Evaluation of carotid artery intima-media complex thickness as a marker of vascular damage secondary to accelerated atherogenesis in progressive systemic sclerosis

Avaliação da espessura do complexo médio-intimal da artéria carótida como marcador de aterogênese acelerada secundária a dano vascular na esclerose sistêmica progressiva

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A B S T R A C T

Objective: To evaluate the intima-media thickness of the common carotid artery in patients with and without scleroderma; to verify a possible association with disease severity; to assess the relationship of intima-media thickness with known cardiovascular risk factors. **Methods:** In a case - control study, thirty patients with scleroderma and 30 without the disease were selected and matched according to age, sex and cardiovascular risk factors such as hypertension, diabetes mellitus and hypercholesterolemia. The age ranged from 17 to 79 years (mean 49). All patients underwent carotid artery evaluation by high-resolution vascular Doppler in order to measure the intima-medial thickness of the carotid 2 cm from the bifurcation. In all the analysis was considered the greatest value of intima-media thickness in right and left carotid arteries. **Results:** The sample consisted of 30 patients, 29 (96.67%) women and one man (3.3%). In this sample, 11/30 (36.67%) had high blood pressure, 5/30 (16.67%) had diabetes mellitus, 6/30 (20%) had dyslipidemia and 2/30 (6.67%) were smokers. Comparing the measure of the increased risk (maximum intima-media thickness between the left and right side), was obtained an average of 0.77 mm for group scleroderma and a value of 0.70 mm for the control group (p = 0.21). In assessing the association between disease severity and carotid intima-media thickness, was found no significant association (p= 0.925). **Conclusion**: Was found a slight increase in intima-medial thickness of common carotid artery in patients with scleroderma but without statistical significance. Regarding the severity of the disease and intima-medial thickness of common carotid artery, there was no significant difference.

Key words: Patients. Scleroderma, systemic. Carotid arteries. Atherosclerosis. Carotid intima-media thickness.

INTRODUCTION

Systemic scleroderma is an autoimmune rheumatic disease that has vascular injury as one of its main clinical markers[1]. This injury is an important cause of increased morbidity, mortality and loss in quality of life of this group of patients[1]. Some possible mechanisms responsible for ischemic events are vasospasm, endothelial damage by immune activity and abnormalities of glucose homeostasis[2]. It is believed that the interaction of genetic predisposition to the stimulation of environmental factors can lead to vascular dysfunction and ischemia resulting in tissue fibrosis in advanced stages of disease [3].

The most obvious clinical manifestation and early vascular involvement is Raynaud's phenomenon, which occurs as the first manifestation in 70% of patients and in up to 95% of cases over the course of the disease[4]. It is defined as an abnormal vasoconstrictor response to cold that causes episodes of recurrent spasms of the digital arteries, arterioles and cutaneous arterio-venous shunts. It is observed that a significant reduction in blood flow can occur leading to complete closure of the vessel lumen[5]. All these changes can cause chronic tissue hypoxia and irreversible tissue damage, with the formation of recurrent ulcers, fibrosis and, in severe cases, gangrene or even amputation of the extremities[5].

Although the microvascular involvement is a marker of systemic scleroderma, the involvement of macrovasculature or macrovascular disease is also often associated with significant morbidity and mortality [6]. However this latter form of vascular involvement in scleroderma is not widely accepted, although some authors have described this association[6].

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Atherosclerotic disease may be a contributing element to the macrovascular lesion in systemic scleroderma. This assumption becomes attractive when it is observed that patients with long term inflammatory disease have accelerated atherogenesis[7]. This atherogenesis is generated by the persistence of the inflammatory process with release of mediators such as interleukin (IL) -6, tumor necrosis factor alpha (TNF-a), C-reactive protein (CRP) and adhesion molecules that contribute to endothelial dysfunction, formation of atheroma, unstable plaque and development of thrombi[7].

The association between subclinical atherosclerosis and severity of the inflammatory response is clearly demonstrated in diseases such as rheumatoid arthritis and systemic lupus erythematosus [8]. However in scleroderma (a rarer disease), these studies are not conclusive. In this sense, the documentation of accelerated atherogenesis in patients with systemic scleroderma is of fundamental importance since the prevention of risk factors may act as a modifier of prognosis.

