amount of neutrophil-derived H_2O_2. Although palmitic acid acts as a scavenger of H_2O_2,[20,45] it is thought that H_2O_2 produced by neutrophils in acne vulgaris exceeds the amount that palmitic acid can neutralize.[45]

One of the other major contributing factors to acne development is thought to be *P. acnes*.[15,16] *P.acnes* seems to launch the inflammatory process in acne by producing neutrophil chemoattractants which prompt the accumulation of neutrophils at the site of acne comedones.[15-17] Both attracted neutrophils and *P. acnes* release lysosomal enzymes that damage follicular epithelium.[17,46] The follicular content extrude through the damaged follicle wall into the dermis, and this material both elicit a foreign body reaction and intensify the inflammatory process in these areas.[17,18,21,22] Attracted neutrophils also produce toxic molecules including ROS that further aggravate tissue damage and inflammation.[18,31] This tissue destruction at the inflammation site is called auto-oxidative damage.[47]

The first clinical investigation regarding the oxidative status of acne patients was performed by Michaëlsson and Edqvis.[48] In their study, they showed that levels of glutathione-peroxidase (GSH-Px), which is an antioxidant enzyme, were significantly lower than that of controls in male acne patients.[48] Additionally, researchers questioned other plasma oxidative parameters of acne patients including H_2O_2,[17] superoxide dismutase (SOD), catalase (CAT), glucose-6-phosphate dehydrogenase (G6PD), myeloperoxidase (MPO), malondialdehyde (MDA), nitric oxide (NO), xanthine oxidase (XO) and TAC.[18,21-23]

Although included a number of contradictory results, there are more other individual researches concluding acne patients are under systemic OS.[17,18,21,22] Still, an important question to consider before assuming OS as a putative etiologic factor in acne is whether OS is a notable cause or just merely a downstream consequence of acne inflammation.[22] In fact, human body is a dynamic system in which every metabolic process is interrelated trying to maintain oxidant-antioxidant equilibrium, despite the constant attack of free radicals.[27] On the other hand, even though the organism represents a state of overall response in terms of OS, since it is too complex and differs in detail among individuals, we hypothesize that this may be something of an overestimation to interpret the oxidative status of a person just with respect to his illness.[27] In this context, further studies with more detailed measurements are needed to comment on the oxidative status of patients with principal diseases, including acne vulgaris.

To our knowledge, this is the first prospective *study* to investigate the TAC, TOS levels and OSI values in acne patients. On the contrary to our expectations, we found serum TOS levels and OSI values of the patients lower than the controls, whereas serum TAC levels of both groups were almost similar. TAC and TOS levels of participants were measured with novel automated direct measurement methods, which are both developed by Erel. These methods are more sensitive and reliable, but since they do not match with the ones in the previous studies, it is difficult to make a definitive comparison. Moreover, as we stated before, the role of OS in acne pathogenesis, the so-called egg or chicken dilemma, still remains to be solved. Indeed, the information in the literature about oxidative status of patients with acne vulgaris is limited. On the other hand, we need to mention some limitations of our study, such as relatively small sample size and the lack of investigation of more OS parameters.

Data suggesting OS exists in acne patients spur researchers to study on therapeutic options that would increase antioxidant state of these patients.[17,18,21,22] There is compelling evidence that in addition to their antibacterial effects, some antibiotics, especially tetracyclines have an anti-inflammatory action.[49,50] Tetracyclines decrease the number of *P.acnes*, and also suppress liberation of

inflammatory mediators and inhibit neutrophil chemotaxis. Besides, tetracyclines are approved to repress the production of ROS which are produced by neutrophils. In contrast to our postulations, the sum of these data seems to suggest that both OS exist in acne patients and *P. acnes* is of importance in the pathogenesis of acne inflammation.[17]

