Effect of Systemic Retinoids on Proteins Oxidative Modification during the Treatment of Patients with Acne in Dynamics

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ABSTRACT

32 patients with acne were surveyed to study changes in total protein oxidative modification of blood. Along with the generally accepted clinical and laboratory findings in patients electrophoresis of serum proteins by the severity of oxidative stress on the content of carbonyl derivatives (in spontaneous oxidative modification of proteins) was determined.

It is proved that the treatment of acne patients with systemic retinoids is accompanied by oxidative modification of serum proteins. The consequence of these processes can be aggravating oxidative stress and increased body harmful effects caused by free radicals in tissues.

Considering not sufficient study of the effects of systemic retinoid therapy, the treatment of acne should be strictly controlled, and in the selection of the dosage form should be dominated by the principles of more bioavailability and maximum effective dosage.

Keywords: acne, oxidative modification of proteins, reactive oxygen species, protein electrophoresis, isotretinoin.

INTRODUCTION

Acne (syn: vulgaris) - extremely common worldwide chronic skin disease that affects both teenagers and adults. Different forms of acne occur in 80% of adolescents in puberty, thus, 20% of patients revealed severe illness accompanied by the formation of deep scars, virtually no effective treatment [9,10]. Besides long-term physical effects, severe acne cause psychological suffering, causing disruption of social adaptation and the development of depression. This dermatosis characterized by the severity of the inflammatory process, damaging the connective tissue with metabolic disorders of the skin and subcutaneous tissue, causes a change in the microbial landscape.

In the etiology and pathogenesis of inflammatory processes of the skin, acne have different value system interrelated factors: - the accumulation of DHT in the sebaceous glands; - Family history; - Change in the skin metabolism and other systems; - Seborrhea; - Follicular hyperkeratosis; - Violations of immune homeostasis, functions of the endocrine glands and the gastrointestinal tract; - Colonization of microorganisms; - Environmental factors and others [10,11].

Metabolic processes in the body during normal operation of hemostasis systems are accompanied by the formation of free radicals and reactive oxygen species. The content of free radicals at the physiological level is controlled with balanced work of pro- and antioxidant systems. Imbalance due to the activation of prooxidant system leads to an intensification of a free-radical process [7] and of the oxidative stress. Under these conditions a carbonyl compound having a cytotoxic effect [3,13].

Under pathological conditions effective traps generated active oxygen species are lipids, nucleic acids, proteins. The presence of pronounced peroxide oxidation of these substrates have been shown in patients with severe chronic dermatoses [5,12] and, in particular, acne [1]. However, oxidative modification of proteins (OMB) number of authors is regarded as one of the early and reliable markers [14].

Currently being sought therapy protocol based torpidly occurring acne. In the treatment of severe forms of the disease are increasingly using the system, the active ingredient isotretinoin, a chemical analog of vitamin A. These drugs are known for their cytotoxicity and even teratogenic. [2,6,8] Therefore, control of the state and destructive oxidative processes in proteins for the treatment of inflammatory processes of the skin with isotretinoin may be important in the selection of the dose and type of drug.

The purpose of the research is to study changes in the general oxidative modification of blood proteins in normal and acne treatment with systemic retinoids dynamics.

MATERIALS AND METHODS

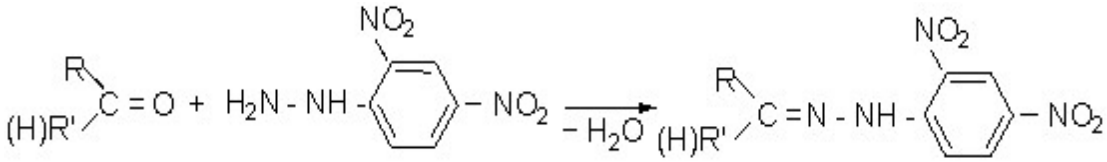
We examined 32 patients with acne. The average age of the surveyed was 21,3 ± 3,7 years. In the patient treating drugs with isotretinoin (aknekutan and roaccutane) were used.

Therapy with aknekutan or roakkutan prescribed for long term (average rate - 4-9 months). For each patient, the dose is calculated individually depending on the weight and shape of acne.

Roaccutan is used in Russia for over 20 years in capsules of 10 mg and 20 mg. Aknekutan appeared in Russia in 2010 and produced by innovative technology Lidose, developed and patented in Belgium. Product produced in capsules of 8 mg and 16 mg.

22 patients were treated with aknekutan, 10 with roakkutan. To treatment were excluded patients with dysfunction of the gastrointestinal tract, liver and lipid metabolism. The control group consisted of 20 healthy subjects of comparable age with no signs of cutaneous pathology. 3 surveys were conducted of patients: the first before treatment with systemic retinoids, the second - after 1 month, the third - after 2 months of treatment. During each assessment the study of serum protein fractions by electrophoresis was performed to determine the degree of spontaneous OMB on the level of carbonyl derivatives [3]. The basis of our method is the

definition of serum amounts of 2,4-dinitrophenylhydrazone of oxidized amino acid residues, which are formed as a result of oxidative processes in the protein molecule (Fig. 1).