Thus, this study aimed to verify: (1)- the existence of accelerated atherosclerotic process in patients with systemic sclerosis by measuring the thickness of the intima-media complex (ECMI) of the common carotid artery compared with the population without a systemic inflammatory disease ; (2) To associate this thickness with disease severity.

METHODS

This is a prospective analysis, case-control study developed in the clinic of Rheumatology and Vascular Surgery of the Evangelical Hospital in Curitiba, Paraná, Brazil. Patients with scleroderma diagnosis according to preliminary criteria of the American College of Rheumatology[9] were selected by active search in the period November 2010 to August 2011.

This study was approved by the local Ethics Committee and all patients signed an informed consent.

The sample consisted of 30 patients with scleroderma who underwent carotid artery evaluation by high-resolution vascular ultrasound. For the control group, we selected 30 patients without scleroderma, without any other inflammatory disease and matched according to age, sex and cardiovascular risk factors such as hypertension, diabetes mellitus and hypercholesterolemia.

The protocol for data collection consisted of a questionnaire with clinical history, data collected from patient's chart and clinical value of carotid artery doppler ultra sound. From chart review we recorded: a) demographic data (sex, current age, age of onset and duration of the disease); b) lipid profile, fasting glucose levels , blood pressure and tobacco exposure. Lipid profile values were considered abnormal if total cholesterol > 240 mg%, LDL-C> 160 mg%, HDL-C <40 mg% and triglycerides> 200 mg%[10], diabetes mellitus (blood glucose> 126mg/dl)[11]. Hypertension was considered when systolic blood pressure > 140mmHg and/or diastolic blood pressures was> 90 mmHg in at least two occasions[12]; c) form of scleroderma and profile of clinical involvement defined by ACR criteria[13] to measure the disease index of severity or Medsger index [14]. This severity index is a scale from zero to 36 which is scored according to the impairment of the locomotor system and skin, muscle weakness and general symptoms such as weight loss, gastrointestinal involvement, presence of Raynaud's, cardiac and pulmonary and renal involvement. Zero is the absence of involvement and 36 is maximum severity.

The measurement of carotid artery - ECMI - was done in the common carotid artery in the 2 cm distal from carotid bifurcation. The greatest value of ECMI in right and left carotid arteries was considered throughout the analysis. For this measurement we used the apparatus of vascular ultrasound Esaote My Lab 70 XVG and a 7.5 MHz linear transducer with frequency between 7 and 9 MHz, in longitudinal section, B-mode. The thickness of measurement was done considering the distance between two echogenic lines represented by the lumen-intima interface and media-adventitia of the arterial wall. All examinations were performed by the same operator who was unaware of patients' clinical data. The intima-media complex of 0.8 mm thickness[14] was considered normal. For purposes of statistical analysis, we used the worst value found in the right or in the left carotid as it translated the risk of stroke.

For comparison of two groups with regard to quantitative variables, the Student's t test was used for independent samples. For comparison of scleroderma patients and controls, in relation to the thickness of the carotid artery intima-media was considered the multivariate analysis of variance. To assess the association between disease severity and the thickness an estimative was made through the Spearman correlation coefficient. For a description of the results obtained in relation to the quantitative variables were presented descriptive statistics of mean, median, minimum and maximum values and standard deviation. For a description of qualitative variables were expressed by the results of frequencies and percentages. P values less than 0.05 were considered statistically significant.

RESULTS

The sample of 30 scleroderma patients studied consisted of 29 (96.67%) women and one man (3.3%) aged between 17 and 79 years (mean 48 years). In this sample there were 11/30 (36.67%) with hypertension, 5/30 (16.67%) with diabetes mellitus, 6/30 (20%) with dyslipidemia and 2/30 (6.67%) smokers. The analysis of distribution of forms of scleroderma showed that 31.8% of patients had a diffuse, limited to 59.09% and 9.09% how

to overlap with another connective tissue disease (one with systemic lupus erythematosus and one with polymyositis).

In the control group there were 100% women, 5/30 (20%) cases of dyslipidemia, 2/30 (6.67%) of smokers, 12/30 (36.37%) of hypertension and 6/30 (30%) of diabetes mellitus. Data from the pairing of the sample between scleroderma patients and controls can be appreciated in table 1.

