Serum Angiotensin Converting Enzyme in Patients with Psoriasis

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Abstract

Background: Controversial data concerning the elevation of serum angiotensin-converting enzyme in psoriasis are reported in the literature. In order to verify whether this abnormality exists in Iranian patients, we performed this study.

Method: Serum angiotensin-converting enzyme level was measured in 40 psoriatics. According to clinical forms of psoriasis, patients were further divided into three groups: common plaque type (n=24), pustular psoriasis (n=10) and erythrodermic psoriasis (n=6).

Results: Serum angiotensin-converting enzyme shows some increase in patients with psoriasis; the greatest increase in serum angiotensin-converting enzyme level was observed in patients with erythrodermic psoriasis.

Conclusion: Our results suggest that angiotensin-converting enzyme may have a role in the aetiopathogenesis of psoriasis but further studies are warranted to evaluate the possible role of this enzyme in psoriasis *(Iran J Dermatol 2009;12: 127-130)*

Keywords: angiotensin, angiotensin converting enzyme, psoriasis

Introduction

Psoriasis vulgaris is a chronic inflammatory skin disease characterized by skin induration, scaling and erythema accompanied by histological evidence of inflammation, abnormal keratinocyte proliferation and dermal angiogenesis. Although the multifactorial aetiology of psoriasis is well established, the exact pathogenesis of this disease is still unknown [1].

Angiotensin converting enzyme (ACE) is a carboxypeptidase that has a crucial role in blood pressure regulation by catalysing the conversion of the inactive decapeptide angiotensin I (Ang I) to vasoactive angiotensin II (Ang II) [2]. This enzyme also affects the kallikrein-kinin system by degradation of bradykinin [3] which is also implicated in the pathogenesis of psoriasis [4]. ACE is expressed in a wide range of tissues including vascular endothelia cells, renal epithelial cells and skin. ACE and its related products are known to have wide-ranging effects on cutaneous immune and inflammatory responses [5-6] .

The purpose of the present study was to investigate the serum level of ACE in Iranian patients with psoriasis and to compare the values with those of the normal population and also to compare the serum level of ACE in three different forms of psoriasis (common plaque type, pustular type, and erythrodermic). To our knowledge, no similar study was ever performed in Iran.

Patients and Method

The study was performed in 40 patients with psoriasis (22 males and 18 females) with a mean age of 37.5±15.6 at the Department of Dermatology, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences. All patients were diagnosed clinically by an expert dermatologist. According to clinical forms of psoriasis, the patients were further divided into three groups: common plaque type psoriasis (n=24), pustular psoriasis (n=10) and erythrodermic psoriasis (n=6).

None of the patients had taken any systemic or topical medication and or any phototherapy for at least two month prior to blood sampling. The patients were not taking antioxidants (vitamins, carotenes, etc), ACE inhibitors and oral contraceptive pills. Participants with a history of cigarette smoking, alcohol abuse, diabetes mellitus,

cardiovascular disease and other inflammatory disorders (such as rheumatoid arthritis, asthma and atopic dermatitis) were excluded from the study.

Blood samples from the patients were collected from April 2007 to April 2008 in order to obtain whole blood, plasma and serum. None of the collected samples were icteric or haemolysed. The serum ACE level was determined by using ACE kit (Irland UK, Lot number 7854, Mean value of normal population: 36.5 mg/dL, normal range: 8-65 mg/dL).

The statistical analysis was performed using SPSS version 16. The differences between psoriatic patients serum ACE level and normal population was assessed using student T test. To evaluate the differences between the three groups, one way ANOVA test was used. A P-value less than 0.05 was considered statistically significant. All the measurements were expressed as mean ± standard deviation (S.D)

The study was conducted according to the principles of the declaration of Helsinki and was approved by the Medical Ethics Review Board of the Dermatology Research Center of Shahid Beheshti University of Medical Science. A written consent was obtained from each participant.