Carbonyl derived protein

2,4-dinitro-phenylhydrazine

2,4-dinitrophenylhydrazone

Fig. 1. Reaction of carbonyl derivatives protein (aldehydes and ketones) with 2,4-dinitrophenylhydrazine

Absorbance formed by aldehyde and ketone-dinitro phenylhydrazone was recorded on SF-56 spectrophotometer (Spectrum Lomo, Russia) at wavelengths of 270 nm (aldehyde derivatives of neutral character), 430 nm (aldehyde derivatives main character), 370 nm (ketone derivatives neutrality), 530 nm (ketone derivatives main character).]

For data processing program Microsoft Office Excel 2010 was used.

RESULTS AND DISCUSSION

To characterize the protein homeostasis in patients with acne, we performed a serum protein electrophoresis. In the dynamics of treatment we revealed Dysproteinemia characterized by a statistically significant increase in α2 and β-globulin (Table).

Table

Indicators of electrophoretic separation of serum proteins at norm and acne (M ± m), %

		Albumins	α_1	α_2	β	ϒ
Before treatment (n=32)		54,21±0,65	3,78±0,07*	10,12±0,17*	12,21±0,47*	19,65±0,67
aknekutan	After 1 month	55,09±0,99	3,97±0,15	10,48±0,48*	11,94±0,42	18,51±0,58
	After 2 m-s	57,95±1,85	3,44±0,22*	9,13±0,39	10,98±0,75	18,49±1,25
roakkutan	After 1 month	58,00±2,6	3,78±0,17*	10,26±0,74	10,29±0,59	17,11±1,86
	After 2 m-s	51,58±0,99	4,17±0,43	11,18±0,99*	12,39±0,47*	20,66±1,45

*- statistically significant differences with the control group ($p < 0.05$)

Taking into account the available literature data, it indicates not only acute, but also on the severity of dermal manifestations. Note that hypergammaglobulinemia is not detected and it may indicate a possible immunodeficiency. Upon repeated dynamic examination of patients after

30 and 60 days, the ratio of protein fractions in serum was normalized. Thus, patients had acute-phase inflammatory response.

To modify the content of oxidative modification of proteins (aldehyde and ketone groups) we can predetermine the degree of cell damage under oxidative stress, as well as the reserve capacity of the organism to peroxidation. In the study of spontaneous OMB in the serum of patients we found a significant increase in the level of aldehyde groups neutrality of 1.5 times and ketone groups neutrality of 1.6 times in patients with acne relative to the control group. The level of ketone main character groups significantly reduced of 4.2-fold (Fig. 2).

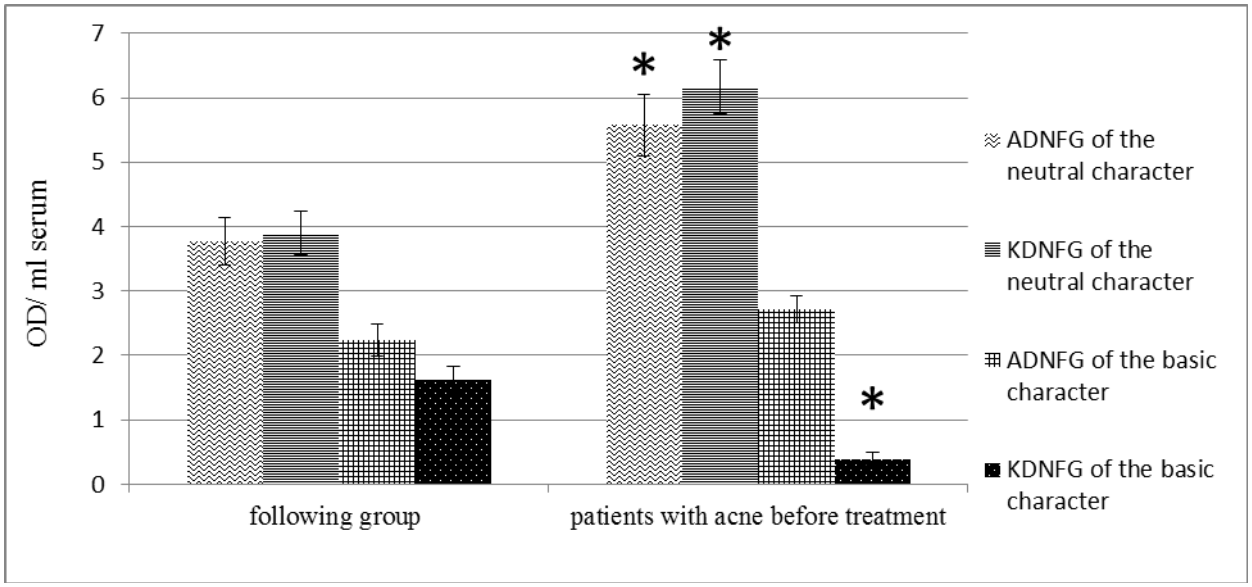


Fig. 2. The level of carbonyl derivatives of proteins in blood serum of the control group and patients with acne

* - statistically significant differences with the control group ($p < 0.05$)

ADNFG - aldehyde-dinitrophenylhydrazone

KDNFG - ketone-dinitrophenylhydrazone

Increasing the level of aldehydic and ketonic groups in patients with acne indicates that for inflammatory processes and in the conditions of oxidative stress different tissue damage occurs, including the cellular level. Reduction of ketone main character groups happens probably due to the process of intensive destruction of oxidized amino acid residues of the protein.

