

Clinical Research

Serum Nitric Oxide Metabolites Concentration in Patients with Psoriasis

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Abstract

The blood serum of psoriasis patients, regardless of the clinical forms of the disease, contains a high concentration of the main stable nitric oxide metabolites. The complex therapy resulted in significant clinical improvement and a considerable decrease in the nitric oxide concentration, in all the studied forms of dermatosis. As the measurement of the nitric oxide concentration is a very important link in the chain of nonspecific body reactivity, it permits an objective assessment of the pathological activity process and therapy efficacy. *IJBM* 2011; 1(4):210-212. © 2011 International Medical Research and Development Corporation. All rights reserved.

Key words: nitric oxide, endothelial NO-synthase, inducible NO-synthase, peroxynitrite.

Introduction

Psoriasis is the chronic inflammatory immune dependent genodermatosis of multifactorial genesis characterized by enhanced proliferative keratitis activity. Articular expressions of psoriatic skin are the results of a long-term inflammatory process against the background of the development of complex interdependent pathoimmune and biochemical mechanisms connected with changes in the regulatory systems, intensity of the catabolic processes and oxidative metabolism, besides epidermal proliferation.

Serum nitric oxide (NO), acts as one of the universal regulators of physiological and biochemical processes and has, therefore, attracted the special attention of researchers, over recent years [1, 2]. DNA damage leads to impairment of NO synthesis from L-arginine, the main enzymes of which include, the NO-synthases (NOS): neuronal (nNOS), endothelial (eNOS), inducible (iNOS) and mitochondrial (mNOS) synthases. NO-small pleiotropic free radical is a vital alarm molecule in inflammatory diseases and hyperplastic processes.

The inflammatory component is one of the essential symptoms of the pathogenesis of psoriasis, which progresses, with periodic aggravations, accompanied by an inflammatory reaction, of varying severity. In this study, the role of nitric oxide (NO) in inflammation regulation is

intensively studied.

NO can influence various stages of inflammation, either blocking or stimulating the inflammatory response [3]. This depends upon the NO concentration, type and degree of cell activation, effect of other inflammation mediators etc. Skin changes during dermatosis are assumed to be connected with its interaction with neutrophilic leukocytes and activated T-lymphocytes, increased expression of proinflammatory cytokines, changes in their receptors, as well as the state of the NO system. As the morphofunctional changes of epidermal keratinocytes have been noted to play a significant role in the pathogenesis of psoriasis, the literature data relating to iNOS and NO identification in the keratinocytes have attracted special interest [4]. One of explanations for the hyperproliferation of keratinocytes in psoriasis is the local decrease in iNOS activity and, therefore, insufficient NO production. The biphasic antiproliferative NO effect has been described: low NO concentrations stimulate keratinocyte proliferation *in vitro*; while high NO concentrations inhibit cellular proliferation, thus inducing differentiation. Therefore, the multifunctional alarm NO molecule, present in several growth regulators, as well as in keratinocyte differentiation, is recognized as one of the key factors in psoriasis pathogenesis [4].

In this context, a probable relationship between the NO-system and processes of keratinocyte growth regulation and their differentiation can be assumed, and therefore, any disturbance in its activity could be an indicator of its important role in the pathogenesis of psoriasis.

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Material and methods

The study included 82 patients with the various clinical forms of psoriasis, between the ages of 18 and 50 years, the average age being 37.4 years. There were 51 men and 31 women in all. The disease had been present from between 1 and 30 years. The hereditary character of dermatosis was observed in 15 (18.3%) patients. The clinical picture of disease was characterized by papulo-squamous eruptions. The arthropathic form of the disease was established in 21 patients. In patients with psoriatic arthritis, the arthritis was most often diagnosed in the distal and interphalangeal joints. The control group included 20 practically healthy volunteers, similar in age.

Assessment of the NO-system was performed by measuring the concentration of blood serum NO, including eNOS and iNOS activities.