Results

Forty psoriatic patients (mean age: 37.5±15.6, max: 70, min: 16), including 24 patients with common plaque type psoriasis, 10 patients with pustular and 6 with erythrodermic psoriasis, were included in this study. Mean disease duration was 6.8±6.6 year (min: 1, max: 30 years). The mean level of ACE was 65.4 (mg/dl) ± 20.8 in psoriatic patients that seems to have some increase in comparision with mean level in the normal population (P-value <05). The greatest increase in serum level was observed in patients with erythrodermic psoriasis, followed by those with pustular and plaque type psoriasis (Table 1).

The study group consisted of 22 males and 18 females. We also analyzed the values according to gender but no significant difference was found (P-value>0.05).

Table 1. *Serum ACE level in three clinical form of psoriasis*

Group	Common plaque type	Pustular	Erythrodermic	P-Value
ACE (mg/dl)	56.3±22	77.6±5.6	79.8±10.1	0.003

Discussion

In the present study, the serum level of ACE was investigated in 40 patients with psoriasis and compared with the normal population. This study demonstrated that serum ACE level was significantly elevated in patients with psoriasis, as compared with the normal population. Thus, it appears that this enzyme may contribute to the pathogenesis of psoriasis.

Huskic et al [7-8] and Ryder et al, [9] reported elevated serum activity of ACE in psoriasis, but Thestrup-Pedersen et al [10] and Ena et al, [11] reported normal values of serum ACE level and activity in psoriasis. Furthermore, administration of ACE inhibitors can induce or exacerbate psoriasis in clinical practice [12-16]. The reason of these discordant results may be different actions of ACE.

ACE has a crucial role in blood pressure regulation and electrolyte balance by hydrolyzing angiotensin I into angiotensin II. Among other effects, Ang II increases both the generation of reactive oxygen species (ROS) and the synthesis of cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8), thus exerting proinflammatory effects [17-18]. ACE inactivates bradykinin which promotes vasodilation by enhanced formation of nitric oxide (NO), increases vascular permeability, and stimulates the synthesis of proinflammatory cytokines such as IL-6 and IL-8; all of the mentioned effects play a major role in the development of psoriasis [19-22]. In addition, ACE degrades substance P (SP), a member of the tachykinin family of neuropeptides. SP increases both vasodilation and vascular permeability, upregulates the expression of intercellular adhesion molecule-1 (ICAM-1) on human dermal microvascular endothelial cells, stimulates the proliferation of human T lymphocytes and enhances the expression of proinflammatory cytokines. All these functions have been shown to contribute to the development of psoriatic lesions [23-25]. Moreover, both Ang II and bradykinin have already been shown to increase the expression of endothelin-1 (ET-1).

ET-1 is a 21-amino acid peptide which is synthesized by different cell types including monocytes and endothelial cells. Besides its effects on vasoregulation, ET-1 acts as a mitogen for keratinocytes and mediates proinflammatory pathways by both the synthesis of cytokines such as IL-6 and monocyte chemoattractant protein -1 (MCP-1) and the activation of nuclear factor kappa beta (NFjB). Increased plasma ET-1 concentrations have already been found among psoriatic patients, and a correlation between plasma ET-1 levels and

Psoriasis Area and Severity Index (PASI) scores has been reported. In addition, overexpression of ET-1, both at the protein and mRNA levels, has been demonstrated in psoriatic lesions compared to the normal skin [26-35]. Thus, it appears that ACE on the one hand promotes inflammation but on the other hand, inhibits it by degradation of bradykinin and substance P.

In our study, the greatest increase in ACE level was seen in erythrodermic patients which points to the pronounced inflammation in this type. By analyzing the serum activity of ACE, Huskic et al, demonstrated that the greatest increase was found in psoriatic patients with multiple disseminated lesions, followed by solitary psoriatic lesions and erythrodermic [8]. However, when they analyzed tissue ACE activity [36], they found that the greatest increase was in patients with erythrodermic psoriasis, followed by those with multiple disseminated lesions and solitary psoriatic lesions. All these contradictory results point to the fact that our knowledge of molecular action of ACE is very little and that studying the potential role of ACE in psoriasis may help us to understand the aetiopathogenesis of this disorder.

