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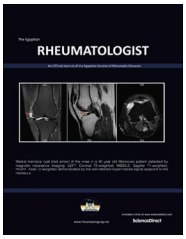

ORIGINAL ARTICLE

Determinants of atherosclerosis in an Egyptian cohort of systemic sclerosis: Relation to disease activity and severity

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KEYWORDS

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Atherosclerosis

Abstract *Background:* Systemic sclerosis (SSc) is a rare multi-system autoimmune disease characterized by vascular abnormalities with an increased prevalence of macrovascular disease.

Aim of the work: To evaluate macro-vascular disease (atherosclerosis) in SSc patients and determine its relation to the disease activity and severity.

Patients and methods: Twenty-five SSc patients and 20 matched controls were included. The modified Rodnan skin score (mRss) and disease severity by Medsger's severity score were assessed. Carotid intima-media thickness (IMT) and flow mediated vasodilatation (FMD) of the brachial artery were measured. Traditional vascular risk factors were assessed by thorough history taking and laboratory investigations.

Results: The age of the patients ranged from 15 to 60 years and they were 22 females and 3 males. 15 had limited and 10 diffuse cutaneous SSc. All SSc patients had an increased IMT (1.24 ± 0.29 mm) which was normal in the control subjects (0.77 ± 0.09 mm) ($p < 0.0001$). SSc patients had significantly lower HDL, thickened IMT and lower FMD than controls ($p = 0.005$, $p < 0.0001$ and $p < 0.0001$ respectively). The younger age of disease onset was significantly associated with more FMD impairment ($r = -0.4$, $p = 0.04$) and Medsger's severity score ($r = 0.5$, $p = 0.009$). The mRss and Medsger's severity score significantly correlated with the IMT ($r = 0.84$, $p = 0.01$ and $r = 0.56$, $p = 0.003$ respectively). A significant negative correlation was found between FMD and IMT ($r = -0.77$, $p < 0.0001$). Medsger's severity score significantly correlated with FMD ($r = -0.44$, $p = 0.02$).

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Conclusion: SSc is associated with an increased risk of atherosclerosis when compared to age and sex-matched controls. Determinants of this include; younger age of disease onset and more sever disease and low levels of HDL.

1. Introduction

Systemic sclerosis (SSc) is a rare multi-system autoimmune disease of multifactorial origin that is characterized by vascular abnormalities and diffuse fibrosis in the skin and joints, and by progressive involvement of the internal organs [1]. SSc is about eight times more common among women than men [2]. It is most common in the third to fifth decades of life and is rare in children [3].

The most common initial symptoms and signs are vascular, such as Raynaud's phenomenon, which is often long-lasting, as well as insidious swelling of the distal extremities with puffy fingers, followed by gradual thickening of the skin of the face and fingers with late skin ulcers. On the basis of the extent of skin involvement, SSc can be categorized into two forms: diffuse and limited cutaneous SSc [4].

Atherosclerosis is considered as a chronic inflammatory disease where monocytes, macrophages and *T*-cells as well as autoantibodies, autoantigens and cytokines play a role. It is considered the leading cause of death in developed countries. Atherosclerosis affects large and medium-sized arteries and can cause coronary heart disease, stroke and peripheral vascular disease [5].

The vasculopathy of SSc typically affects the small arteries and capillaries, but an increased prevalence of macrovascular disease has also been suggested [6]. Subclinical coronary artery abnormalities were reported in Egyptian SSc patients [7]. The pathophysiology of SSc involves endothelial and vascular damage and the activation of fibroblasts; consequently, collagen and other extracellular matrix proteins are overproduced in almost all tissues. The innate and adaptive immune systems are activated in the perivascular areas, releasing their component immunological mediators such as cytokines and growth factors (transforming growth factor-β, platelet-derived growth factor, endothelin-1) and extensive fibrosis in the dermal and subcutaneous layers develops [8]. In other studies on Egyptian SSc patients, increased cluster of differentiation 36 (thrombospondin receptor) was considered as a marker of vascular involvement and severity [9] and the serum cartilage oligomeric matrix protein was significantly increased [10].

Thus, there is both vasospasm in the small vessels, and endothelial dysfunction. Such endothelial dysfunction has been shown to predict future cardiovascular (CV) events in many clinical situations via the development of large vessel (macrovascular) atherosclerosis over time [11]. Furthermore, the novel non-traditional CV risk factors for atherosclerosis are also present in SSc, such as increased lipoprotein (a), oxidized LDL, adrenomedullin and inflammation [12]. Moreover, markers of vascular damage like Von Willebrand Factor (vWF) and increased levels of vascular adhesion molecules are present in SSc which are also linked to atherosclerosis [13]. In this regard, it is of great importance to delineate the macrovascular disease (atherosclerosis) in SSc.

The present study aimed at evaluating the macro-vascular disease (atherosclerosis) in patients with SSc and determining its relation to the disease activity and severity.

2. Patients and methods

2.1. Clinical evaluation

The present case control study was carried out on 25 SSc patients who attended the rheumatology outpatient clinics of Ain Shams and Cairo University hospitals. Patients were recruited from October 2013 to November 2014. Twenty healthy volunteers matching in age and sex served as a control group. Written consent was obtained from every patient and control which was approved by Ain Shams medical Ethical Committee.

Systemic sclerosis (SSc) was diagnosed according to the criteria of the American College of Rheumatology [14] and was classified as limited or diffuse cutaneous subtypes according to the criteria of Le Roy et al. [15]. Patients were subjected to full medical history taking with special emphasis on disease duration, body mass index (BMI) calculation and thorough clinical examination. The severity and extent of skin sclerosis were assessed using the modified Rodnan skin score (mRss) [16]. Disease severity was assessed by Medsger's severity score of 9 organs [17].

2.2. Laboratory assessment

Venous blood (8 ml) was withdrawn from each patient where, five ml was placed in EDTA tube for performing complete blood count (CBC) and erythrocyte sedimentation rate (ESR) and three ml of blood was collected in plain vacutainers for analysis of anti-nuclear antibody (ANA) and anti-double stranded deoxyribonucleic acid (anti-dsDNA). Serum samples were stored at −20 °C until time of assay. CBC was done using Coulter counter (T660), ESR was done by the Westergren method. ANA was done using indirect immunofluorescence assay using IMMCO Diagnostics, USA (ANA on Hep-2 substrate). As well, lipid profile was assessed; total cholesterol, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL). The C-reactive protein (CRP) and serum insulin levels were also assessed in patients and control.

2.3. Radiological assessment

2.3.1. Carotid duplex

The patients were examined using Voluson S8 (GE Health care) Ultrasonography apparatus with color Doppler and high resolution 12 MHZ linear array transducer. Common carotid, the carotid bulbs, the proximal internal and external carotid arteries were evaluated by gray scale. The patients were placed