The NO level was evaluated as the sum of the stable metabolites of nitrates and nitrites (NO_2 and NO_3) using the technique followed by Golikov et al. [5]. The activity of eNOS was measured using the method developed by Sushbaev V.V. and Yasinskiy I.M. [6]. The iNOS activity was estimated by the change in the reaction velocity of enzyme NADPH-dependent HP, which was determined by the procedure developed by Vavilova T.P. and Petrovich Y.A. [7]. The level of peroxynitrite (ONNO_2^-) was determined by employing technique followed by Asimov R.K. and Komarin A.S. [8]. The endothelin 1 (ET-1) level was measured using the hard-phase immune enzyme assay (IEA).

Results

An analysis of the obtained results revealed that in all the patients, irrespective of the clinical forms of psoriasis, high concentrations of the basic stable NO metabolites were noted in the blood serum. Significantly, in patients with the vulgar and arthropathic forms of psoriasis, the blood serum NO concentrations were found to be 38.37 ± 1.364 and 40.95 ± 1.625 $\mu\text{mol/l}$; these values were higher than the control value by 25.5% ($p < 0.01$) and 33.9% ($p < 0.01$), respectively.

Considering that the NO level is controlled by eNOS and iNOS activities, a study of their working mechanisms in the blood of psoriasis patients is of particular interest.

Analysis of the data showed that the eNOS activity in the blood serum decreased, while the activity of iNOS correspondingly increased. Therefore, in patients with the vulgar and arthropathic forms of psoriasis, the eNOS blood serum levels were noted to be 29.24 ± 1.851 and 30.72 ± 1.487 $\mu\text{mol/min/l}$; these were lower than the value of the control data by 29.1% ($p < 0.001$) and 25.5% ($p < 0.01$), respectively.

Simultaneously, the iNOS activity in the blood serum of the patients with the vulgar and arthropathic forms of psoriasis was observed, and noted to be 0.47 ± 0.027 and 0.56 ± 0.028 $\mu\text{mol/min/l}$; these were higher than the control value by 23.7% ($p < 0.001$) and 47.4% ($p < 0.02$), respectively.

Thus, the investigations performed showed that the

inhibition of eNOS activity with the corresponding stimulation of the iNOS expression could be one of the possible causes for the mechanisms of NO concentration in the blood serum of patients with the various clinical forms of psoriasis. With the latter, the increase in concentration of the highly cytotoxic compound (ONNO_2^-) in the blood, could be significant.

To confirm this suggestion, an investigation was conducted in this study, to observe the (ONNO_2^-) concentration in the blood serum of psoriasis patients. The investigations performed showed that patients with the vulgar and arthropathic forms of psoriasis had (ONNO_2^-) concentrations in the blood serum of 0.16 ± 0.008 $\mu\text{mol/l}$ and 0.17 ± 0.006 $\mu\text{mol/l}$, respectively; these were definitely higher than the control values by 45.5% ($p < 0.01$) and 54.5% ($p < 0.001$), respectively.

Therefore, based on the data obtained, it may be suggested that the increase in the (ONNO_2^-) could be a sequence to the iNOS high activity. (ONNO_2^-) expression is capable of free radical oxidation. With the latter, an interaction with angiotensin II can be suggested, which produces a strong vasoconstrictor effect. The effect of angiotensin II is closely connected with the increase in ET-1. This was the basis on which this investigation was conducted to study the ET-1 content in the blood.

The results of these investigations showed that in patients with the vulgar and arthropathic forms of psoriasis the ET-1 concentration accounted for 0.53 ± 0.032 ng/ml and 0.57 ± 0.035 ng/ml; these were higher than the values of the parameters in the control by 10.4% ($p < 0.05$) and 18.8% ($p < 0.001$), respectively.

Thus, the investigations performed showed that in the blood serum of the patients with psoriasis the expressions of iNOS, (ONNO_2^-) and ET-1 are noted, which could be one of the causes of the disorders in the NO-system activity.