Treatment of acne with isotretinoin leads to normalization of the increased activity of the sebaceous glands, but its toxicity can lead to excessive formation of free radicals and the inability of the antioxidant system to neutralize them [4,7]. This was confirmed by an increase in serum levels of carbonyl derivatives during the second examination of patients. After a month of treatment with aknekutan the level of ketone groups increased by 1.3 times, and by 1.2 times for the treatment with roakkutan, compared with those before treatment (Fig. 3).

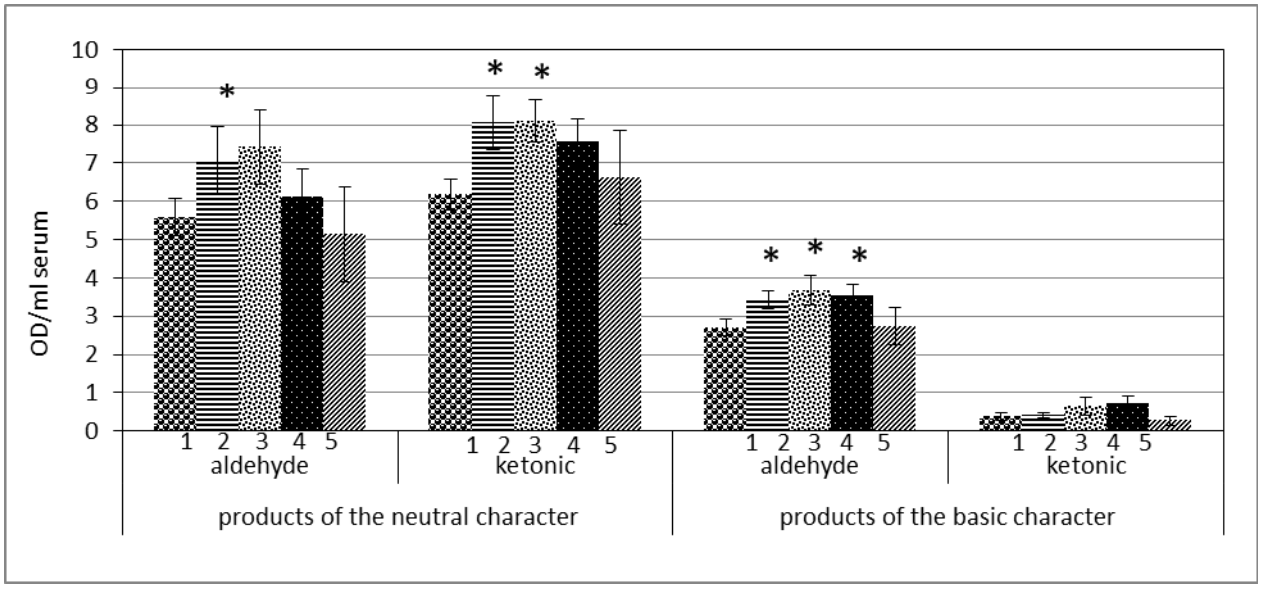


Fig. 3. The level of carbonyl derivatives for the oxidative modification of protein before the treatment with Isotretinoin (1), for the treatment with aknekutan after 1 month (2), after 2 months (3), for the treatment with roakkutan after 1 month (4), after 2 months (5).

* - statistically significant differences to before treatment ($p < 0.05$)]

At the final examination in the course of the treatment with aknekutan still celebrated slightly elevated levels of ketone groups. In the other hand, the result of the treatment with roakkutan leads to indicators reducing to the level specified in the beginning of therapy. None of the tested parameters were observed normalization parameters.

When comparing the level of aldehyde groups statistically significant increase ADNFG neutrality, both before and during the treatment relative to the control group. ADNFG a basic level significantly increased (average 1.3 times) a month after treatment with both drugs. In the third survey studied indices significantly reduced as a result of treatment with roakkutan and the treatment with aknekutan remain high.

RESULTS

It is proved that the treatment of acne patients with systemic retinoids is accompanied by oxidative modification of serum proteins. The consequence of these processes can be aggravating oxidative stress and increased body harmful effects caused by free radicals in tissues.

Considering not sufficient study of the effects of systemic retinoid therapy, the treatment of acne should be stemic retinoid therapy; the treatment of acne should be strictly controlled, and in the selection of the dosage form should be dominated by the principles of more bioavailability and maximum effective dosage.

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