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State of free-radical processes and antioxidant defence of patients with psoriasis and concomitant essential hypertension

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Key words: *Oxidative Stress, Antioxidant Defence, Psoriasis, Hypertension.*

Objective: to study the status of free-radical processes and antioxidant protection parameters in patients with psoriasis and concomitant essential hypertension.

Materials and methods. Study of oxidative status was performed in 95 patients who were divided into 3 groups: I group – psoriasis and hypertension – 25 people; II group – 30 patients with psoriasis only and group III – 40 patients with hypertension only. To assess the severity of skin lesions in psoriasis the index Psoriasis Area and Severity Index (PASI) were used. Protein oxidative destruction markers – aldehydephenilhydrazones and ketophenylhydrazones – were determined under method of B. Halliwell.

Results. Processes of carbonyl stress in the surveyed patients were studied taking into account the level of thiol-disulfide balance. Both spontaneous and stimulated aldehyde phenylhydrazone were the lowest in patients with essential hypertension, in patients with psoriasis and essential hypertension the studied indicators were higher by 75.35 and 22.03 % ($p<0.05$) respectively, in patients with psoriasis – by 123.94 and 47.55 % ($p<0.05$), respectively, than in case of hypertension. Increase of spontaneous and stimulated ketone phenylhydrazone has also been observed in the main group. In case of psoriasis without essential hypertension the considered indicators exceed the respective values of persons with essential hypertension by 123 and 64.16 % ($p<0.05$), respectively, with the presence of essential hypertension – the difference with essential hypertension was only 67.83 and 28.32 % ($p<0.05$), respectively. So, patients with psoriasis and essential hypertension had more obvious changes of indicators stipulating the progressive increase of carbonyl stress processes.

Conclusions. Thus, patients with combined pathology – psoriasis and essential hypertension – have development of oxidative and carbonyl stresses which significantly shift thiol-disulfide balance toward oxidized thiols.

Obtained results showed the activation of oxidative stress in case of the studied comorbid pathology and also complex and ambiguous system of regulation of pro- and antioxidant balance which are presented by increase of free-radical oxidation activity and decrease of physiological antioxidant defence.

Стан вільно-радикальних процесів і параметрів антиоксидантного захисту в пацієнтів, які хворі на псоріаз у поєднанні з гіпертонічною хворобою

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Мета роботи – вивчення стану вільно-радикальних процесів і параметрів антиоксидантного захисту у хворих на псоріаз із супутньою гіпертонічною хворобою.

Матеріали та методи. Вивчили оксидативний стан у 95 пацієнтів, які були поділені на 3 групи: I – псоріаз і гіпертонічна хвороба (25 осіб); II група – пацієнти лише із псоріазом (30 осіб) і III група – пацієнти лише з гіпертонічною хворобою (40 осіб). Для оцінювання тяжкості ураження шкіри при псоріазі використовували Psoriasis Area and Severity Index (PASI). Визначення маркерів окисної деструкції білків – альдегідфенілгідразонів та кетонфенілгідразонів – здійснювали за методом B. Halliwell.

Результати. Процеси карбонільного стресу в обстежених осіб вивчили з урахуванням рівня тіол-дисульфідного балансу. Як спонтанні, так і стимульовані альдегідфенілгідразони були найменшими в осіб із гіпертонічною хворобою, в пацієнтів із псоріазом і гіпертонічною хворобою досліджувані показники були вищими на 75,35 та 22,03 % ($p<0,05$) відповідно, в пацієнтів із псоріазом – на 123,94 та 47,55 % ($p<0,05$) відповідно, при гіпертонічній хворобі та без неї. Збільшення спонтанних і стимульованих кетонфенілгідразонів також було відзначено в основній групі. При псоріазі без артеріальної гіпертензії показники, що вивчали, перевищували відповідні значення осіб із гіпертонічною хворобою на 123 і 64,16 % ($p<0,05$) відповідно, з наявністю артеріальної гіпертензії різниця з гіпертонічною хворобою становила 67,83 і 28,32 % ($p<0,05$) відповідно.

Висновки. Отже, в пацієнтів, які страждають на псоріаз, за наявності гіпертонічної хвороби розвиваються оксидативний і карбонільний стреси, котрі значно порушують тіол-дисульфідну рівновагу в бік окислених тіолів.

Результати свідчать про активацію оксидативного стресу при коморбідній патології, що вивчали, а також про складну та неоднозначну систему регулювання про- та антиоксидантної рівноваги, що проявляється збільшенням активності вільно-радикального окислення та зниженням фізіологічного антиоксидантного захисту.

Ключові слова: *оксидативний стрес, антиоксидантний захист, псоріаз, гіпертонічна хвороба.*

Запорізький медичний журнал. – 2016. – № 4 (97). – С. 21–28

Состояние свободно-радикальных процессов и антиоксидантной защиты у пациентов с псориазом и сопутствующей гипертонической болезнью

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Цель работы – изучение состояния свободно-радикальных процессов и параметров антиоксидантной защиты у больных с псориазом и сопутствующей гипертонической болезнью.

Материалы и методы. Изучение оксидативного состояния проводили у 95 пациентов, которые были разделены на 3 группы: I – псориаз и гипертоническая болезнь (25 человек); II группа – пациенты только с псориазом (30 человек) и III группа – пациенты только с гипертонической болезнью (40 человек). Для оценки тяжести поражения кожи при псориазе использовали Psoriasis Area and Severity Index (PASI). Определение маркеров окислительной деструкции белков – альдегидфенилгидразонов и кетонфенилгидразонов – проводили по методу B. Halliwell.