Analyzing the data on the higher value of ECMI carotid of patients and controls, in table 2, it is shown that there is no differences between patients with systemic sclerosis and controls.

The severity of disease measured by the Medsger index varied between 2 and 15 (median 6). Studying the thickness of the carotid artery intima-media in relationship to the severity of the disease no correlation was found (p = 0, 925, R Spearman 0.02).

DISCUSSION

In this study that was conducted with 30 patients, it is not possible to prove the increased thickness of carotid artery in scleroderma compared to controls. In interpreting these results one should take into account that the analyzed sample is small as it happens in all relatively rare diseases. So the sample may be subject to a statistical type II error. However the study's findings agree with others in the literature, as published by Hettema *et al.*[15] that evaluated 49 patients with scleroderma, compared with a control group and also showed no differences between the ECMI of the carotid arteries of patients with or without scleroderma. These authors suggested that there was no higher prevalence of premature atherosclerosis or macrovascular disease in this group of patients. In another publication[16] where it was evaluated the association of macrovascular disease and atherosclerosis in patients with scleroderma, this association was found. They reported the already documented and proven association between peripheral vascular disease in patients with scleroderma[17,18].

The measure of ECMI carotid artery in patients with scleroderma have been the subject of several studies of similar design as the one discussed here, and have shown conflicting results. In seven evaluated studies, four had significant difference and three had similarities with our results [15,19-23].

Another study[20] was designed to compare the carotid and femoral arteries of scleroderma patients, not only with a control group but also according the scleroderma forms (limited or diffuse). This study, that considered both the ECMI of these arteries and their degrees of elasticity and stiffness, found a significant association between arterial stiffness and the presence of scleroderma; the arteries of the diffuse scleroderma group showed lower elasticity compared to the limited extent and with the control group. Regarding the ECMI of the carotid arteries was an association between scleroderma and increased ECMI, but without reaching statistical significant difference, as in the present work.

In a study to assess endothelial dysfunction as a predictor of atherosclerosis in patients with scleroderma, Szucs *et al.*[20] compared 29 patients with and without scleroderma. These authors evaluated the ECMI by Doppler ultrasound of the carotid arteries and endothelium-mediated dilation and nitroglycerin flow in the brachial artery of these patients. With respect to endothelial dilatation they reported that patients with scleroderma showed less dilatation of arterial layers when compared to the control group,

Table 1 - Data on scleroderma patients and controls pairing.

	Scleroderma n=30	Control n=30	p
Gender (female: male)	29 (96.67%):	1 (3.33%)	30 (100%):0
Dyslipidemia	6/30 (20%)	5/30 (20%)	
Tobacco exposure	2/30 (6.67%)	2/30 (6.67%)	
Hypertension	11/30 (36.67%)	12/30 (36.37%)	
Diabetes mellitus	5/30 (16.67%)	6/30 (20%)	
Mean age ± SD (years)	48.63 ± 14.59	49.83 ± 15.56	

SD= standard deviation.

Table 2 - Data on carotid intima-media thickness (value at higher risk - measured in mm) by ecodopler of patients and controls.

Grupo	n	Mean	Median	Mínimal	Máximum	SD	P value
Scleroderma	30	0.77	0.74	0.42	1.20	0.20	0. 212
Control	30	0.70	0.70	0.40	1.40	0.23	

suggesting less arterial elasticity in patients with scleroderma. When they compared the capacities of arterial dilatation with the administration of nitrates, no significant difference was found. In both groups major arteries vasodilatations occurred. When these authors[20] evaluated the carotid ECMI, they reported a slight increase in scleroderma patients, but also with no statistically significant difference. An important finding of this study was a significant association of the increase of ECMI with age and time of scleroderma.

