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ORIGINAL ARTICLE

Assessment of subclinical atherosclerosis with carotid intima-media thickness in patients with scleroderma

Sklerodermalı hastalarda karotis intima-media kalınlığı ile subklinik aterosklerozun değerlendirilmesi

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ABSTRACT

Aim: Inflammation has an important role in the development of atherosclerosis. The risk of atherosclerosis and its complications is higher for patients with diseases such as systemic lupus erythematosus and rheumatoid arthritis in whom inflammatory activity is higher than for healthy individuals. However, several studies have shown conflicting results in patients with scleroderma. In this study, carotid intima-media thickness (CIMT) was compared in patients with scleroderma and a control group.
Methods: Thirty patients diagnosed with scleroderma (mean age 51.3 ± 11.8 years) and 30 healthy volunteers were included in the study. The groups were similar regarding age, gender, and risk factors for atherosclerosis.
Results: There was no statistically significant difference between the groups in terms of age, gender, lipid level, hypertension, and diabetes mellitus prevalence (p>0.05). The mean CIMT (scleroderma group: 0.070±0.011, control group: 0.048±0.008, p<0.001) and the maximum CIMT (scleroderma group: 0.076±0.013, control group: 0.054±0.009, p<0.001) were statistically significantly higher in the patients with scleroderma. There was a statistically significant correlation between the mean CIMT and hsCRP (r=0.48, p<0.001); and the mean CIMT and the erythrocyte sedimentation rate (r=0.50, p=0.007) in the scleroderma group. The maximum CIMT and the mean CIMT were significantly higher in patients with diffuse type scleroderma compared to the patients with localized scleroderma (p values 0.001 and 0.011, respectively).
Conclusion: Our results show that CIMT is higher in patients with scleroderma compared to the control group, and this is associated with increased inflammatory activity.

Keywords: atherosclerosis; carotid intima-media thickness; inflammation; scleroderma

ÖZ

Amaç: Enflamasyon ateroskleroz gelişiminde önemli bir role sahiptir. Enflamatuvar aktivitenin yüksek olduğu sistemik lupus eritematozus ve romatoid artrit gibi hastalıkları olan hastalarda ateroskleroz ve ateroskleroza bağlı gelişebilecek komplikasyon riski sağlıklı bireylere göre daha yüksektir. Bununla birlikte, birkaç çalışma sklerodermalı hastalarda çelişkili sonuçlar göstermiştir. Bu çalışmada karotis intima-media kalınlığı (KİMK) kullanılarak sklerodermalı hastalar ve kontrol grubu karşılaştırıldı.
Yöntemler: Çalışmaya skleroderma tanısı konan 30 hasta (ortalama yaş 51.3 ± 11.8 yıl) ve 30 sağlıklı gönüllü dahil edildi. Gruplar yaş, cinsiyet ve ateroskleroz için risk faktörleri açısından benzerdi.
Bulgular: Gruplar arasında yaş, cinsiyet, lipid düzeyi, hipertansiyon ve diabetes mellitus prevalansı açısından istatistiksel olarak anlamlı fark yoktu (p>0.05). Ortalama KİMK (skleroderma grubu: 0.070±0.011, kontrol grubu: 0.048±0.008, p<0.001) ve maksimum KİMK sklerodermalı hastalarda (skleroderma grubu: 0.076±0.013, kontrol grubu: 0.054±0.009, p<0.001) istatistiksel olarak anlamlı derecede yüksekti. Ayrıca ortalama KİMK ile hsCRP arasında (r=0.48, p<0.001) ve ortalama KİMK ile eritrosit sedimantasyon hızı arasında (r=0.50, p=0.007) skleroderma grubunda istatistiksel olarak anlamlı fark izlendi. Diffüz tip sklerodermalı hastalarda maksimum KİMK ve ortalama KİMK, lokalize sklerodermalı hastalara göre anlamlı olarak daha yüksekti (sırasıyla p değerleri 0.001 ve 0.011).
Sonuç: Sonuçlarımız, kontrol grubuna göre sklerodermalı hastalarda KİMK'nin daha yüksek olduğunu ve bunun artmış enflamatuar aktivite ile ilişkili olabileceğini göstermektedir.

Anahtar kelimeler: ateroskleroz; enflamasyon; karotis intima-medya kalınlığı; skleroderma

Introduction

Atherosclerosis is a process that develops in the intima layer of large and intermediate arteries. The most obvious event is endothelial dysfunction and low-grade inflammatory activity in the pathophysiological process. Today, atherosclerotic disease is accepted as a low-grade inflammatory event (1). Revealing the association between high sensitive C-reactive protein (hsCRP), which has recently gradually gained importance as an indicator of inflammatory activity, suggests that inflammatory activity has a role in determining the progression and complications of atherosclerosis in addition to its initiation (2). Flow-mediated vasodilation (FMD) and carotid intima-media thickness (CIMT) in the brachial artery are two non-invasive tests used for subclinical atherosclerosis, vascular structure and function (3,4). CIMT can be

used to diagnose structural change in the vessel wall early. CIMT increase is correlated with cardiovascular risk factors (5,6) and is an independent predictor of cardiovascular and cerebrovascular events (7,8).

