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Serum and Tissue Angiotensin Converting Enzyme in Patients with Psoriasis

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ABSTRACT

Recent evidence suggests that the angiotensin converting enzyme (ACE) is present in skin. The real value of the determination of ACE activity as a clinical-biochemistry test for the diagnosis of psoriasis has not been attained. Serum and tissue ACE were measured in 60 patients with psoriasis, 20 patients with lichen planus, 20 patients with seborrhoic dermatitis and in 20 healthy individuals. The serum and tissue ACE activity was determined before and after therapy, using the spectrophotometric method and hippuryl-l-histidyl-l-leucine as a substrate. The results showed that serum ACE activity before therapy was significantly increased in both groups – patients with psoriasis ($p<0.001$) and patients with lichen planus ($p<0,001$) in comparison to healthy individuals. However, there were no significant differences in serum ACE activity among patients with seborrhoic dermatitis and healthy individuals. After therapy, serum ACE activity significantly decreased in both groups of patients with psoriasis and patients with lichen planus comparing it to the level found in the control group. The values in both were similar. The tissue ACE activity in altered skin was significantly increased only in the patients with psoriasis in comparison to uninvolved skin of these patients, as well as the skin of healthy individuals. After therapy, there were no significant differences in tissue ACE activity between the treated skin and the healthy skin. In conclusion, determination of tissue angiotensin converting enzyme activity can be used in the differential diagnostic of indistinct clinical forms of psoriasis.

Key words: *angiotensin converting enzyme, psoriasis, serum, tissue*

Introduction

The renin angiotensin system (RAS) plays a crucial endocrine role in the physiology of blood pressure and electrolyte balance[1]. An increasing number of studies suggest the existence of local angiotensin generating systems which operate, in whole or in parts, independently of the circulating RAS[2]. These have been described for brain, kidney, adrenal gland, testis, artery walls, heart, and other tissues. Recent findings suggest that the complete RAS is present in human skin and plays a role in normal cutaneous homeostasis.

Angiotensin converting enzyme (ACE; kininase II, EC 3.4.15.1), one of the key elements of the RAS, is a zinc metalloendopeptidase that is widely distributed on the surface of endothelial and epithelial cells. ACE removes the carboxy terminal dipeptide from the decapeptide angiotensin I to generate angiotensin II, a potent vasoconstrictor, and degrades bradykinin, a vasodilator[3–4].

Investigations of ACE in dermatology are very scarce and little is known about the possible role of ACE in the pathogenesis of skin diseases.

Raff et al.[5] first found an increase of serum ACE in patients with psoriasis, and this was confirmed by other studies[6–9]. Recent studies have shown that ACE inhibitors have been implicated in its cause. However, the mechanism by which ACE inhibitors could cause a flare up of the pre-existing disease is not clear.

However, no firm attitude on the determination of the ACE activity as a clinical-biochemistry test for the diagnosis of psoriasis has been attained.

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An increase of level ACE was also found in the sinovial fluid[7] in patients with psoriasis. Furthermore, there are no published data on the ACE activity in the tissue of skin except for a preliminary study in a low number of patients with psoriasis[10].

The effect of therapy on serum ACE activity in psoriasis has been examined only in a few studies. It was observed that serum ACE activity decreased after therapy[8]. In our recent study we also found the decrease of serum ACE activity after treatment of the disease, and there was no significant difference response between various forms of treatment[11].

Furthermore, the effect of therapy on tissue ACE activity in patients with psoriasis was not studied.

The aim of the present study was to investigate serum and tissue ACE activity in patients with psoriasis and the possible influence of therapy on serum and tissue ACE activity.

Subjects and Methods

Subjects

The sample of subjects included 60 patients suffering from psoriasis; 20 patients suffering from lichen planus; 20 patients with seborrhoic dermatitis, while 20 subjects served as Control. The patients with diseases that might influence the serum ACE activity (sarcoidosis, arterial hypertension, pulmonary tuberculosis, hepatic diseases, diabetes mellitus, and others) were excluded from the study. Patients with psoriasis included 60 patients of both sexes, aged 35–45 years, who were being medically treated. The diagnosis of psoriasis was made on the basis of a clinical examination and biopsy findings at the Department of Dermatology, the University Clinic Centre in Sarajevo. Patients with psoriasis received matching either local therapy (10% ol. candidi, 5–10% salicylvaseline), photochemotherapy (8-methoxypsoralen as photosensibilisator in dose 0.6 mg/kg body weight) or cytostatic therapy (methotrexate 25 mg per week, total dose 100 mg). The patients with lichen planus included 20 patients of both sexes (10 men and 10 women), aged 35–45 years, who were being medically treated. The diagnosis of lichen planus was made on the basis of a clinical examination and biopsy findings at the Department of Dermatology, the University Clinic Centre in Sarajevo. The patients with seborrhoic dermatitis included 20 patients of both sexes (10 men and 10 women), aged 35–45 years, who were being medically treated. The diagnosis of seborrhoic dermatitis was made on the basis of clinical examination and biopsy findings at the Department of Dermatology, the University Clinic Centre in Sarajevo. The control group consisted of subjects of both sexes (10 men and 10 women), aged 35–45 years, who were healthy according to their subjective and objective findings.

