Endothelin-1 in systemic sclerosis

Mehrdad Aghaei, Farhad Gharibdost[1], Habib Zayeni[2], Maryam Akhlaghi[1], Sima Sedighi, Abduo Rahman Rostamian[1], Naser Aghdami[1], Mahdieh Shojaa[3]

Department of Rheumatology, Faculty Member of Golestan University of Medical Sciences, [1]Faculty Member of Tehran University of Medical Sciences, [2]Faculty Member of Gilan University of Medical Sciences, [3]Research Center of Osteoporesis, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Introduction: Scleroderma is a systemic disorder with unknown etiology most notably characterized by skin thickening and organ damage. Endothelin-1 (ET-1) plays a role in skin fibrosis. The aim of this study was survey and comparison of ET-1 level in Systemic Sclerosis (SSc) patients with and without digital ulcer. **Material and Methods:** A cross-sectional analytical study conducted among the 95 patients with scleroderma in 2006 who were referred to the Rheumatology clinic in Shariati hospital of Tehran. The questionnaire was completed for every patient. Plasma level of endothelin-1 was also measured in all of them. The data was analyzed using SPSS software and statistical tests. **Results:** The result indicated, relationship among digital ulcers and digital pitting scars with plasma level of ET-1 were significant (P value < 0.05). We could not find any significant relationship between age and plasma level of ET-1. **Conclusion:** These data indicate plasma level of ET-1 in scleroderma patients with digital ulcer was higher than patients without digital ulcer. Thus, increase in plasma level of ET-1 could be effective in vascular damage, fibrosis, and skin thickness.

Key words: Digital ulcer, endothelin, scleroderma

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Address for correspondence:
Mrs. Mahdieh Shojaa, Shariati Hospital, Jalal High Way, Tehran University of Medical Sciences, Tehran, Iran.
E-mail: mahdieh.shojaa_mw@yahoo.com

INTRODUCTION

Systemic Sclerosis (SSc) is a chronic, multisystem, connective tissue disorder most notably characterized by skin thickening and fibrosis of the skin and internal organs such as lungs, kidneys and heart with vascular damage. Its etiology and pathogenesis are unknown.[1,2] SSc is divided into two subgroups; limited and diffuse. Limited scleroderma typically has a gradual onset and is restricted to certain areas of the skin in extremities and face. Diffuse scleroderma, on the other side, is defined as skin thickening in distal and proximal of limbs, body and face along with the involvement of internal organs; particularly kidneys, heart, and lungs.[3,4]

According to high prevalence of disease in specific ethnic groups, genetic factors are believed to be strong variables leading to the expression of the disease. On the other hand, environmental factors may also be effective in the development of scleroderma.[5] Increasing prevalence of the disease in recent years could be due to the improved diagnosis of mild disease.[6] In the US, the prevalence of the disease was initially estimated to be 242.0 cases per million adults with an annual incidence of 19.3 new cases per million adults per year.[7] While the age of onset of the disease varies, it rarely occurs in children and men younger than 35 years.[8] Scleroderma is more common in women. Diffuse forms of the disease are more prevalent in black women and white women aged between 35–44 years and 45–54 years, respectively.[9] In patients with scleroderma, plasma level of ET-1, a member of peptides family, increase.[10,11] ET-1 can damage the vasculature by regulating vascular growth-promoting factors and inducing vascular remodeling, both of which are important mechanisms of skin fibrosis.[10-12] Not many studies have assessed the role of ET-1 in the development of digital ulcers in scleroderma patients. As a result, the present study was designed to compare the plasma levels of ET-1 in scleroderma patients with and without digital ulcers.

MATERIALS AND METHODS

This cross-sectional analytical study was carried out on 95 patients with scleroderma who were referred to the Rheumatology clinic in Shariati Teaching Hospital affiliated to Tehran University of Medical Sciences between June 2006 and August 2007.

All patients who fulfilled the American College of Rheumatology criteria[13] for the diagnosis of SSc were recruited. At first, a written informed consent was obtained from each patient and then a questionnaire was completed for all of them. The questionnaire was designed to gather information on the demographic) age, sex) of the patients as well as the characteristics of their disease, including the presence of digital ulcer or digital pitting scar, the number of ulcers and scars, and the presence of skin thickening. Five milliliter blood sample was taken for measuring ET-1 level. The samples were centrifuged at 5000 rpm in EDTA containing sterile tubes for 5–10 minutes stored until a clear separation was performed. The plasma was then transferred into Eppendorf sterile tubes and stored at −20°C and plasma level of ET-1 was measured by ELISA test. Statistical analysis was performed using SPSS software version 13.0. The normal distribution of data was studied using Kolmogorov Smirnov test. Quantitative variables were presented as median and standard deviation. T-test was used to compare these values. The association between the studied variables was assessed using logistic regression. *P* values less than 0.05 were considered statistically significant.

