PREVALENCE OF MACROVASCULAR DISEASE IN SYSTEMIC SCLEROSIS

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ABSTRACT

Objective: *To detect the prevalence of macrovascular disease in systemic sclerosis.*

Methods: *Thirty patients with systemic sclerosis and ten normal controls matched in age and sex were included in the study. All subjects were screened for atherosclerosis risk factors and non-invasive vascular assessment as carotid duplex scanning and measurement of ankle brachial blood pressure index.*

Results: *There was no significant difference in risk factors as cigarette smoking, systolic, diastolic blood pressure, cholesterol, triglycerides and glucose levels between patients and controls groups.*

Twenty three out of 30 patients (76.7%) had carotid artery disease compared to (30%) of normal controls with a highly significant difference.

Conclusion: *Macrovascular disease is a common finding in systemic sclerosis. Early identification allows early intervention and treatment with better control of high rate of cardiovascular mortality.*

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease of unknown etiology characterized by fibrotic changes of the skin, subcutaneous tissues, and viscera; abnormalities of the microvasculature; and immune dysfunction *(Person et al., 2004).* SSc is characterized by essential vasomotor

disturbances, fibrosis, subsequent atrophy of the skin, subcutaneous tissue, muscles and internal organs (e.g. alimentary tract, lungs, heart, kidney, CNS); and immunological disturbances accompanying these findings *(Person et al., 2004).* The function and activities of smooth muscle cells in the artery are dependent on the milieu created by the surrounding cells and the components of the extracellular matrix *(Ranies & Ross 1993).*

Many factors, including environmental factors, can lead to immunologic system disturbances and vascular changes. Endothelial alterations may lead to a cascade of stimulatory changes that involve many cells, including fibroblasts, T lymphocytes, macrophages and mast cells. In turn, the activated cells secrete a variety of substances, including cytokines and their soluble receptors and enzymes and their inhibitors. These substances lead to changes in the extra cellular matrix compounds including fibronectin, proteoglycans and collagen types 1, 3, 5, and 7. Increased collagen deposition in tissues is a characteristic feature of SSc. Increased collagen production or disturbances in its degradation can cause excessive collagen deposition in tissues *(Person et al., 2004).*

The microvascular involvement in systemic sclerosis is characterized by endothelial damage and smooth muscle cell migration in the intima. The vasculopathologic modification in SSc is strikingly similar to those of atherosclerosis. SSc is also characterized by an accelerated macrovascular disease *(Fatini et al., 2004).*

Microvascular disease is one of the hallmarks of systemic sclerosis, but macrovascular involvement also exists. Some SSc patients may have severe raynauld's phenomenon characterized by refractory digital ulcerations *(Taylor, 2002).*

The atherosclerosis may be the result of a specialized chronic inflammatory fibroproliferative process which has become excessive and in its excess this protective response has become the disease state. *(Ross & Aguis 1992 and Ross 1993).* It is entirely conceivable that this chronic, excessive, inflammatory and fibroproliferative response can be reversed, given sufficient opportunity for the factors that have led to the endothelial and arterial wall injury causing these events to be taken into hand and modified *(Ross,1993).*

MATERIALS AND METHODS

Patients:

Thirty consecutive patients fulfilling the 1980 American College of Rheumatology (ACR) criteria for systemic sclerosis (diffuse and limited cutaneous disease) were recruited from the Rheumatology and

Rehabilitation Department of Ain Shams University Hospitals. Any patients with another connective tissue disease or rheumatoid arthritis were excluded from the study.

Controls:

Ten normal controls of similar sex and age were also recruited. All our patients were subjected to a thorough clinical evaluation including duration of the disease, history of smoking, claudications, Raynaud's phenomena, drug history, regular or intermittent steroid therapy and any cardiovascular symptoms.

All were screened for conventional atherosclerotic risk factors.

Laboratory tests:

1- Complete blood picture, erythrocyte sedimentation rate, C reactive protein.

2- Random blood cholesterol, high density lipoprotein (HDL), triglycerides and random blood glucose.

3- Rheumatoid factor, anti-DNA, anti-ENA, anti-SCL70 and anticentromere antibody.

Vascular assessment:

The non-invasive vascular assessment as a measure of peripheral arterial disease was done on all subjects. It includes: carotid duplex scanning and ankle brachial pressure measurements (ABPI).

a- Ankle brachial pressure index:

Bilateral ankle and brachial arterial systolic pressures were measured. The ABPI was calculated by dividing the posterior tibial artery pressure in mm Hg by the brachial pressure. The normal value of ABPI is 1.0, any value below this figure is considered as abnormal. The severity of the arterial disease is inversely proportional to the ABPI.

b- Carotid duplex scanning:

It is used for detection of arterial stenosis and plaque by using B – mood ultrasound and pulsed color Doppler.

Grades (according to *Faris et al. (1992)* are as follow:

Grade 1: Normal.

Grade 2: Minimal disease (less than 20% lumen stenosis).