In conclusion, our results suggested that ACE might have a role in the aetiopathogenesis of psoriasis; however, in view of the reported association between ACE inhibitors and the exacerbations of psoriasis, it might be interesting to study the potential pharmacologic role of ACE inhibitors. The main restriction of this study was lack of control group that we could not add in the study design due to some financial and procedural limitations. However, our result could suggest the variation of ACE level in psoriatics and furthur controlled studies should be performed to address this issue more exactly.

References

1. Weger W, Hofer A, Wolf P, El-Shabrawi Y, Renner W, Kerl H, Salmhofer W. The angiotensin-converting enzyme insertion/deletion and the endothelin -134 3A/4A gene polymorphisms in patients with chronic plaque psoriasis. Exp Dermatol 2007;16:993-8.
2. Ehlers MR, Riordan JF. Angiotensin-converting enzyme: new concepts concerning its biological role. Biochemistry 1989:28: 5311–8.
3. Murphey LJ, Gainer JV, Vaughan DE, Brown NJ. Angiotensin-converting enzyme insertion/deletion polymorphism modulates the human in vivo metabolism of bradykinin. Circulation 2000;102:829-32.
4. Schremmer-Danninger E, Hermann A, Fink E, Fritz H, Roscher AA. Identification and occurrence of mRNAs for components of the kallikrein–kinin system in human skin and in skin diseases. Immunopharmacology 1999: 43: 287–91.
5. Scholzen TE, Ständer S, Riemann H, Brzoska T, Luger TA. Modulation of cutaneous inflammation by angiotensin-converting enzyme. J Immunol 2003;170:3866–73.
6. Chang YC, Wu WM, Chen CH, Lee SH, Hong HS, Hsu LA. Association between the insertion/deletion polymorphism of the angiotensin I-converting enzyme gene and risk for psoriasis in a Chinese population in Taiwan. Br J Dermsatol 2007 ;156:642-5.
7. Huskić J, Mulabegović N, Alendar F, Ostojić L, Ostojić Z, Simić D, Milicević R, Naletilić M. Serum and tissue angiotensin converting enzyme in patients with psoriasis. Coll Antropol 2008;32:1215-9.
8. Huskić J, Alendar F, Matavulj A, Ostoić L. Serum angiotensin converting enzyme in patients with psoriasis. Med Arh 2004;58:202-5.
9. Ryder KW, Epinette WW, Jay SJ, Ransburg RC, Glick MR. Serum angiotensin converting enzyme activity in patients with psoriasis. Clin Chim Acta 1985;153:143-6.
10. Thestrup-Pedersen K, Rømer FK, Jensen JH, Brodthagen H. Serum angiotensin-converting enzyme in sarcoidosis and psoriasis. Arch Dermatol Res 1985;277:16-8.
11. Ena P, Madeddu P, Rappelli A, Cerimele D. Serum angiotensin-converting enzyme activity in psoriasis. Dermatologica 1987;174:110-3.
12. Cohen AD, Bonneh DY, Reuveni H, Vardy DA, Naggan L, Halevy S. Drug exposure and psoriasis vulgaris: case-control and case-crossover studies. Acta Derm Venerol 2005: 85: 299–303.
13. Coulter DM, Pillans PI. Angiotensin-converting enzyme inhibitors and psoriasis. N Z Med J 1993: 106: 392–3.
14. Gilleaudeau P, Vallat VP, Carter DM, Gottlieb AB. Angiotensin-converting enzyme inhibitors as possible exacerbating drugs in psoriasis. J Am Acad Dermatol 1993: 28: 490–2.
15. Wolf R, Tamir A, Brenner S. Psoriasis related to angiotensin-converting enzyme inhibitors. Dermatologica 1990:181:51–3.
16. Steckelings UM, Artuc M, Wollschlager T, Wiehstutz S, Henz BM. Angiotensin-converting enzyme inhibitors as inducers of adverse cutaneous reactions. Acta Derm Venereol 2001:81:321–5.
17. Takahashi T, Taniguchi T, Okuda M, et al. Participation of reactive oxygen intermediates in the angiotensin II-activated signaling pathways in vascular smooth muscle cells. Ann NY Acad Sci 2000: 902:283–7.
18. Kranzhofer R, Schmidt J, Pfeiffer CA, Hagl S, Libby P, Kubler W. Angiotensin induces inflammatory activation of human vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 1999: 19:1623–9.
19. Tschöpe C, Schultheiss HP, Walther T. Multiple interactions between the renin-angiotensin and the kallikrein-kinin systems: role of ACE inhibition and