Результаты. Процессы карбонильного стресса у обследуемых лиц были изучены с учётом уровня тиол-дисульфидного баланса. Как спонтанные, так и стимулированные альдегидфенилгидразоны были наименьшими у лиц с гипертонической болезнью, у пациентов с псориазом при гипертонической болезни изучаемые показатели были выше на 75,35 и 22,03 % ($p<0,05$) соответственно, у пациентов с псориазом – на 123,94 и 47,55 % ($p<0,05$) соответственно, при гипертонической болезни и без неё. Увеличение спонтанных и стимулированных кетонфенилгидразонов также отмечено в основной группе. При псориазе без артериальной гипертензии рассматриваемые показатели превышали соответствующие значения лиц с гипертонической болезнью на 123 и 64,16 % ($p<0,05$) соответственно, с наличием артериальной гипертензии – разница с гипертонической болезнью составила 67,83 и 28,32 % ($p<0,05$) соответственно.

Выводы. Таким образом, у пациентов с псориазом при наличии гипертонической болезни развиваются оксидативный и карбонильный стрессы, которые существенно смещают тиол-дисульфидное равновесие в сторону окисленных тиолов.

Полученные результаты свидетельствуют об активации оксидативного стресса при изучаемой коморбидной патологии, а также сложной и неоднозначной системе регулирования про- антиоксидантного равновесия, которая проявляется увеличением активности свободно-радикального окисления и снижением физиологической антиоксидантной защиты.

Ключевые слова: *оксидативный стресс, антиоксидантная защита, псориаз, гипертоническая болезнь.*

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In spite of successful results in research of the main pathogenetic aspects of psoriasis and development of innovative methods in remission achievement, the present pathology still remains one of the most actual and complicated problems of the modern dermatology. Wide prevalence of the above mentioned dermatosis among people (0.1–3 %), considerable part in structure of the general dermatologic morbidity (3–10 %), absence of unified ethiopathogenetic concept of disease are attracting attention not only of dermatologists but doctors of other specialization within many decades [1]. During last years there is held the opinion that associations of psoriasis skin manifestations with lesion of other organs, systematicity of lesions in case of psoriasis and as the result of this the definition "psoriatic disease" is more often used in scientific literature. Psoriasis is stipulated by complexity of pathogenetic inflammatory mechanisms and has many common immunologic features with other diseases of complex pathogenesis such as cardiovascular pathology [2].

During last years all researchers consider that immune disorders are the main link in psoriasis pathogenesis. In case of psoriasis there was stated the change of quantity of T- and B-lymphocytes ratio, lymphocyte ability for contact sensabilization and increase of IgG, IgA, IgE content when normal IgM level is maintained. Besides there were revealed antibodies to antigens of stratum corneum epidermal cells and stratum granulosum, antibodies to epidermis cell nuclei in extracts of lymphocytes and neutrophils. The depositions of immunoglobulins, immune complexes, antibodies and complement were revealed in epidermis of psoriatic elements by means of direct immunofluorescence technique. It may happen that development of the primary psoriatic focus is promoted by damage of epidermis owing to autoimmune aggression that confirms assumption about existence of typical psoriasis antigens to cell surface in the damaged skin. Apoptosis occurs not only in epidermis keratinocytes but first of all in derma and T-cells infiltrating epidermis [3].

It is supposed that development of comorbidities is probably based on commonness of pathogenesis of combined diseases and not depended on life style, availability of medical aid or economic factors and usually has tendency to increase with age. It is stated that psoriasis is accompanied with progressive disorganization of connective tissue combined with systemic proliferative destructive vasculitis that is the source of visceral pathology in case of the present disease. Almost part of patients with psoriasis, aged 65 and older, has at least three comorbidities and two thirds has two and more comorbidities [4]. It was mentioned that patients with exudative and pustular psoriasis have evident somatic burden. Besides of similar immunologic mechanisms there were revealed genes which are common for psoriasis and comorbidities which are occurred in case of psoriasis. This statement will be correct also for this comorbid pathology such as psoriasis and essential hypertension. Essential hypertension is still the leader in the list of the most common diseases and affects one third of adults in Ukraine. The modern therapeutic regimens of arterial hypertension based on blocking of key neurohumoral systems have permitted to decrease considerably the rate of the main cardiovascular complications of this disease (cerebral stroke and cardiac infarction) [5].

It is important to mention that combined pathology – psoriasis and essential hypertension is complex process which can not be brought to one particular mechanism. One of the most significant factors is oxidative stress. The main damaging agents in organism are the reactive oxygen species which form as the result of number of physical and chemical processes. If oxygen is included in the organism vital activity processes, the activated molecular oxygen derivatives – reactive oxygen species (ROS) shall be formed. ROS initiate reactions of free-radical oxidation (lipid peroxidation is included) leading to chemical modification and destruction of biomolecules. In tissues, due to available complicated enzymatic complexes with specific electron-transport prosthetic and coenzyme groups, oxygen recovery process occurs according to multi-level mechanism that minimizes the possibility of high reactive intermediate oxygen compounds formation [6].

Enzymatic antioxidants (AO) are stipulated by high specificity of activity and also by cell and organ localization and use of some metals (Cu, Zn, Mn, Fe) as catalysts. Level of intracellular enzymatic AO is under genetic control. In conditions of hypoxia and hyperoxia which intensify formation of reactive oxygen species the level of intracellular enzymes of AO system is increased, that is connected with mechanisms for maintaining the organism resistance to oxidative stress [7].

Many researches have proved that oxidative protein modification (OPM) is one of the first intracellular indicators of tissue lesion in case of different pathological processes including both as in case of psoriatic lesion of skin and essential hypertension. As the result of oxidative protein modification reactions the significant depression of many enzymes activity, including the Krebs cycle enzymes and antioxidant defence factors, occurs.