Laboratory and other analyses

Routine laboratory analyses, including erythrocyte and leukocyte counts, erythrocyte sedimentation rate, hematocrit, hemoglobin, urea, uric acid, creatinine, triglycerides, cholesterol, and glucose levels, as well as a complete urine analysis, were performed in each patient. A biopsy of skin was taken in all patients with psoriasis for a pathohystologic analysis

Serum and tissue sampling

Serum and tissue ACE activity was measured in patients with psoriasis before and after therapy. Blood samples for the determination of serum ACE activity were taken from the cubital vein. After coagulation and centrifugation at 2,000 *g* for 5 min, the serum was frozen at –20 °C until analysis. After the biopsy all the tissues skin samples were weighed and washed extensively with 0.9% NaCl solution (4 °C) for blood elimination. The tissues were placed in the mixture of sodium phosphate buffer (0.065 mol/L, pH 8.3, and 0.5 mol/L NaCl; 50 mg/mL) and stored at –20°C. The tissues were homogenized in a Teflon coated Potter-Elvehjem homogenizer, adding one drop of a nonionic surfactant (Nonidet P 40) to each samples. After centrifugation at 4,000 *g* for 30 min, the supernates were frozen at –25 °C until determination of ACE activity.

Measurement of ACE activity

Serum and tissue ACE was determined by the spectrophotometric method using hippuryl-*l*-histidyl-*l*-leucine (Sigma, St. Louis, Mo., USA) as a substrate (12), and a Perkin Elmer 550 S spectrophotometer for optical readings. The enzyme activity is expressed in units: 1 U corresponds to 1 nmol of hippuric acid released by hydrolysis of hippuryl-*l*-histidyl-*l*-leucine per minute and liter of serum or 50 mg of the tissue.

Statistics

Serum ACE activity is expressed as mean values ± SEM. Differences between the mean values were statistically compared using Student's and paired t-test. Probability values of less than 0.05 were considered significant.

Finally as an methodological remark. We are aware of the fact that we did not include data of the severity/size of the psoririatic tensions, but we believe that since: (a) we excluded patients with diseases that might influence the serum ACE activity, and (b) we performed extensive statistical analysis it did not influence our conclusions significantly.

Results

Figure 1 shows the mean values of the serum ACE activity in patients with psoriasis, lichen planus and seborroic dermatitis before and after treatment.

Serum ACE activity was significantly increased in both patients with psoriasis (35.02 ± 2.07; X ± SEM; $p<0.001$) and patients with lichen planus (35.90 ± 2.09; $p<0.001$) before therapy in comparison to the healthy individuals (28.16 ± 1.70). However, there were no significant differences in serum ACE activity among patients with seborrhoic dermatitis before therapy (31.44 ± 2.79)

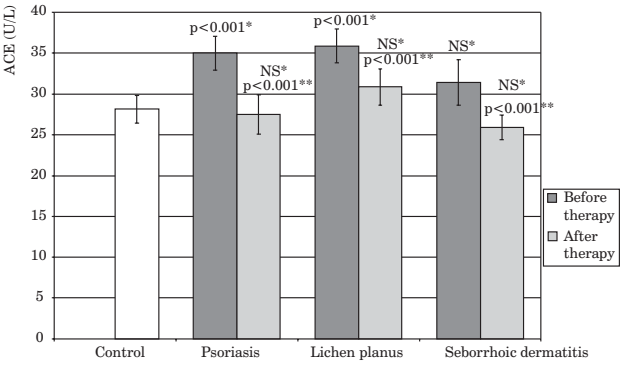

*Fig 1. Serum ACE activity (mean ± SEM) in patients with psoriasis, lichen planus and seborrhoic dermatitis before and after therapy (Control – control group; Psoriasis – patients with psoriasis; Lichen planus – patients with lichen planus; Seborrhoic dermatitis – patients with seborrhoic dermatitis; NS – not significant: p – probability; * – in comparison with control group; ** – in comparison with the values before therapy.*

and healthy individuals. After therapy, serum ACE activity significantly decreased in both patients with psoriasis and patients with lichen planus to a level which was similar to the control group.