RESULTS

From among the 95 studied patients, 96% were female. Their mean age was 38 ± 12.29 years, ranging from 17 to 72 years. Diffuse cutaneous SSc was diagnosed in 52 patients and limited cutaneous SSc in 43 patients. There was no significant relationship between mean plasma ET-1 level and age (r = 0.037, *P* value = 0.72) or skin thickening (r = 0.023, *P* value = 0.82). Digital ulcer was found in 17 of the cases (18%) [Figure 1]. There was a statistically significant difference between mean plasma ET-1 level in patients with and without digital ulcer (*P* value <0.05). It means plasma level of ET-1 in patients with digital ulcer was higher than other patients without digital ulcer. The relation between plasma level of ET-1 and the number of ulcers and scars in the feet and hands of the studied patients was statistically significant [Table 1]. There was similarly a significant relation between mean plasma ET-1 levels and the concomitant presence of scar and ulcer in the fingers of patients with scleroderma [Table 1].

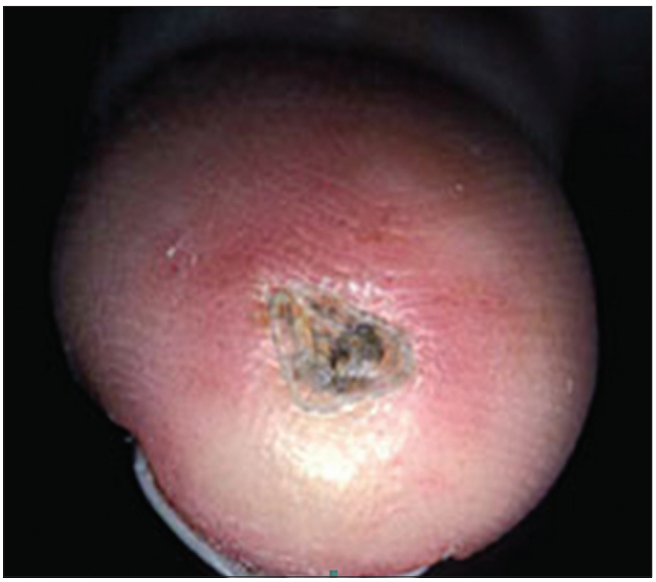

Figure 1: Digital ulcer

DISCUSSION

Endothelins are a family of 21 amino-acid peptides, produced by vascular endothelial cells. They not only play an important role in vasoconstriction but also stimulate proliferation of smooth muscle cells.[14,15] ET-1, which stimulates the secretion of vascular endothelial growth factor (VEGF), is also considered as a substance leading to vascular damage.[12] Not many studies have assessed the serum level of ET-1 in scleroderma patients with and without digital ulcers. It is estimated that 30 to 40% of patients suffer from digital ulcer, which is much higher than the present study.[12] Some studies have reported significantly higher plasma level of ET-1 in patients with SSc.[16,17] Corroborating our study, some studies have pointed towards a significant relation between the plasma level of ET-1 and the number of digital ulcers.[18,19] The present study also showed a significant correlation between the plasma level of ET-1 and the number of digital ulcers and scars. Such an association, however, was not reported in any of the previous studies. It seems that any increase in the plasma levels of ET-1 can cause a considerable vascular damage, fibrosis, and skin thickening in patients with scleroderma.

CONCLUSION

In line with other studies, the present research revealed higher plasma level of ET-1 in patients with scleroderma. The rate, however, depends on the symptoms and the severity of the disease. The plasma level of ET-1, therefore, can be used as diagnostic tool in these patients. In our study, we did not have a control group and we could not compare mean plasma ET-1 level between patients with scleroderma and normal population.

Table 1: Independent variables distribution in scleroderma patients

Variable		Number (%)	ET-1 mean	T Score	*P* value
Digital ulcer	Yes	17(18)	39.52 ± 16.89	2.94	<0.05
	No	78(82)	18.01 ± 5.83		
Scar	Yes	66(69)	7.13 ± 91/26	2.63	0.01
	No	29(31)	8.32 ± 85/10		
Concomitant presence of scar and ulcer	Yes	16(17)	16.80 ± 87/41	3.23	0.002
	No	79(83)	5.76 ± 98/17		

Hence, it is recommended to design a case-control study to determine and compare the role of ET-1 in the pathogenesis of scleroderma.

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