OPM products damage membranes of mithochondria leading to the stable metabolic disturbances. OPM causes changes

of physical and chemical properties of the protein molecule: fragmentation, aggregation and susceptibility to proteolysis. As the result, the formation of products with high functional activity will occur. Acute intensification of oxidative processes in case of insufficient antioxidant defence system will lead to development of oxidative stress which is one of the universal mechanisms for damages of the organism tissues. Accumulation of OPM products will cause toxic and apoptotic death of cells of different organs and systems [8].

Superoxide dismutase (SOD) is enzyme which catalyzes reaction of dismutation of superoxide anion radicals with formation of hydrogen peroxide and triplet oxygen. SOD belongs to the most widely studied proteins because it is the key enzyme providing directly break of oxygen dependent free radical reactions chains in cells of aerobic organisms. Up to now there are obtained three types of human SOD. For their functioning there are required manganese, copper and zinc. Copper-zinc form (Cu, Zn-SOD) is contained in cytosol and intermembranous space of mithochondria, Mn-SOD is located in mithochondria. Extracellular high molecular form of SOD, containing copper, is considered the third type of enzyme – eSOD [9].

Catalase (H_2O_2-oxidoreductase) – is enzyme related to the class of oxidoreductases and catalyses heterolytic decomposition of O-O-bond in hydrogen peroxide and, thus, is the synergist of superoxide dismutase in the cell. Catalase is always available in systems where the transportation of electrons with participation of cytochromes performs, i.e. where hydrogen peroxide, toxic for the cell, is generated. It locates mainly in the cell peroxisomes where its concentration is 10^{-6} mole and cytoplasm. Besides the typical function of catalase – high-effective catalysis of hydrogen peroxide decomposition into water and oxygen, the enzyme shows moderate peroxide activity, i.e. catalyzes reactions of different electron donors oxidation with hydrogen peroxide [10].

Now processes of peroxidation of protein structures are rather actively studied by different researchers but in the modern literature there is lack of information as to pathogenetic meaning of metabolism disturbance of free radicals as an important link of vascular endothelium functional state disturbance, in particular, among patients with associated psoriatic pathology that stipulates actuality for studying of this problem and open new possibilities for searching the methods for correction of these disturbances [11]. Numerous concomitant somatic diseases, which the patients with psoriasis have, considerably impede selection of effective and adequate treatment method. Many drugs intended for psoriasis treatment are not combined in complex therapy and if they are simultaneously prescribed they can cause exacerbation of the process or its transition into more complicated form. As the result of this the attention is paid to the perspective for investigation of key pathogenesis links of this combined pathology such as psoriasis and essential hypertension, search for new therapy methods of this comorbidity with regard to efficiency and safety even during long-term application [12].

Objective: studying of oxidative status parameters of patients having psoriasis with concomitant essential hypertension.

Subject and methods of research

Results of the present research are based on data of complex examination and dynamic observation of 55 patients with psoriasis who had treatment in hospital of "Dermatovenerologic Clinical Dispensary of Zaporizhzhia region" of Zaporizhzhia Region Council; among them 25 persons have arterial hypertension. Experimental group was presented by 40 patients with essential hypertension who had been examined in Cardiologic Department of Municipal Hospital No.7 in Zaporizhzhia. For reliability of results the patients with arterial hypertension presented by only essential hypertension of II stage with 1–3 stage hypertension level of different cardiovascular risk without adequate systematic antihypertensive therapy participate in this research. According to complex clinical, anamnestic, instrumental and laboratory examination all patients had no data indicating chronic kidney disease or lesion of renal vessels. Groups of patients were compared according to the main clinic-demographic data. Psoriasis was diagnosed under "Adapted Clinic Guide" (2013) for diagnostics and treatment of psoriasis. Essential hypertension was diagnosed under recommendations of Association of cardiologists of Ukraine (2013). All patients agreed in written form for participation in this research.

Thus, all patients were divided into 3 groups: I – psoriasis + essential hypertension – 25 persons; II group – patients only with psoriasis – 30 persons and III group – patients with essential hypertension – 40 persons. In the I and the II groups the lesion of skin among the majority of patients was widespread. In order to estimate severity of psoriasis there was used Psoriasis Area and Severity Index (PASI), which is the objective clinical system for determination of affected surface of body and intensity of dermatosis the main symptoms. If PASI index is 10 – the mild rate of psoriasis is stated, PASI index from 10 to 30 characterizes the medium rate of psoriasis, PASI index of more or equal 30 – the heavy rate of psoriasis.

All patients of the I and the II groups had standard treatment in dermatological hospital. They had detoxicating and hyposensitizing therapy, hepatoprotectors, sedative drugs, vitamins, in case of heavy forms – cytostatics (methotrexate); physiotherapy; all patients had topical therapy. After examination the traditional adequate antihypertensive therapy with personal selection of treatment was prescribed for patients of the I and the III groups.