Iso, the drug that is affirmed to mark a new era in the treatment of severe forms of acne, has also become subject of researches about OS and yet, it has not been revealed whether it decreases or increases oxidative status.[23-26,51-54] Although few, both human and animal model studies have been conducted in order to clarify this issue.[23-26,51-54] Originally, the fundamental idea which underlies these studies was the chemopreventive benefits of retinoids.[51,52,54] One of the researches carried out on patients with adult T-cell leukemia (ATL) revealed that Iso induces apoptosis of human T-cell leukemia virus type I (HTLV-I) positive lymphocytes which are found to be increased in ATL. This effect of Iso is considered to act via generation of peroxides.[51] Another chemopreventive study regarding Iso demonstrated the protective effects of the molecule against mutagenicity and carcinogenicity. Nevertheless, on the contrary to the former, results of this study displayed the antioxidant features of Iso.[52]

Besides as a chemopreventive agent, retinoids are also used in inflammatory diseases such as psoriasis and rheumatoid arthritis because of their anti-inflammatory and immunomodulatory properties.[53] As a suggestion for the treatment of inflammatory glomerular diseases, Iso is found to weaken iNOS activity/expression and NO-mediated cytotoxicity as in a manner to establish these features.[53] Iso is also known to be a potent teratogen and one of the presumed mechanisms of Iso teratogenesis is production of toxic ROS.[24-26,55] It has been shown that incubation of neural crest cell culture with Iso evokes an increased release of ROS.[25] Similarly, in another study it has been suggested that because Iso is metabolized by prostaglandin synthase to a toxic peroxyl radical, a prostaglandin synthetase inhibitor, acetylsalicylic acid may emerge as an anti-teratogenic agent.[26] Moreover, Iso teratogenicity in mouse embryos is supposed to decrease when these embryos cultured with zinc, which is an inducer of important tissue antioxidant, embryonic metallothionein.[24]

The only prospective human study about effects of Iso on OS which is conducted on acne patients was reported by Georgala et al.[23] In this study, Georgala et al. found that before treatment with Iso, both plasma TAC and 8-hydroxy-2-desoxyguanosine (8-OHdG), a serum marker of DNA oxidative damage, levels were lower in acne patients. Whereas, when compared with controls, in patients plasma TAC levels were significantly lower, but 8-OHdG levels were higher. Based on these results, Georgala et al. suggest the assumption that Iso induces DNA oxidative damage.[23]

CONCLUSION

As we have revealed increased serum TOS levels and OSI values but no significant difference in the serum TAC levels in patients after Iso, we also conclude Iso increases OS. However, existing data about the effects of Iso on OS is not only meager, but also already complicated by the divergent approaches of the researchers. Emerging researches *will further shed light in* elucidating the specific mechanisms involved in the action of Iso, thereby the role of Iso on OS and also the role of OS in the pathogenesis of acne vulgaris.

REFERENCES

1. Webster GF. The pathophysiology of acne. Cutis 2005;76(2 Suppl):4-7.
2. Burkhart CG, Burkhart CN, Lehmann PF. Acne: a review of immunologic and microbiologic factors. Postgrad Med J 1999;75(884): 328-31.
3. Fabbrocini G, Annunziata MC, D'Arco V, De Vita V, Lodi G, Mauriello MC, et al. Acne scars: pathogenesis, classification and treatment. Dermatol Res Pract 2010;2010:893080. doi:10.1155/2010/893080.
4. Newman MD, Bowe WP, Heughebaert C, Shalita AR. Therapeutic considerations for severe nodular acne. Am J Clin Dermatol 2011; 12(1):7-14.
5. Zouboulis CC. Isotretinoin revisited: pluripotent effects on human sebaceous gland cells. J Invest Dermatol 2006;126(10):2154-6.
6. Zelickson AS, Strauss JS, Mottaz J. Ultrastructural changes in sebaceous glands following treatment of cystic acne with isotretinoin. Am J Dermatopathol 1986;8(2):139-43.