Figure 2 shows the tissue ACE activity in patients with psoriasis.

The tissue ACE activity was significantly increased in the skin lesions of the patients with psoriasis (4.14 ± 0.43); the mean activity was by 122% higher than in skin of the healthy subjects (1.86 ± 0.16; $p<0.0001$). There were no significant differences in the tissue ACE activity between the uninvolved skin of the patients with psoriasis (2.25 ± 0.18) and the skin in healthy subjects.

Figure 3 shows the mean values of the tissue ACE activity in patients with psoriasis, lichen planus and seborroic dermatitis before and after therapy.

Before treatment the ACE activity was increased in the lesional skin of the patients with psoriasis in comparison with the skin of the control group ($p<0.001$). However, the tissue ACE activity in the skin lesions of both

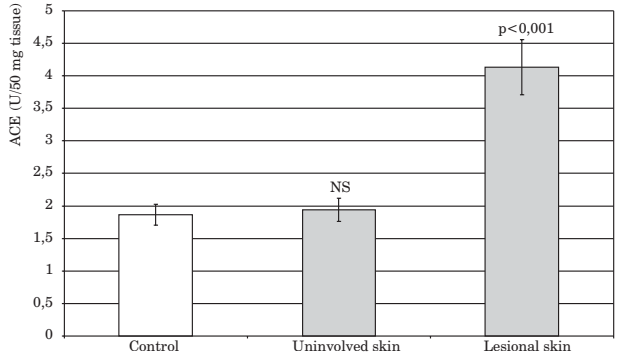

Fig 2. Tissue ACE activity (mean ± SEM) in patients with psoriasis (Control – control group; Uninvolved skin – Uninvolved skin of patients with psoriasis; Lesional skin – Lesional skin of patients with psoriasis; NS – not significant; p – probability).

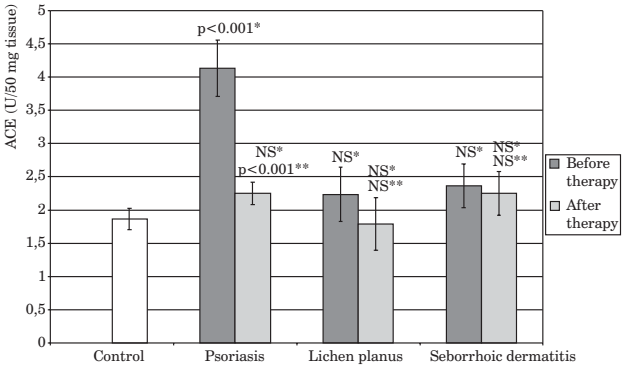

Fig. 3. Tissue ACE activity (mean ± SEM) in patients with psoriasis, lichen planus and seborrhoic dermatitis before and after therapy. (Control – control group; Psoriasis – patients with psoriasis; Lichen planus – patients with lichen planus; Seborrhoic dermatitis – patients with seborrhoic dermatitis (N=20; 10 men

the patients with lichen planus and the patients with seborrhoic dermatitis was similar to the skin of the control group.

The effect of treatment on the tissue ACE activity in patients with psoriasis is also shown in figure 3. The tissue ACE activity in the skin lesions decreased by 46%after treatment in the patients with psoriasis in comparison with the mean activity before therapy ($p<0.001$).

Discussion

Conflicting data concerning the presence of enhanced serum angiotensin-converting (SACE) activity in psoriasis are reported in literature[13–15]. Our study clearly showed that the mean serum ACE activity is significantly increased in both groups of patients with psoriasis and patients with lichen planus in comparison with healthy subjects. These results are in accordance with previous studies[6–9]. However, no significant difference in the serum ACE activity was observed between the patients with dermatitis seborrhoica and the healthy individuals. In addition, our earlier study showed no significant differences in the serum ACE activity in the different clinical forms of psoriasis[16]. The presented results indicate that a determination of the serum activity cannot be helpful in differential diagnosis of psoriasis and for a differentiation of the clinical forms of psoriasis.