Protein oxidative destruction markers – aldehydephenilhydrazones (AFH); ketophenylhydrazones (KFH) was determined under method of B. Halliwell which is based on reaction of interaction of oxidized amino-acid residues with 2,4-dinitrophenylhydrazine (2,4-DNPhH) with formation of 2,4-dinitrophenylhydrazones [18,19]. For initiation of oxidative protein modification there was used Fenton's medium (0.1 M phosphate buffer pH 7.4, 1 mM Fe^{2+}, 0.3 mM H_2O_2). For oxidative protein modification there was performed their preliminary sedimentation by means of 20% trichloracetic acid solution. 0.1 ml of 25% trichloracetic acid is to be added into 0.1 ml of plasma and centrifuged within 30 minutes at 3000 rev./min (at temperature of 15 °C). 1 ml of 2,2% 2,4- dinitrophenylhydrazine (prepared on the basis of 7% hydrochloric acid solution) shall be added to sediment which had been remained after centrifugation and shall be incubated within 1 hour at temperature of 37 °C, then it shall be centrifuged within 10 minutes at 3000 rev./min (at temperature of 15 °C). The sediment shall be flushed with 3 ml of ethyl acetate and diluted in 3 ml of 50% urea solution and 1 drop of 7% hydrochloric acid solution shall be added and

12-fold diluted with distilled water. Prepared solution shall be processed with spectrophotometer at the wave length of 274. 363 nm, compensation solution is 0.5 M phosphate buffer. If the wave length is 274 nm the content of AFH shall be determined and if the wave length is 363 nm the content of carboxylphenolhydrazones (CPhH) shall be determined. There were determined spontaneous and metal-catalysed (with tdivalent iron) AFH and CPhH.

Determination of SOD activity. Principle of the method: SOD competes with nitroblue tetrazolium (NBT) for superoxideradicals which form as the result of aerobic interaction of NAD and phenazine methosulfate (PhMS). As result of this reaction NBT will be recovered to hydrazinetetrazolium. If SOD is present, the percentage of NBT recovery will be changed.

The study of heart rate variability was performed using computerized diagnostic system "CARDIOLAB" ("Cardiloab plus", complete SEC "KAI-Medicom", Kharkiv, Ukraine) according to standards working group of the European Society of Cardiology and the North American Society of stimulation and Electrophysiology. Evaluated the following options: SDNN (total index variability values of RR intervals for all the period), pNN50 (The percentage of pairs of successive intervals NN, differing by more than 50 ms – the total number of NN intervals), CV (coefficient of variation). Settings frequency analysis included: TP (total power of heart rate variability spectrum), HF (Relative power high frequency); LF (low frequency relative power), VLF (very low relative power frequency); LF / HF (ratio low to high frequency part of the spectrum), as well as the ratio of sympathetic and parasympathetic influences.

Studied values are presented in form: selective average value ± standard error of the average meaning. Normality of distribution was estimated under criteria of Kolmogorov-Smirnov (D), Lilliefors and Shapiro-Wilk (W). In case of distribution which differs from the normal one or analysis of order constants there was used Mann-Whitney U for two unbounded sampling for more samplings Kruskal-Wallis H criterion with further comparison under Games-Howell was used. To study and assess the impact of factors and possible covariance on the several dependent variables multivariate analysis of variance (MANOVA) was performed. Results of research were processed with application of statistical package of license program STATISTICA® for Windows 6.0 (StatSoft Inc., No. AXXR712D833214FAN5) in Medical Informatics Department of Zaporizhzhia State Medical University and also by means of SPSS 16.0, Microsoft Excel 2010. Separate statistical procedures and algorithms are implemented in form of specially written macros in the certain programs. Results are presented in form: average value ± standard error of representation of the average value. Differences at level of significance of<0.05 were considered valid.

Results and their discussion

Numerous researches of different authors show that the main pathologic processes in case of psoriasis are disturbance of dynamic balance of structural processes in epidermis – proliferation, differentiation and apoptosis (programmed death of cells) which regulate cellular homeostasis; immune skin inflammation owing to disturbances in immunity cellular link and changes of cytokine profile; disturbances of neurohumoral and lipid metabolism of skin and macroorganism. During many years the role of each of these factors is being studied. In many native and foreign publications there was stated that all above mentioned systems are closely connected with each other and the shifts in any of them directly react with certain changes in other systems which intended for compensation of initial systems. When possibilities of compensations on the part of other systems are exhausted the development of pathological processes with appropriate clinical presentations shall start [13].

Required constancy of qualitative and quantitative parameters enables the following processes: cellular regeneration, well-directed migration of cells in epidermis, cytodifferentiation with transformation of keratinocytes into corneocytes; death of keratinocytes, rejection of corneocytes from the epidermis surface or exfoliation; intercellular interactions. Now many researchers suppose that in case of psoriasis one of pathogenetic mechanisms is disturbance of dynamic balance of structural processes in epidermis: proliferation, differentiation and cellular death which regulate cellular homeostasis. Some researchers believe that morphologic sense of psoriasis is in disturbance (acceleration) of division of epidermis cells and this disease should be considered as presentation of the skin hyperplastic potential [14].

Besides the scientists determine the place of processes which influence the following differentiation and apoptosis of epidermis cells in the psoriasis pathogenesis [15]. Apoptosis is required for formation and maintaining of normal organism structure and is the protection mechanism and also can cause development of many diseases.

Activation of free-radical oxidation is one of the factors causing damage of endothelium, disorganization of biomembranes and cell junctions, decrease of anti-thrombogenic potential and enables further disturbance of microcirculation and homeostasis. Increased formation and accumulation in tissues of reactive oxygen species (ROS), reactive molecules and free radicals cause overstress and failure in functioning of antioxidant defence (AOD) having the minimum potential with formation of oxidative stress in connective tissue [16].

Human Antioxidant system (AOS) is the system blocking formation of highly active free radicals, i.e. ROS. In normal physiological conditions small quantity of oxygen is constantly converted into superoxide anions, hydrogen peroxide and hydroxyl radicals. Excess products of these radicals are the damaging factor, compensatory mechanism of which is AOS. The main component of this system is AOD enzyme network: superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT) and paraoxonase (PON). System of antioxidant enzymes performs its main functions in the following way: superoxide dismutase connects reactive oxygen species with formation of hydrogen peroxide; catalase destroys peroxides into lipid hydroperoxides; glutathione peroxidase reduces lipid hydroperoxides due to oxidation of glutathione; glutathione reductase regenerates glutathione by means of NADPH which is regenerated through cytochrome chain and system of natural antioxidants (α- tocopherol, ascorbic acid, flavonoids). In this case the activity of enzymes is evolutionary and genetically programmed for optimization of balance of oxidative processes and activity of antioxidant defence systems [17,18].