7. Dalziel K, Barton S, Marks R. The effects of isotretinoin on follicular and sebaceous gland differentiation. Br J Dermatol 1987;117(3):317-23.
8. Goldstein JA, Comite H, Mescon H, Pochi PE. Isotretinoin in the treatment of acne: histologic changes, sebum production, and clinical observations. Arch Dermatol 1982;118(8): 555-8.
9. Merritt B, Burkhart CN, Morrell DS. Use of isotretinoin for acne vulgaris. Pediatr Ann 2009;38 (6):311-20.
10. James KA, Burkhart CN, Morrell DS. Emerging drugs for acne. Expert Opin Emerg Drugs 2009;14(4):649-59.
11. Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol 2006;54(4): 644-6.
12. Haider A, Shaw JC. Treatment of acne vulgaris. JAMA 2004;292(6):726-35.
13. Layton A. The use of isotretinoin in acne. Dermatoendocrinol 2009;1(3):162-9.
14. Ghalamkarpour F, Nasiri S. Isotretinoin in treatment of acne: its efficacy, side effects, and recurrence rate of disease. Arch Iran Med 2006;9(3):228-30.
15. Zouboulis CC, Eady A, Philpott M, Goldsmith LA, Orfanos C, Cunliffe WC, et al. What is the pathogenesis of acne? Exp Dermatol 2005;14(2):143-52.
16. Kurokawa I, Danby FW, Ju Q, Wang X, Xiang LF, Xia L, et al. New developments in our understanding of acne pathogenesis and treatment. Exp Dermatol 2009;18(10):821-32.
17. Akamatsu H, Horio T, Hattori K. Increased hydrogen peroxide generation by neutrophils from patients with acne inflammation. Int J Dermatol 2003;42(5):366-9.
18. Arican O, Kurutas EB, Sasmaz S. Oxidative stress in patients with acne vulgaris. Mediators Inflamm 2005;2005(6):380-4.
19. Bickers DR, Athar M. Oxidative stress in the pathogenesis of skin disease. J Invest Dermatol 2006;126(12):2565-75.
20. Briganti S, Picardo M. Antioxidant activity, lipid peroxidation and skin diseases. What's new. J Eur Acad Dermatol Venereol 2003;17(6):663-9.
21. Kurutas EB, Arican O, Sasmaz S. Superoxide dismutase and myeloperoxidase activities in polymorphonuclear leukocytes in acne vulgaris. Acta Dermatovenerol Alp Panonica Adriat 2005;14(2):39-42.
22. Sarici G, Cinar S, Armutcu F, Altinyazar C, Koca R, Tekin NS. Oxidative stress in acne vulgaris. J Eur Acad Dermatol Venereol 2010; 24(7):763-7.
23. Georgala S, Papassotiriou I, Georgala C, Demetriou E, Schulpis KH. Isotretinoin therapy induces DNA oxidative damage. Clin Chem Lab Med 2005;43(11):1178-82.
24. Blain D, Kubow S, Chan HM. Zinc pretreatment inhibits isotretinoin teratogenicity and induces embryonic metallothionein in CD-1 mice. J Nutr 1998;128(7):1239-46.
25. Davis WL, Crawford LA, Cooper OJ, Farmer GR, Thomas D, Freeman BL. Generation of radical oxygen species by neural crest cells treated in vitro with isotretinoin and 4-oxo-isotretinoin. J Craniofac Genet Dev Biol 1990; 10(3):295-310.
26. Kubow S. Inhibition of isotretinoin teratogenicity by acetylsalicylic acid pretreatment in mice. Teratology 1992;45(1):55-63.
27. Kohen R, Nyska A. Oxidation of biological systems: oxidative stress phenomena, antioxidants, redox reactions, and methods for their quantification. Toxicol Pathol 2002;30(6):620-50.
28. Cornelli U. Antioxidant use in nutraceuticals. Clin Dermatol 2009;27(2):175-94.
29. Tak PP, Zvaifler NJ, Green DR, Firestein GS. Rheumatoid arthritis and p53: how oxidative stress might alter the course of inflammatory diseases. Immunol Today 2000;21(2):78-82.
30. Yardim-Akaydin S, Sepici A, Ozkan Y, Simşek B, Sepici V. Evaluation of allantoin levels as a new marker of oxidative stress in Behçet's disease. Scand J Rheumatol 2006;35(1):61-4.
31. Davies KJ. Oxidative stress: the paradox of aerobic life. Biochem Soc Symp 1995;61:1-31.