AT1 receptor blockade. J Cardiovasc Pharmacol 2002;39:478-87.
20. Hayashi R, Yamashita N, Matsui S, Fujita T, Araya J, et al. Bradykinin stimulates IL-6 and IL-8 production by human lung fibroblasts through ERK- and p38 MAPK-dependent mechanisms. Eur Respir J 2000:16: 452–8.
21. Fritz H, Jochum M, Muller-Esterl W. Kinins 1925–2000. Biol Chem 2001:382:3–4.
22. Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. J Clin Invest 2004:113: 1664–75.
23. Scholzen TE, Luger TA. Neutral endopeptidase and angiotension-converting enzyme -- key enzymes terminating the action of neuroendocrine mediators. Exp Dermatol 2004: 13 suppl: 22–6.
24. Kanda N, Watanabe S. Substance P enhances the production of interferon-induced protein of 10 kDa by human keratinocytes in synergy with interferon-gamma. J Invest Dermatol 2002:119: 1290–7.
25. Quinlan KL, Song IS, Bunnett NW, Letran E, Steinhoff M, et al. Neuropeptide regulation of human dermal microvascular endothelial cell ICAM-1 expression and function. Am J Physiol 1998: 275: C1580–90.
26. Kahaleh MB, Fan PS. Effect of cytokines on the production of endothelin by endothelial cells. Clin Exp Rheumatol 1997:15: 163–7.
27. Imai T, Hirata Y, Emori T, Yanagisawa M, Masaki T, Marumo F. Induction of endothelin-1 gene by angiotensin and vasopressin in endothelial cells. Hypertension 1992:19: 753–7.
28. Levin ER. Endothelins. N Engl J Med 1995:333: 356–63.
29. Bagnato A, Venuti A, Di Castro V, Marcante ML. Identification of ETA receptor subtype that mediates endothelin induced autocrine proliferation of normal human keratinocytes. Biochem Biophys Res Comm 1995;209: 80–6.
30. Wilson SH, Simari RD, Lerman A. The effect of endothelin-1 on nuclear factor kappa B in macrophages. Biochem Biophys Res Commun 2001;286: 968–72.
31. Browatzki M, Schmidt J, Kubler W, Kranzhofer R. Endothelin-1induces interleukin-6 release via activation of the transcription factor NF-kappaB in human vascular smooth muscle cells. Basic Res Cardiol 2000;95: 98–105.
32. Bonifati C, Mussi A, Carducci M, et al. Endothelin-1 levels are increased in sera and lesional skin extracts of psoriatic patients and correlate with disease severity. Acta Derm Venereol 1998;78: 22–6.
33. Trevisan G, Stinco G, Giansante C, Fiotti N, Vidimari P, Kokelj F. Psoriasis and endothelins. Acta Derm Venereol Suppl (Stockh) 1994;186:139-40.34)
34. Cecchi R, Giomi A, Ciuti M, Gironi A, Seghieri G. Increased levels of plasma endothelin-1 in patients with psoriasis. Clin Chim Acta 1994;226:113–5.
35. Yildiz L, Akcay F, Aktas A, Yildiz F, Sahin YN. Increased concentrations of plasma endothelin-1 and fibronectin in psoriasis. Acta Derm Venereol 1997;77: 166–7.
36. Huskić J, Alendar F. Tissue angiotensin-converting enzyme in patients with various clinical forms of psoriasis. Bosn J Basic Med Sci 2007;7:103-6.