A lot of data of different researchers confirm our idea that oxidative stress is one of nonspecific links of pathogenesis of

many diseases including psoriasis and essential hypertension and stipulated by increasing of free radicals level. Free radicals are very reactive and damage cells of cutaneous covering and vascular endothelium with development of hyperkeratosis and inflammation process in keratinocytes and increased vasoconstriction [19]. Disturbance of dynamic balance pro- and antioxidant system leads to change of generation of free radicals that, in its turn, sufficiently influences metabolism of nitric oxide (NO) – universal biological regulator of vascular tone and peripheral blood flow, enabling disturbance of processes of its bioavailability and stipulating demonstration of endothelial dysfunction. Excess products of superoxide, its accumulation in tissues of vessels and prevalence over antioxidants cause oxidative stress state which starts or intensifying many reactions of vasospasm and hyperkeratosis. Superoxide directly or through product of its interaction with nitric oxide – peroxynitrites ($ONOO^-$) enables to initiate processes of free-radical oxidation and damage of biopolymers of vessel wall mainly lipids. If direct role of superoxide radical in oxidation of low-density lipoproteins is considered obvious, the effect of peroxynitrite is undoubted for causing excess products of oxidated low-density lipoproteins. These mechanisms of oxidative stress (disturbance of vascular endothelium and activation of hyperkeratosis process) enable progression of disease and increase of cardiovascular risk of development of complications in case of essential hypertension [20].

Free radicals damage proteins along the whole length of polypeptide chain disturbing not only the secondary and tertiary but the primary structure of proteins. In case of oxidative stress depending on intensity of regeneration processes of reactive oxygen species, almost all amino acids are subject to oxidative modification that is accompanied with aggregations and fragmentation of protein molecules. As result of free-radical oxidation the protein modification changes its antigenicity, makes it more sensible to endogenous proteolysis. Proteolytic enzymes (trypsin, chymotrypsin, pepsin, cathepsins D, subtilopeptidase A) more quickly disintegrate oxidized proteins than native ones [21]. Formed pool of damaged proteins activates proteolysis that enables further increase of intensification of destructive processes in area of inflammation. Many researches in different time had proved that products of protein free-radical oxidation mediate oxidative damages of DNA. Protein peroxidation also leads to decrease of protein function in electron carrier chain, selectiveness of activity of transport pores. Oxidative protein modification is one of the earliest indicators of tissue lesion in case of free-radical pathology [22].

When the protein oxidation occurs the aldehydic and ketonic groups of amino-acid residues (carbonyl groups) shall be formed. Their increased level can be early and sensible marker of free-radical damage since the plasma proteins which had been subject to oxidative destruction have sufficiently long period of half-disintegration. It was proved by numerous researches showing that OPM products, in case of oxidative stress, appear in tissues earlier and they are more stable than LPO products (malondialdehyde, diethenoid conjugates, schiff bases) [23]. With all advantages of methods for determination of lipid peroxidation it is shown that after several minutes LPO products are subject to detoxication in contrast to them the oxidized proteins can be kept in cells for hours and even days. All above mentioned facts permit to consider change of oxidative level and modified proteins and their products (carbonyl groups) as the most stable and perspective markers which reflect intensity of free-radical processes and oxidative stress in case of comorbid pathology such as psoriasis and essential hypertension [24].

Processes of carbonyl stress of the examined persons were studied by means of estimation of level of aldehyde and ketonic forms of phenylhydrazones (*Table 1*). Persons with essential hypertension had the minimum both spontaneous and stimulated AFH and persons with psoriasis and essential hypertension had the values higher for 57.43% ($p<0.05$) and 47.55% ($p<0.05$) respectively, patients with psoriasis – for 23.27% ($p<0.05$) and 22.03% ($p<0.05$) respectively, than in case with essential hypertension. Increase of spontaneous and stimulated KFH was mentioned in groups of patients with psoriasis. In case of psoriasis without arterial hypertension the studied indicators exceeded the existing values among persons with essential hypertension for 24.35% ($p<0.05$) and 28.32% ($p<0.05$) respectively, in case of arterial hypertension the difference with essential hypertension made 48.19% ($p<0.05$) and 64.16% ($p<0.05$) respectively. Thus, patients with psoriasis and essential hypertension have more obvious changes in indicators stipulating progressive increase of carbonyl stress processes.

During analysis of antioxidant systems (*Table 2*) the results showing progressive disturbance of antioxidant link were obtained. Thus, content of catalase among persons with psoriasis together with essential hypertension is for 37.04% ($p<0.05$) lower than among patients with psoriasis without essential hypertension and for 41.27% ($p<0.05$) lower than in case with essential hypertension. Difference between two last groups of examined persons was valid and made 124.37% ($p<0.01$). Among patients with psoriasis and essential hypertension there

Table 1

Differences of protein molecule oxidative modification processes in the studied groups

Indicator, unit	Patients with psoriasis		Patients with essential hypertension
	Without essential hypertension	With essential hypertension	
AFH spontaneous, conven. unit/g protein	2.49±0.06(2.37–2.62)*	3.18±0.11(2.96–3.39) *#	2.02±0.17 (1.08–2.75)
AFH stimulated, conven. unit/g protein	3.49±0.07(3.36–3.63)*	4.22±0.13(3.97–4.47) *#	2.86±0.26 (2.34–3.38)
KFH spontaneous, conven. unit/g protein	4.8±0.17(4.46–5.15)*	5.72±0.29(5.13–6.31) *#	3.86±0.31 (2.24–4.49)
KFH stimulated, conven. unit/g protein	5.8±0.21(5.38–6.21)*	7.42±0.4(6.61–8.22) *#	4.52±0.48 (3.57–5.48)

Notes: * – differences with essential hypertension are valid ($p<0.05$); # – differences comparing to group with psoriasis without essential hypertension are valid ($p<0.05$).

