Serum and Tissue Angiotensin Converting Enzyme in Patients with Lichen Planus

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Abstract

Serum and tissue angiotensin-converting enzyme (ACE) was measured in 20 patients with lichen planus before and after therapy, and in 20 healthy individuals. Serum and tissue ACE activity was determined by spectrophotometric method using hippuryl-l-histidyl-l-leucine as a substrate. The enzyme activity is expressed in the following units: 1 U corresponds to 1 nmol of hippuric acid released by hydrolysis of hippuryl-l-histidyl-l-leucine per minute and one liter of serum or 50 mg tissue. Before therapy, serum ACE activity was significantly increased in patients with lichen planus (35,9 ± 2,33 U/L) in comparison to healthy individuals (28,16 ± 1,7 U/L). Tissue ACE activity was increased in patients with lichen planus (2,24 ± 0,41 U/50 mg) in comparison to healthy individuals (1,86 ± 0,16 U/50 mg), but the difference was not significant. After therapy, serum and tissue ACE activity decreased and no significant dif¬ference in ACE activity was found. The determination of serum ACE activity may be a good non-specific parameter for the assessment of therapeutic effects.

KEY WORDS: angiotensin converting enzyme, lichen planus, serum, therapy.

Introduction

Angiotensin converting enzyme (ACE; kininase II, EC 3.4.15.1) is widely dis¬tributed at the surface of endothelial and epithelial cells. This enzyme catalyzes the conversion of inactive decapeptide angiotensin I into active octapeptide angiotensin II, and the inactivation of the nonapeptide bradykinin (1). Subsequent investigations showing the existence of a local renin angiotensin system in the brain, kidney, adrenal gland, testis, artery walls, heart, skin and other tissues, alongside the circulatory renin angiotensin system, have pointed to a new physiological role of this very complex system (2). Investigations of ACE in dermatology are very scarce and little is known about potential role of ACE in pathogenesis of skin diseases. Recent studies have shown changes in renin angiotensin system in various skin diseases (3-5). Lichen planus is a relatively common skin disorder of unknown etiology. While most cases of lichen planus are idiopathic, some may be caused by the ingestion of certain medications (6). Recent studies have shown that angiotensin-converting enzyme inhibitors were implicated in its cause (7,8). However, the mechanism by which ACE inhibitors could flare the pre-existing disease is not clear. Raff et al. (3) reported that the serum ACE activity is increased in patients with lichen planus. However, the real value of ACE activity determination as a clinical-biochemistry test for the diagnosis of lichen planus has not been attained. Furthermore, the effect of therapy on serum ACE activity in patients with lichen planus was not studied and no data on tissue ACE activity in patients with lichen planus were published. The aim of the present study was to investigate serum and tissue ACE activity in patients with lichen planus and the possible influence of therapy on serum and tissue ACE activity.

Subjects and Methods

1. SUBJECTS

Patients with diseases that may influence serum ACE activity (sarcoidosis, arterial hypertension, pulmonary tuberculosis, hepatic diseases, diabetes mellitus, and others) were excluded from the study. Control group consisted of 20 subjects of both sexes (10 male and 10 female) 35-45 years of age, who were healthy according to subjective and objective findings. Study group included 20 patients with lichen planus of both sexes (10 male and 10 female), 35-45 years of age, who were medically treated. The diagnosis of lichen planus was made on the basis of clinical examination and biopsy findings at the Department of Dermatology, University Hospital in Sarajevo.

2. 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 on each patient. A biopsy of the skin was done in all patients with lichen planus for a pathohystologic analysis.

3. SERUM AND TISSUE SAMPLING

Serum and tissue ACE activity was measured in patients with lichen planus before and after therapy. Blood for the determination of serum ACE activity was drawn from cubital vein. After coagulation and centrifugation at 2,000 g for 5 min, serum was frozen and stored at -20 °C until further analysis. After biopsy, all tissues were weighed and extensively washed in 0,9% NaCl solution (40C) for blood elimination. The tissues were placed in 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 Teflon coated Potter-Elvehjem homogenizer, with one drop of a nonionic surfactant (Nonidet P 40) in each sample. After centrifugation at 4,000 g for 30 min, the supernates were frozen at -20 °C until determination of ACE activity.

4.MEASUREMENT OF ACE ACTIVITY

Serum and tissue ACE was determined by spectrophotometric method using hippuryl-l-histidyl-l-leucine (Sigma, St. Louis, Mo., USA) as a substrate (9), and Perkin Elmer 550 S spectrophotometer for optical reading. The enzyme activity is expressed in the following units: 1 U corresponds to 1 nmol of hippuric acid released by hydrolysis of hippuryl-l-histidyl-l-leucine per minute in one liter of serum or 50 mg of the tissue.

4. STATISTICS

Serum ACE activity is expressed as mean values ± SEM. Differences between the mean values were statistically compared using Student's and paired t-tests. P-values less than 0,05 were considered significant.