32. Luppi F, Hiemstra PS. Epithelial responses to oxidative stress in chronic obstructive pulmonary disease: lessons from expression profiling. Am J Respir Crit Care Med 2007;175(6): 527-8.
33. Erel O. A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation. Clin Biochem 2004;37(4):277-85.
34. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005;38(12):1103-11.
35. Mosam A, Vawda NB, Gordhan AH, Nkwanyana N, Aboobaker J. Quality of life issues for South Africans with acne vulgaris. Clin Exp Dermatol 2005;30(1):6-9.
36. Martin AR, Lookingbill DP, Botek A, Light J, Thiboutot D, Girman CJ. Health-related quality of life among patients with facial acne -- assessment of a new acne-specific questionnaire. Clin Exp Dermatol 2001; 26(5):380-5.
37. Katsambas A, Dessinioti C. New and emerging treatments in dermatology: acne. Dermatol Ther 2008;21(2):86-95.
38. Pappas A, Johnsen S, Liu JC, Eisinger M. Sebum analysis of individuals with and without acne. Dermatoendocrinol 2009;1(3):157-61.
39. Janiczek-Dolphin N, Cook J, Thiboutot D, Harness J, Clucas A. Can sebum reduction predict acne outcome? Br J Dermatol 2010; 163(4):683-8.
40. Stewart ME, Benoit AM, Downing DT, Strauss JS. Suppression of sebum secretion with 13-cis-retinoic acid: effect on individual skin surface lipids and implications for their anatomic origin. J Invest Dermatol 1984;82(1):74-8.
41. Downing DT, Stewart ME, Wertz PW, Strauss JS. Essential fatty acids and acne. J Am Acad Dermatol 1986;14(2 Pt 1):221-5.
42. Pappas A, Anthonavage M, Gordon JS. Metabolic fate and selective utilization of major fatty acids in human sebaceous gland. J Invest Dermatol 2002;118(1):164-71.
43. Akamatsu H, Horio T. The possible role of reactive oxygen species generated by neutrophils in mediating acne inflammation. Dermatology 1998;196(1):82-5.
44. Akamatsu H, Komura J, Miyachi Y, Asada Y, Niwa Y. Suppressive effects of linoleic acid on neutrophil oxygen metabolism and phagocytosis. J Invest Dermatol 1990;95(3):271-4.
45. Akamatsu H, Niwa Y, Matsunaga K. Effect of palmitic acid on neutrophil functions in vitro. Int J Dermatol 2001;40(10):640-3.
46. Whiting DA. Acne. West J Med 1979;131(6): 551-7.
47. McCord JM, Fridovich I. The biology and pathology of oxygen radicals. Ann Intern Med 1978;89(1):122-7.
48. Michaëlsson G, Edqvist LE. Erythrocyte glutathione peroxidase activity in acne vulgaris and the effect of selenium and vitamin E treatment. Acta Derm Venereol 1984;64(1):9-14.
49. Webster G, Del Rosso JQ. Anti-inflammatory activity of tetracyclines. Dermatol Clin 2007;25(2):133-5, v.
50. Gange RW. Neutrophil chemotaxis in the presence of antibiotics: a re-evaluation using an agarose technique. Br J Dermatol 1980;103 (1):51-9.
51. Furuke K, Sasada T, Ueda-Taniguchi Y, Yamauchi A, Inamoto T, Yamaoka Y, et al. Role of intracellular redox status in apoptosis induction of human T-cell leukemia virus type I-infected lymphocytes by 13-cis-retinoic acid. Cancer Res 1997;57(21):4916-23.
52. Sultana S, Alam A, Sharma S, Khan N. 13-cis Retinoic acid ameliorates benzoyl peroxide-induced oxidative stress and hyperproliferative response in murine skin: a chemopreventive study. Cancer Detect Prev 2004;28(3): 200-7.
53. Datta PK, Lianos EA. Retinoic acids inhibit inducible nitric oxide synthase expression in mesangial cells. Kidney Int 1999;56(2):486-93.
54. U-Taniguchi Y, Furuke K, Masutani H, Nakamura H, Yodoi J. Cell cycle inhibition of HTLV-I transformed T cell lines by retinoic acid: the possible therapeutic use of thioredoxin reductase inhibitors. Oncol Res 1995;7(3-4):183-9.
55. Karadağ AS, Çalka Ö, Akdeniz N. [Evaluation of side effects of isotretinoin in 150 patients with acne vulgaris]. Turkderm 2011;45(1):37-42.