Table 2

State of activity of antioxidant systems of examined persons

Indicator, unit	Patients with psoriasis		Patients with essential hypertension
	Without essential hypertension	With essential hypertension	
Catalase, conven. unit./mg protein/min	1.89±0.1(1.69–2.09)*	1.19±0.11(0.97–1.41) *#	2.67±0.08 (1.51–2.84) *
Superoxide dismutase, conven. unit./mg protein/min	32.58±1.63*	24.21±1,44 *#	36.84±1.09

Notes: * – differences with essential hypertension are valid ($p<0.05$); # – differences comparing to group with psoriasis without essential hypertension are valid ($p<0.05$).

was noticed the valid decrease of SOD content. Difference between values of persons with psoriasis affected by essential hypertension and of persons with psoriasis without essential hypertension made 25.69% ($p<0.05$), in its turn their average values were for 13.08% ($p<0.05$) and 52.17% ($p<0.05$) lower respectively than in case with essential hypertension. Hence, the development of psoriasis affected by essential hypertension was accompanied by multidirectional change on the part of antioxidant systems activity.

Performed multiple-factor analysis of variance within frames of mathematical simulation showed that clinical state (level of PASI index) of patients with psoriasis affected by essential hypertension was determined by integral changes of oxidative status (was estimated under ratio of level of SOD to AFH stimul.) at $F=22.13$ ($p<0.01$) and was conjugated with severity of arterial hypertension ($F=9.61$, $p<0.05$), degree of circadian rhythm variability violation ($F=4.88$, $p<0.05$). Thus, performed analysis of available literary data and our results shows that psoriasis should be considered as typical multiple-factor disease aggravated by comorbidity with arterial hypertension. In these complicated pathogenetic mechanisms of combined pathology the important role belongs to oxidative stress as the reason of damage and degeneration of keratocytes.

Pathogenesis of free-radical damage affected by psoriasis is explained by the following reasons. Mitochondria are the main energy producers in the cell and form adenosine triphosphate (ATPh) by means of oxidative phosphorylation. These organelles react to any changes in intra- and extracellular matrix and participate in programmed cell death – apoptosis. The important regulator of normal mitochondrion functioning is the mitochondrial pore. It is high-selective potential-depending ion channel of the inner membrane. The most important role of mitochondrial pore is to maintain required pH-gradient and membrane potential for performing oxidative phosphorylation [25]. Calcium overburden enables opening of mitochondrial pore causing disjunction of oxidative phosphorylation process. It leads the excess quantity of water supply into mitochondria, their swelling and break of the external mitochondrial membrane with release of cytochrome C and other pro-apoptotic factors into cytosol. Number of experimental researches showed that inhibition of oxidative stress can decrease permeability of mitochondrial pore and prevent programmed death of the cell. In particular, natural antioxidant of mitochondria electron-transport chain – coenzyme Q10 (ubiquinone) can limit damage of mitochondria in case of oxidative stress. However there are problems with its supply into mitochondria because it can be integrated not only in mitochondrial membranes but others. This limitation is removed by means of ions penetrating into mitochondria [26].

Quick development of obvious oxidative stress in organism cells is connected with damage and death of these cells under necrosis mechanism. Since necrosis is connected with sharp damage of membranes, the protein peroxidation processes, which are considered as nonspecific mechanisms of membrane pathology, play the main role in implementation of this scenario of the cell death. Necrosis process is accompanied with development of the secondary damage of adjacent cells group to the affected area. Cells involved into necrosis are swollen and this process is accompanied with lysis of their organelles and formation of the secondary lysis stipulating by specific and rather complicated morphology. Necrotic death of cells naturally leads to development of local inflammation process which is able to cause death of adjacent cells [27]. Apoptotic death of cells is also accompanied with activation of peroxidation of lipids but in less extent it is connected with protein oxidative modification processes. Multiple impacts, inducing apoptosis, implement their effect through oxidative stress development. Role of LPO in development of apoptosis is mainly connected with free-radical destruction of cardiolipin in the mitochondrion internal membrane. Oxidative destruction of cardiolipin is considered as important factor of redistribution of cytochrome C from mitochondria into cytoplasm that is the main event in apoptosis induction under the internal mechanism. Oxidative stress causes changes in mitochondrion membrane permeability. In case of apoptosis the so-called PTP-pores (permeability transient channels) are opened in membranes of mitochondria. Their opening is accompanied with exit of mitochondrial content into cytosol, disturbance of oxidative phosphorylation due to depolarization of the internal membrane of mitochondria, intensive penetration of calcium ions and water into mitochondria that finally will lead to swelling of mitochondria. The latter is finished with lysis of mitochondrial membranes with redistribution of mitochondrial content into cytosol [28].