Results

Figure 1 illustrates that serum ACE activity was significantly increased in patients with lichen planus; the latter having a mean value by 27% higher than that found in healthy subjects ($p<0,001$). No signifi-

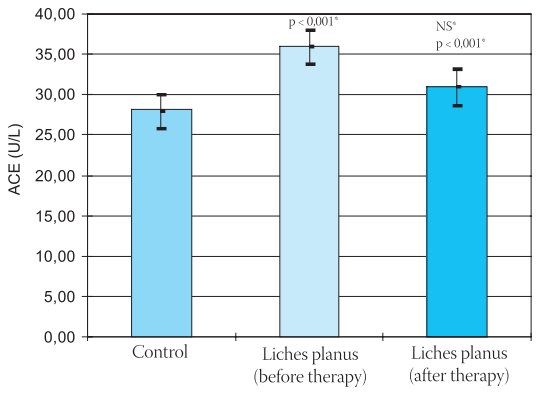

FIGURE 1. Serum ACE activity (mean±SEM) in patients with lichen planus before and after therapy.
CONTROL – control group (healthy subjects; N=20;10 male and 10 female)
LICHEN PLANUS - patients with lichen planus (N=20; 10 male and 10 female)
NS - not significant
* - in comparison with control group
** - in comparison with the values before therapy

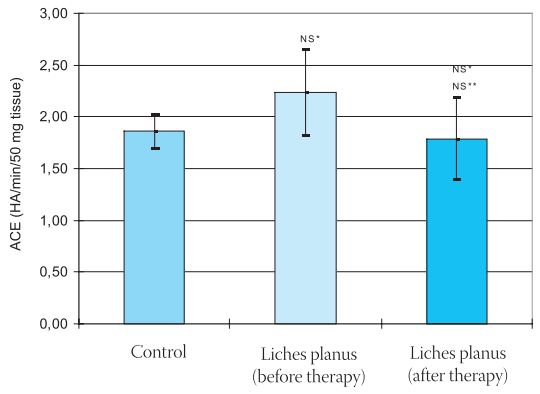

FIGURE 2. Tissue ACE activity (mean±SEM) in patients with lichen planus before and after therapy.
CONTROL – control group (healthy subjects; N=20;10 male and 10 female)
LICHEN PLANUS - patients with lichen planus (N=20; 10 male and 10 female)
NS – not significant
* - in comparison with control group
** - in comparison with the values before therapy

cant sex-related dif¬ferences in serum ACE activity, either in the control group or in the patients with lichen planus (data not shown) were found. Following the therapy serum ACE activity decreased by 14% in patients with lichen planus when compared with the values recorded before therapy (p<0,001). Data on tissue ACE activities in the control group and in patients with lichen planus are shown in Figure 2. Tissue ACE activity was 20% higher in patients with lichen planus than in their healthy counterparts. However, there was no significant difference in the mean ACE levels. Also, no significant difference was found between the tissue ACE activity in patients with lichen planus before and after therapy.

Discussion

Our study clearly showed that mean serum ACE activity is significantly increased (27% higher) in patients with lichen planus in comparison to healthy subjects. These results concur with the clinical study performed by Raff et al. (3). Accordingly, these results indicate the existence of potential role for ACE in patogenesis of lichen planus, although we found no significant differences in tissue ACE activity in patients with lichen planus in comparison to healthy subjects. More developed and extensive lesions in patients with lichen planus may be difficult to diagnose seeing as lesions of this sort may mimic psoriasis. In this case, the determination of serum ACE activity cannot be helpful in the diagnosis of lichen planus. Accordingly, numerous studies have shown that serum ACE activity increased in patient with psoriasis in comparison to healthy subjects (3,10,11). In the present study, we also investigated the effects of therapy on serum ACE activity in patients with lichen planus. The results showed that serum ACE activity significantly decreased in patients with lichen planus following the therapy in comparison with the values recorded before therapy (p<0,001). This suggests that the determination of serum ACE activity could be one of the discriminators used to assess the effects of therapy. Lichen planus is a skin condition of unknown origin that is frequently linked to diseases that may influence serum ACE activity [liver diseases (12,13), diabetes mellitus (14,15), sarcoidosis (16) and others]. Recent studies have demonstrated that ACE inhibitors can induce lichen planus (7,8). Unfortunately, mechanisms by which ACE inhibitors can flare a pre-existing disease are unknown. In our opinion, the investigation of this mechanism is very important because it should provide information about the pathogenesis of lichen planus. Angiotensin-II, a product of ACE activity, stimulates the release of pro-inflammatory cytokines, increases oxidant stress, and suppresses nitric oxide synthesis (17). Since ACE is present in the skin, this suggests that angiotensin-II may have a role in lichen planus, a condition in which inflammation is known to play a significant role. The ACE effectively controls bioavailability of peptide mediators released from sensory nerves and the immune and skin cells during the cutaneous response

to endogenous or exogenous noxious stimuli (18). It is possible that the peripheral nervous system is implicated in immunopathogenesis of lichen planus and lichenoid reactions. However, this data fails to show whether an increase in serum ACE activity in patients with lichen planus is a primary process, has a pathogenic role, or is only secondary to some independent process. Obviously, this is the main question which should be answered in further investigations.

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