Grade 3: Moderate disease (20-49%).

Grade 4: Severe disease (50-69%).

Grade 5: Critical disease (>= 70%).

Statistics:

Analysis and comparison was done using the student's t test and a p value of <0.05 was considered as statistically significant.

Correlations were done using Pearson's correlations coefficient.

RESULTS

Thirty patients with scleroderma were included in this study. Their age ranged from 30-67 years (mean age 44.46±9.06). Females to males were 26:4. Diffuse forms to limited form were 17: 13. The disease duration ranged from 1-6 years with a mean of 2.68 ± 1.38.

Ten normal control subjects participated in this study, they were matched with the patients' group as regard the age and sex.

There were no significant differences in the risk factors as measured between patients and controls including smoking status, cholesterol level, high density lipoprotein, triglycerides, blood sugar, and systolic blood pressure (table 1).

Table (1): Demographic details and risk factors profile.

	Patients	Controls	p value
Females: males (total)	26:4 (30)	8:2 (10)	NS
Age (median/ range) years	30-67 (44.5±9.1)	28-60 (38.6±4.20)	NS
Diffuse: limited	17:13	--	--
Disease duration (median / range) years	1- 6 (2.7±1.4)	--	--
Smokers	2 (6.7%)	1 (10%)	NS
Cholesterol mean (SD)	172.66±19.98	124.00±20.21	NS
HDL means (SD)	42.83±11.42	38.82±10.62	NS
Triglycerides mean (SD)mmol	102.33±31.47	80.0±20.72	NS
Blood sugar	120.6±26.30	100.0±20.40	NS
Systolic blood pressure means (SD) mmHg	136.33±17.90	120.0±15.40	NS

NS= Non significant.

The age, disease duration, ankle systolic pressure, brachial systolic pressure, cholesterol level, high density lipoprotein, triglycerides, blood sugar and ankle brachial pressure index, all were found to be statistically of non-significant difference when compared to Raynauld's positive or negative cases (table 2).

Table (2): Comparison of Raynauld's with different variables.

	Raynauld's	Mean±SD	t	p	Sig.
Age	-ve	48.54±11.01	1.965	>0.05	NS
	+ve	42.10±6.99	1.746	>0.05	NS
Disease duration	-ve	2.40±1.39	-0.823	>0.05	NS
	+ve	2.84±1.38	-0.822	>0.05	NS
Ankle systolic pressure	-ve	121.36±14.15	-1.105	>0.05	NS
	+ve	127.63±15.39	-1.171	>0.05	NS
Brachial systolic pressure	-ve	130.90±16.40	1.276	>0.05	NS
	+ve	139.47±18.40	1.317	>0.05	NS
Cholesterol	-ve	176.36±16.89	0.765	>0.05	NS
	+ve	170.52±21.72	0.819	>0.05	NS
HDL	-ve	44.54±12.73	0.816	>0.05	NS
	+ve	41.84±10.82	0.591	>0.05	NS
Triglyceride	-ve	104.54±26.21	0.288	>0.05	NS
	+ve	101.05±34.78	0.311	>0.05	NS
Blood sugar	-ve	125.45±26.59	0.763	>0.05	NS
	+ve	117.78±26.44	0.762	>0.05	NS
ABPI	-ve	0.92±6.7E-2	0.529	>0.05	NS
	+ve	0.91±5.22E-2	0.493	>0.05	NS

The limited and diffuse forms of scleroderma were found to have a statistical significant difference with ankle systolic pressure and cholesterol level. The diffuse form was found to be statistically significant with brachial systolic pressure, as shown in table 3.

Table (3): Comparison of forms of scleroderma with different variables.

		Mean±SD	t	p	Sig.
Ankle systolic pressure	limited	119.23±13.82	-2.050	<0.05	S
	diffuse	130.00±14.57	-2.065	<0.05	S
Brachial systolic pressure	limited	129.23±14.41	-1.990	>0.05	NS
	diffuse	141.76±18.78	-2.068	<0.05	S
Cholesterol	limited	184.61**+**18.53	3.32	<0.05	S
	diffuse	163.52±16.17	3.260	<0.05	S

Carotid duplex scanning showed that 23 patients had evidence of carotid artery disease (76.7%) in comparison to the control group (30%) with a highly significant difference ($p< 0.001$).

Carotid duplex results compared with all variables showed a statistical significant difference with blood sugar and ankle brachial pressure index (table 4), while the results were not significant with the rest of variables.

Table (4): Comparison of duplex scanning with other variables.

Grade	1	2	3	4	5	F	p	Sig.
Blood Sugar	114.28± 17.18	108.90± 15.26	130.0± 30.00	125.41± 40.41	156.66± 25.16	2.796	<0.05	S
ABPI	1.00± 0.0	0.916± 2.51E-2	0.915± 1.93E-2	0.870± 5.9	0.835± 2.63	23.924	<0.05	S

Plaques were found to be statistically significant with blood sugar and there was no significant difference (F: 3.302) with the rest of other variables as ankle brachial pressure index, ankle systolic pressure, brachial systolic pressure, cholesterol level, high density lipoprotein or triglycerides.