Very often in pathogenesis of different pathologies including such combined pathology as psoriasis and essential hypertension the oxidative stress is combined with carbonyl one, which is occurred as result of aldehyde and carbonyl groups containing active compounds concentration increasing. These compounds include glyoxal, methyl glyoxal, 3-hydroxyglucozone which are the products of oxidation of glucose and other sugars. Active carbonyl compounds are also malondialdehyde and 4-hydroxynonenal. The above mentioned compounds modify aminoacid residues of proteins and nitrogenous bases of nucleic acids and change the properties of these important biomolecules. Modi-

fied proteins are the markers of diseases and other pathologies occurred in case of oxidative stress. Oxidative modification processes occur in organism with normal functioning due to systems of oxidation catalyzing by metals [29]. At the present moment protein oxidation is considered as one of the regulating factors of protein synthesis and disintegration and it is considered that rate of turnover of intracellular proteins depends on ration of oxidative modification processes with further proteolysis and synthesis de novo. Selective proteolysis prevents accumulation of oxidized molecules and formation of protein aggregates in the cell [30]. It permits to make conclusion that formation and progress of psoriasis affected by essential hypertension are reliably connected with activation of free-radical processes with parallel depression of organism antioxidant systems.

Conclusions

1. Obtained results of complex examination and dynamic observation for patients show the activation of oxidative stress in case of the comorbid pathology such as psoriasis and essential hypertension and also complex and ambiguous system of regulation of pro- and antioxidant balance which are presented by increasing of free-radical oxidation activity and decreasing of physiological antioxidant defence.

2. Patients with combined pathology – psoriasis and essential hypertension have development of oxidative and carbonyl stresses which significantly shift thiol-disulfide balance toward oxidized thiols that enables mitochondrial dysfunction with lack of cell energy reserves that, in particular, is actively developed in comorbid state conditions.

Perspectives of further researches. In future the perspective trends are the estimation of influence of antioxidant therapy on intensity of dermatological signs in patients with psoriasis in particular in combination with essential hypertension.

Conflicts of Interest: authors have no conflict of interest to declare.

References

1. Peluso, I., Cavaliere, A., & Palmery, M. (2016) Plasma total antioxidant capacity and peroxidation biomarkers in psoriasis. *J Biomed Sci*., 4, 23(1), 52. doi: 10.1186/s12929-016-0268-x.
2. Borska, L., Andrys, C., Krejsek, J., Palicka, V., Chmelarova, M., Hamakova, K., et al. (2014) Oxidative damage to nucleic acids and benzo(a)pyrene-7,8-diol-9,10-epoxide-DNA adducts and chromosomal aberration in children with psoriasis repeatedly exposed to crude coal tar ointment and UV radiation. *Oxid Med Cell Longev*., 2014, 302528. doi: 10.1155/2014/302528.
3. Gubskij, Yu. I., Belenichev, I. F., Levickij, E. L., & Pavlov, S. V. (2005) Toksikologicheskie posledstviya okislitel´noij modifikacii belkov pri razlichnykh patologicheskykh sostoyaniyakh [Toxicological consequences of protein oxidative modification in case of different pathological states]. *Suchasni problemy toksikolohii*, 3, 20–26. [in Ukrainian].
4. Lin, X., & Huang, T. (2016) Oxidative stress in psoriasis and potential therapeutic use of antioxidants. *Free Radic Res*., 50(6), 585–95. doi: 10.3109/10715762.2016.1162301.
5. Sirenko, Yu. M. (2011) *Hipertonichna khvoroba i arterialni hipertenzii [Essential hypertension and arterial hypertensions]*. Donetsk: Zaslavskyi O. Yu. [in Ukrainian].
6. Gu, X., Nylander, E., & Coates, P. J. (2015) Oxidation reduction is a key process for successful treatment of psoriasis by narrow-band UVB phototherapy. *Acta Derm Venereol*., 95(2), 140–6. doi: 10.2340/00015555-1905.
7. Bakry, O. A., El Hefnawy, S., & Mariee, A. H. (2016) Urinary Biopyrrins: A New Marker of Oxidative Stress in Psoriasis. *Indian J Dermatol.*, 61(2), 169–73. doi: 10.4103/0019-5154.177756.
8. Schesnokova, N. P., Ponikalina, E. V., & Bizenkova, M. N. (2006) Melokulyarno-kletochnye mekhanizsmy inaktivacii svobodnykh radikalov v biologicheskikh sistemakh [Molecular-cellular mechanisms of inactivation of free radicals in biological systems]. *Uspekhi sovremennogo estestvoznaniya,* 7, 29–36. [in Russian].
9. Nemati, H., Khodarahmi, R., Sadeghi, M., Ebrahimi, A., Rezaei, M., & Vaisi-Raygani, A. (2014) Antioxidant status in patients with psoriasis. *Cell Biochem Funct*., 32(3), 268–273. doi: 10.1002/cbf.3011.
10. Doroshuk, A. D. (2007) *Strukturno-funkcionalnye osobennosti mitokhondrij pri e´xperimental´noj gepertonii razlichnogo geneza* (Dis… dokt. biol. nauk). [Structural and functional features of mitochonria in case of experimental hypertension of different genesis. Dr. biol. sci. diss.]. Moscow. [in Russian].
11. Yazici, C., Köse, K., Utaş, S., Tanrikulu, E., & Taşlidere, N. (2016) A novel approach in psoriasis: first usage of known protein oxidation markers to prove oxidative stress. *Arch Dermatol Res*., 308(3), 207–12. doi: 10.1007/s00403-016-1624-0.
12. Menshikova, E. B., Zenkov, N. K., Lankin, V. Z., et al. (2008) *Okislitel´nyj stress: patologicheskie sostoyaniya i zabolevaniya [Oxidative stress: pathological states and diseases]*. Novosibirsk: ARTA. [in Russian].
13. Asefi, M., Vaisi-Raygani, A., Khodarahmi, R., Nemati, H., Rahimi, Z., Vaisi-Raygani, H. et al. (2014) Methylentetrahydrofolatereductase (rs1801133) polymorphism and psoriasis: contribution to oxidative stress, lipid peroxidation and correlation with vascular adhesion protein 1, preliminary report. *J Eur Acad Dermatol Venereol*., 28(9), 1192-8. doi: 10.1111/jdv.12262.
14. Rajappa, M., Shanmugam, R., Munisamy, M., Chandrashekar, L., Rajendiran, K., & Thappa, D. M. (2016) Effect of antipsoriatic therapy on oxidative stress index and sialic acid levels in patients with psoriasis. *Int J Dermatol.,* 55(8), e422-30. doi: 10.1111/ijd.13196.
15. Menshikova, E. B., Zenkov, N. K., & Lankin, V. Z. (2006) *Okislitelnyi stress: perooksidanty i antioksidanty [Oxidative stress: Peroxides and antioxidants]*. Moscow: Slovo. [in Russian].
16. Elango, T., Dayalan, H., Gnanaraj, P., Malligarjunan H., & Subramanian, S. (2014) Impact of methotrexate on oxidative stress and apoptosis markers in psoriatic patients. *Clin Exp Med*., 14(4), 431–7. doi: 10.1007/s10238-013-0252-7.
17. Sezer, U., Şenyurt, S. Z., Gündoğar, H., Erciyas, K., Üstün, K., Kimyon, G., et al. (2016) Effect of Chronic Periodontitis on Oxidative Status in Patients With Psoriasis and Psoriatic Arthritis. *J Periodontol*, 87(5), 557–65. doi: 10.1902/jop.2015.150337.
18. Kolesnik, Yu. M., Belenichev, I. F., & Gancheva, O. V. (2005) Signal´naya rol´ aktivnykh form kisloroda v regulyacii fiziologicheskikh funkcij [Signal role of reactive oxygen species in regulation of physiological functions]. *Pathologia,* 2(1), 4–10. [in Ukrainian].
19. Aydin, E. Karabacak, E., Ozcan, O., & Dinc, M. et al. (2013) Comment on "Serum methylglyoxal level and its association with oxidative stress and disease severity in patients with psoriasis". *Arch Dermatol Res*., 305(7), 671–2. doi: 10.1007/s00403-013-1400-3.
20. Sunitha, S., Rajappa, M., & Thappa, D. M. (2015) Comprehensive lipid tetrad index, atherogenic index and lipid peroxidation: Surrogate markers for increased cardiovascular risk in psoriasis. *Indian J Dermatol Venereol Leprol*., 81(5), 464–71. doi: 10.4103/0378-6323.163734.
21. Kilic, S., Emre, S., Metin, A., Isikoglu, S., & Erel, O. (2013) Effect of the systemic use of methotrexate on the oxidative stress and paraoxonase enzyme in psoriasis patients. *Arch Dermatol Res.*, 305(6), 495–500. doi: 10.1007/s00403-013-1366-1.
22. Golikov, A. P., Boitsov, S. A., & Mikhin, V. P. (2003) Svobodno-radikalnoe okislenie i serdechno-sosudistaya patologiya: korrekciya antioksidantami [Free-radical oxidation and cardiovascular pathology: correction with antioxidants]. *Lechaschij vrasch*, 4, 70–74. [in Russian].