Cheng *et al.* [24] compared the ECMI of the carotid and femoral arteries of patients with primary and secondary Raynaud phenomenon and compared them to a control group without Raynaud's. They concluded that there was a significantly thickened ECMI carotid arteries in patients with Raynaud's secondary to scleroderma compared to patients with the primary form. With respect to the femoral arteries, they found no association between all groups. These data raise the possibility that some of the pathophysiological mechanisms of scleroderma, in particular (for example, those involved in Raynaud's phenomenon) are associated with the findings from the intima-media rather than the whole. In other rheumatic diseases like lupus erythematosus and rheumatoid arthritis, increased atherogenesis has been attributed to damage of the endothelial wall by oxidative stress secondary to generalized inflammation[25]. This fact cannot be proved in scleroderma, which suggests that there are important pathophysiological differences between this disease and other rheumatic diseases

In the present study, we cared to match the samples to avoid bias in the analysis of the results. This is because there are many factors that influence the increased thickness of the intima-media layer such as dislipidemia or tobacco exposure diabetes and hypertensiom[3,26].

In an article published by Sherer *et al.*[23], an early association of atherosclerosis and autoimmune markers in patients with scleroderma was examined. Forty-four patients with scleroderma underwent Doppler examination of the carotid ECMI and matched for age, type of disease and classic risk factors for atherosclerosis. Unlike the present study, these authors found a significant statistical value for the ECMI in scleroderma patients, but age was the main benchmark significantly higher.

A Brazilian study[24] evaluated prospectively a case series of 20 patients with scleroderma and tried to graduate the macrovascular involvement in these patients. The vast majority were women and were evaluated by Doppler ECMI the carotid arteries of upper limbs, lower limbs and abdominal aortic atheromatous plaques to search. The authors observed that in the lower limbs arteries the ankle-brachial index was normal in all patients. They also found an increase in ECMI in 12 patients (or 60%) of the patients. With respect to vascular sites evaluated, the prevalence of affected places were 45% in the abdominal aorta, 35% in lower limb arteries, carotid and 30% in only 5% in the upper limb arteries. With these results, they affirm that the found macrovascular changes are not necessarily associated with scleroderma and may arise from the atherosclerotic process.

The present work shows that there is no association of thickening of the intima-media in patients with scleroderma, suggesting that there is not accelerated atherogenesis in these patients. Similarly, we can say that scleroderma is mainly a microvascular disease. With the advent of intravascular ultrasound to further evaluate the vascular endothelium, and with the advancement of laboratory tests of inflammatory markers for scleroderma, the scientific community may still contribute to a better quality of life for patients with this disease.

In conclusion, it can be inferred that there is no significant difference in the thickening of the intima-common carotid artery to compare patients with and without scleroderma. There is no association between severity of scleroderma and thickening of the intima-media of common carotid.

R E S U M O

Objetivo: *Avaliar a espessura da camada médio-intimal da artéria carótida comum em pacientes com e sem esclerodermia e verificar possível associação com sua gravidade.* ***Métodos:*** *Em estudo caso-controle, foram selecionados 30 pacientes com esclerodermia e 30 sem a doença e pareados de acordo com a idade, sexo, hipertensão arterial sistêmica, diabete melito e hipercolesterolemia. Todos os pacientes foram submetidos à avaliação das artérias carótidas pela ultrassonografia vascular de alta resolução e realizada a medida do espessamento da camada médio-intimal das carótidas comuns a 2 cm da bifurcação carotídea. Em toda a análise foi considerado o maior valor da camada médio-intimal nas artérias carótidas direita e esquerda.* ***Resultados:*** *A amostra foi composta de 30 pacientes estudados, sendo 29 (96.67%) mulheres e um homem (3,3%) com idade de 17 a 79 anos (média de 48 anos). Nesta amostra existiam 11/30 (36,67%) com hipertensão arterial, 5/30 (16,67%) com diabete melito, 6/30 (20%) com dislipidemia e 2/30 (6,67%) fumantes. Ao comparar a medida do maior risco (espessura máxima entre o lado esquerdo e o lado direito), obteve-se média de 0,77mm para o grupo esclerodermia e valor de 0,70 mm para o grupo controle (p=0,212). Ao avaliar a associação entre gravidade da doença e a camada médio-intimal da carótida, não se encontrou associação significativa (p=0,925).* ***Conclusão****: Encontra-se discreto aumento do espessamento da camada médio-intimal da artéria carótida comum em pacientes com esclerodermia, mas sem significância estatística. Com relação à gravidade da doença e o espessamento da camada médio-intimal da carótida comum, não foi verificada diferença.*

Descritores: *Pacientes. Escleroderma sistêmico. Artérias carótidas. Aterosclerose. Espessura íntima-média carotídea.*

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