Qualitative data analysis using Pearson's chi-square test showed no significant difference between Raynaud's phenomenon and the diffuse form of scleroderma (0.032), corticosteroid intake (1.148), and carotid duplex scanning (7.435) or plaques (6.213).

There was no significant difference between the diffuse form and either corticosteroid (3.529), carotid duplex (1.997) or plaques (4.014).

The corticosteroid intake was found not to be correlated with either carotid duplex scanning (1.368) or plaques (6.375).

The qualitative data analysis results showed no significant difference between carotid duplex results and plaques (16.421).

DISCUSSION

Veale and his colleagues (1995) demonstrated a greater prevalence of macrovascular disease in SSc patients than had been found in a neighboring population. Intermittent claudications are found in ten SSc patients (two with diffuse and eight with limited SSc) (21.7%), compared with a prevalence rate of 4.6% for claudications in Edinburgh artery study (EAS). Out of these ten patients three experienced clinical events attributable to occlusion of a major artery proven on angiography. Four patients had hypertension; there were three current and four ex-smokers. None of them had diabetes.

Yousef et al. (1993) found that 11% of the women scleroderma had a severe morbidity from macrovascular disease of the arms and legs in the presence of minimal underlying vascular risk factors. This was a greater than three folds increase above the expected proportion of symptomatic vascular disease seen in the population study. They concluded an association of both CREST syndrome and scleroderma with macrovascular disease.

Yousef and his colleagues (1995) reported that the peripheral vascular disease occurred in 18 (58%) of limited systemic sclerosis compared to 3 (9.6%) of the controls.

Stafford and his colleagues (1998) studied the distribution of macrovascular disease in scleroderma and its anatomical distribution. They found that the ulnar arteries in scleroderma patients were significantly narrower than those of the negative cohort. The arterial walls were also characterized by smooth thickening along their entire length. The characteristics of the other arteries, including those of the lower limbs, were not significantly different from those of the negative cohort. They concluded that the ulnar artery seems to be specifically targeted in SSc patients. Assessment of the ulnar artery should be considered in the patients by means of a modified Allen's test or Doppler sonography especially in the presence of digital gangrene.

An Allen's test should be performed routinely on all SSc patients with severe Raynaud's phenomenon and refractory digital ulceration to investigate the possibility of ulnar artery occlusive disease. The authors, recommended ulnar artery revascularization with or without digital sympathectomy should be considered in patients with suspected ulnar artery occlusion confirmed by angiography or ultrasonography *(Taylor et al., 2002).*

Peripheral macrovascular disease was shown to be increased in patients with limited cutaneous sclerosis *(Hoogen & Jong, 1995).* Our results showed that 76.7% of systemic sclerosis had carotid artery disease in comparison to 30% in controls. These results were nearly matched with *Meilien et al. (2000)* who found 64% of systemic sclerosis had carotid peripheral vascular disease as compared with only 35% controls. 21% of these patients had moderate disease compared with only 5% controls.

Seventeen percent of SSc patients had evidence of peripheral arterial disease as compared with none of the controls. Our results showed no significant difference in risk factors thath were matched with *Meilien et al. (2002).* They found no significant differences in the basic risk factor profile which included cigarette smoking, systolic and diastolic blood pressure, cholesterol, and triglyceride and glucose concentrations.

Our results showed that both limited and diffuse forms of scleroderma had a significant difference with ankle systolic pressure and cholesterol. The diffuse form was found to be of significant difference with brachial systolic pressure. The ABPI in our study showed no significant difference with either limited or diffuse forms of scleroderma and this was partially correlated with *Wan and his colleagues* study.

Wan et al. (2001), reported that no evidence of reduced ABPI in limited cutaneous disease, they concluded that the severity of large vessel macrovascular disease, as assessed with ABPI, is not dependent on disease subtype. Angiography of the upper limb demonstrated distal disease alone in 86% of SSc patients both with and without other vascular risk factors such as smoking. In the lower limb there was a highly significant association between the presence of other risk factors and macrovascular disease potentially amenable to angioplasty, and conversely between the absence of other vascular risk factors and distal disease of the lower limbs *(Dick et al., 2001).*

Our results showed that there was a statistically significant difference between carotid duplex scanning and blood sugar and ABPI. Plaques were found to be of non-significant difference with carotid duplex scanning.

The role of duplex scanning in the investigation of carotid artery disease is well established, and there is evidence to suggest that it has a predictive role in identifying those patients with a greater than normal risk of stroke *(Johnson et al., 1995).* There is no scientific evidence at present to indicate an excessive occurrence of stroke disease in these patients.

Summary:

This study demonstrated a high prevalence rate of macrovascular disease in systemic sclerosis. Early detection and proper management will help in better outcome and attenuation of high rate of cardiovascular deaths in systemic sclerosis.

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