23. Matoshvili, M., Katsitadze, A., Sanikidze, T., Tophuria, D., D'Epiro, S., & Richetta, A. (2015) Evaluation of blood redox-balance, nitric oxide content and CCR6 in the genetic susceptibility during psoriasis. *Georgian Med News*., 240, 37–43.
24. Kaur, S., Zilmer, K., Leping, V., & Zilmer, M. (2013) Serum methylglyoxal level and its association with oxidative stress and disease severity in patients with psoriasis. *Arch Dermatol Res.,* 305(6), 489–94. doi: 10.1007/s00403-013-1362-5.
25. Ikonomidis, I., Makavos, G., Papadavid, E. et al. (2015) Similarities in coronary function and myocardial deformation between psoriasis and coronary artery disease: the role of oxidative stress and inflammation. *Can J Cardiol*., 31(3), 287–95. doi: 10.1016/j.cjca.2014.11.002.
26. Bacchetti, T., Campanati, A., Ferretti, G., Simonetti, O., Liberati, G., & Offidani, A. M. (2013) Oxidative stress and psoriasis: the effect of antitumour necrosis factor-α inhibitor treatment. *Br J Dermatol*., 168(5), 984–9. doi: 10.1111/bjd.12144.
27. Karbach, S., Croxford, A. L., Oelze, M., Schüler, R., Minwegen, D., Wegner, J., et al. (2014) Interleukin 17 drives vascular inflammation, endothelial dysfunction, and arterial hypertension in psoriasis-like skin disease. *Arterioscler Thromb Vasc Biol*., 34(12), 2658–68. doi: 10.1161/ATVBAHA.114.304108.
28. Karababa, F., Yesilova, Y., Turan, E., Selek, S., Altun, H., & Selek, S. (2013) Impact of depressive symptoms on oxidative stress in patients with psoriasis. *Redox Rep*., 18(2), 51–5. doi: 10.1179/1351000213Y.0000000039.
29. Ozdemir, M., Kiyici, A., Balevi, A., Mevlitoğlu, I., & Peru, C. (2012) Assessment of ischaemia-modified albumin level in patients with psoriasis. *Clin Exp Dermatol*., 37(6), 610–4. doi: 10.1111/j.1365-2230.2012.04384.x.
30. Lyakhovych, V. V., Vavilin, V. A., Zenkov, N. K. et al. (2006) Aktivnaya zaschita pri okistitel´nom stresse. Antioksidant-responsivnyj e´lement [Active protection in case of oxidative stress. Antioxidant-responsive element]. *Biokhimiya*, 71(9), 1183–1197. [in Russian].

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