One of explanations of such a significant increase the NO concentration may be expressed by the inflammatory reaction observed at the time of aggravation of dermatosis. All patients received the complex therapy including desensibilization agents, antihistamine preparations, vitamin therapy and photochemotherapy (PUVA) using methoxsalen as the photosensibilizer. The complex therapy for patients with severe clinical signs and torpid evolution of dermatosis included lacto-FLOR, with anti-inflammatory and immune modeling properties, in a 10 ml intravenous dose, 10 injections as a course, as well as an enzymatic preparation "Wobenzym" (Mucos Pharma GmbH, Germany), 5 tablets, thrice daily. Therapy was performed based on routine blood and urine analyses and biochemical blood examination.

On analysis of the results received, it became evident that on termination of the treatment a resolution of the clinical expressions of dermatosis was seen coupled with a significant reduction of the main stable NO metabolites in the blood serum levels, which appeared to approach the values of the control group. Thus, patients with the vulgar and arthropathic forms of psoriasis had concentrations of NO metabolites in the blood serum with values of 30.72 ± 1.369 and 32.2 ± 1.427 $\mu\text{mol/l}$; these were less than the values prior to treatment by 19.9% ($p < 0.05$) and 21.4% ($p < 0.01$), respectively.

It thus appears that among the important factors

encouraging the restoration of the concentrations of the main stable NO metabolites in the blood serum of patients with psoriasis, the activation of eNOS and decrease in the level of the reaction of iNOS were significant.

Therefore, in patients with the vulgar and arthropathic forms of psoriasis, the eNOS activity was noted to be 40.81 ± 1.647 and 39.47 ± 1.233 $\mu\text{mol}/\text{min}/\text{l}$, which were higher when compared with the data before treatment, by 39.6% ($p < 0.001$) and 28.5% ($p < 0.001$), respectively. The expressive activity values of iNOS in the blood serum of patients with the vulgar and arthropathic forms of psoriasis were 0.39 ± 0.027 and 0.39 ± 0.031 $\mu\text{mol}/\text{min}/\text{l}$, which were lower when compared with the data before treatment by 17.0% ($p < 0.01$) and 30.4% ($p < 0.01$), respectively.

Evidently, the highly toxic compound, (ONO_2^-), showed a decrease in the blood serum of the psoriasis patients because of the complex therapy, which resulted in a decrease in the iNOS expression. In patients with the vulgar and arthropathic forms of psoriasis after treatment, the concentration of (ONO_2^-) in the blood serum was 0.11 ± 0.005 $\mu\text{mol}/\text{l}$ and 0.12 ± 0.004 $\mu\text{mol}/\text{l}$, and it dropped lower when compared with the values of the parameters before therapy by 31.25% ($p < 0.001$) and 29.4% ($p < 0.001$).

Positive changes in the NO-system due to complex therapy may be correlated to the attenuation of the local effect of the vasoconstrictor ET-1 on the endothelium. Evidently, in accordance with the data presented in this study, in patients with the vulgar and arthropathic forms of psoriasis, the ET-1 levels accounted for 0.49 ± 0.021 ng/ml and 0.50 ± 0.025 ng/ml until the end of therapy, and they significantly dropped compared with the values of the parameters before treatment, by 7.5% ($p < 0.01$) and 12.3% ($p < 0.05$), respectively.

Conclusion

The data of this study confirmed the vital role played by NO in the pathogenesis of psoriasis. The NO concentration in the blood serum considerably increased in patients with severe symptoms of disease. The complex

therapy resulted in significant clinical improvement and a considerable decrease in the NO concentration, in all the studied forms of dermatosis. The NO level, being pivotal in the system of nonspecific body reactivity and occupying a key position in the pathogenesis of psoriasis, may be considered one of the current high-sensitive criteria of inflammation. Its definition permits an objective estimation of the intensity of inflammatory response, activity of the pathological process, success of the therapy, as well as an opportunity to propose the prognosis of dermatosis.

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