After the treatment, the serum ACE activity in our study decreased in both groups of patients with psoriasis and patients with lichen planus and reached a level, which was not significantly different from that in the control group. Also, the results of our previous studies showed that there was no significant different response among the various forms of treatment of patients with psoriasis[11]. This implies that the serum ACE activity in these patients might be used as an adjunct in the monitoring of the disease activity and may be one of the most important parameters in the assessment of the used therapy effects.

Our study also shows that the tissue ACE activity was significantly increased in the skin lesions of the patients with psoriasis in comparison to the skin of healthy individuals. However, we did not find any alterations of the tissue ACE activity in either groups of patients with lichen planus and the patients with seborrhoic dermatitis. Our results pointed to the possibility that the determination of tissue ACE activity can be used at the differential diagnosis of indistinct clinical forms of psoriasis.

The mechanism responsible for the increase of the serum ACE activity in psoriasis is not clear. Recent studies have demonstrated that ACE inhibitors could induce or exacerbate psoriasis[17–22]. Since the administration of ACE inhibitors would result in increased levels of substance P, Abraham and Farber[23] suggest that ACE inhibitors could provoke an exacerbation of psoriasis by enhancing the substance P-induced neuronal inflammation in the skin. In addition, several reports suggest that substance P, through neuronal inflammation, plays a key role in psoriasis[24–25]. Some authors suggest a build-up of bradikinin as a possible cause of flare of the disease during the treatment with ACE inhibitors. Furthermore, it is well known that vascular ACE is an ectoenzyme mainly expressed in the endothelial cells. In addition, a soluble ACE is found in serum, which is presumably derived from the membrane-bound form[26]. Since it has been suggested that there is a widespread abnormality of the capillaries in the skin of patients with psoriasis[27], we believe that damage to the blood vessel endothelium during psoriasis might be responsible at least for a higher release of ACE from vascular endothelium in the blood. Also more capillaries are perfused in both plaque and uninvolved psoriatic skin then in the normal skin, and capillaries in the psoriatic plaque skin are much larger than in normal skin[28]. Thus, the increased blood flow in the psoriatic plaque[29] might be an additional causative factor for the increased enzyme release in the blood. However, in our presented study we have not found any significant difference in the tissue ACE activity between the uninvolved skin of patients with psoriasis and the skin in healthy subjects. Although the role of locally generated Ang-II is not well established, we believe that it may be involved in the development of psoriatic plaque. These data do not show whether the increase of ACE activity in the skin lesions of patients with psoriasis is a primary process having a pathogenic role or is only a secondary result of some independent process. Obviously, this is the main question that should be answered in further investigations.

In future studies it will be interesting to evaluate the eventual influence of the estrogen level on the sensitivity and specificity of a tissue ACE activity, but also to use eventual multivariate analysis of the differences which are showed to be statistically superior to univariate methods we used herein[30–31].

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SERUMSKI I TKIVNI ANGIOTENZIN-KONVERTIRAJUĆI ENZIM U PACIJENATA S PSORIJAZOM

S A Ž E T A K

U posljednje vrijeme postoje dokazi kako je angiotenzin-konvertirajući enzim (ACE) prisutan u koži. Međutim, valjanost procjene ACE aktivnost kao kliničkog biokemijskog testa za dijagnozu psorijaze još nije utvrđena. Serumski i tkivni ACE mjeren je kod 60 pacijenata sa psorijazom (P), 20 pacijenata s lichen planus-om (LP) i 20 pacijenata koji su bolovali od seboroičnog dermatitisa (SD), kao i kod 20 zdravih pojedinaca koji su služili kao kontrolna grupa (K). Kod P, LP i SD mjerenja su provedena prije i nakon terapije spektrofotometrijski uz upotrebu hippuryl-l-histidyl-l-leucine kao supstrata. Rezultati su pokazali kako je serumska ACE aktivnost prije terapije bila značajno povišena kod P i LP, a u usporedbi s K. Međutim nisu utvrđene značajne razlike između SD i K. Nakon terapije, serumska ACE aktivnost značajno se smanjila kod P i LP. Tkivna ACE aktivnost oboljele kože bila je povećanja samo kod P, a u usporedbi sa zdravom kožom kod istih pacijenata. Nakon terpaije nisu uočene značajne razlike između tretirane kože i zdrave kože. Zaključno. određivanje tkivne ACE aktivnost može se upotrebiti u različitim diferencijalnim dijagnozama kliničkih formi psorijaze.