Connective tissue diseases are diseases characterized by more inflammatory activity than that observed in atherosclerosis. Cardiovascular risk is higher and cannot be explained with conventional risk factors in systemic lupus erythematosus (SLE), a prototype of these diseases (9). In addition, CIMT, a non-invasive method for detecting atherosclerosis, is higher in these patients. Immunological and inflammatory changes are claimed to have a role in these changes (9). Similarly, study results have suggested that subclinical atherosclerosis is seen significantly more in patients with rheumatoid arthritis (RA) (10). However, data have also shown increased histological inflammation and decreased atherosclerosis in patients with rheumatoid arthritis compared to a control group (11). The conflicting results may result from the unique properties of each rheumatologic disease.

Data about scleroderma are limited. Data have shown that CIMT increases with age and disease duration (12). In addition, the flow-dependent vasodilation ability of the brachial artery decreases as an indicator of endothelial dysfunction, and CIMT increases as an indicator of subclinical atherosclerosis in patients with scleroderma (13). However, data suggesting that angiographically-visible coronary artery disease is not different from a control group were also obtained (14). Since low-grade inflammation plays a role in the pathogenesis of atherosclerosis, subclinical atherosclerosis is seen more in the scleroderma group in which immune/inflammatory activity is more prominent. However, there is less information about this issue and conflicts compared to other rheumatologic diseases. Subclinical, early atherosclerosis has been investigated in patients with scleroderma in many groups. Conflicting results were reported in the studies that used CIMT as an indicator of early atherosclerosis. Although some researchers did not find significant changes in CIMT and intraluminal diameter (15-17), others found significant increases in CIMT in patients with scleroderma (13,18).

Therefore, we aimed to evaluate whether CIMT, an indicator of subclinical atherosclerosis that can be evaluated non-invasively, is high or not in patients with scleroderma compared to controls matched for risk factors.

Methods

Patient selection

Patients who were being followed up with a diagnosis of scleroderma at the Rheumatology Clinic of our hospital were included in the study. Patients who did not agree to participate or who had a history of coronary artery disease, cerebrovascular disease, peripheral artery disease, or aortic aneurysm (which are regarded as coronary artery disease equivalent), history of infection within the recent one year, chronic renal failure, or collagen tissue disease except scleroderma were excluded. The control group was matched with the study group regarding age, gender, and coronary artery risk profile to minimize the potential conflicting effect. A total of 60 individuals (30 patients and 30 controls) who met the inclusion criteria and provided informed consent were enrolled in the study. The study protocol was approved by our institute's ethics committee.

Laboratory analysis

Biochemistry tests, fasting plasma glucose, blood urea nitrogen (BUN), creatinine, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, sedimentation rate, C-reactive protein (CRP), and rheumatoid factor (RF) were analyzed. High sensitive CRP and RF were tested with the immunonephelometric method (Dade Behring BN II System, Germany).

Of immunological tests, anti-nuclear antibody (ANA) was the evaluated with the indirect immunofluorescent method, and anticentromer antibody and anti Scl-70 were evaluated with the immunoblot method. These tests were not performed in the control group.

Carotid artery intima-media thickness measurement
B-Mode ultrasonography examinations were conducted with a 13 MHz linear array transducer using Vivid 7 ultrasonography device (Vivid 7, GE Medical Systems Inc., Chicago, USA). All ultrasonography examinations were performed in the right coronary artery by the same operator. Images were recorded in a digital environment and interpreted off-line.

The patient's head in the supine position was taken to mild extension from the neck, and the transducer was placed transverse on the midline of the cervical region. The transducer was mildly shifted to right and left, and the carotid arteries were visualized from the transverse section. The transducer was rotated in the longitudinal section, and the carotid bulbus was localized. Images were obtained from the segment approximately 1 cm before the bulbus level, and the bulbus and internal carotid artery in the longitudinal plane. The lumen-intima and media-adventitia interfaces of the posterior wall of the carotid artery were made visible using the magnification-zooming functions of the device. At least 3 measurements were performed from the posterior wall in each segment, and the mean value was found. The maximum CIMT and the mean CIMT were used for statistical analysis.

Statistical analysis

SPSS 11.5 (Statistical Package for Social Sciences-SPSS, Inc., Chicago, Illinois) for Windows was used to analyze the data. Normally distributed parameters were expressed as mean ± standard deviation (SD) and compared using Student's t test for independent

groups. Parameters not normally distributed were expressed as the median (interquartile range: IQR) in addition to the mean ± standard deviation (SD) and compared with the Mann-Whitney U test. The correlation between the CIMT and inflammatory markers in the scleroderma group was evaluated with the Spearman correlation. A p level of <0.05 was accepted as statistically significant.

Results

A total of 60 patients (30 scleroderma patients and 30 controls) were included in the study. The baseline clinical characteristics of the patients are shown in Table 1. The mean age was 51.3 ± 11.7 years in the patient group and 49.3 ±10.5 years in the control group; no significant difference was found between the groups (p=0.51). No difference was detected between the groups regarding age, diabetes mellitus, hypertension, smoking, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels (Table 1).

Table 1. Comparison of baseline characteristics of the control and patient groups. Values are the mean ± standard deviation or n (%).

	Scleroderma (n=30)	Control (n=30)	P value
Age	51.3 ± 11.7	49.3 ±10.5	0.51
Gender			
Female n (%)	29 (96.7)	29 (96.7)	1.00
Male n (%)	1 (3.3)	1 (3.3)	
Diabetes mellitus n (%)	1 (3.3)	1 (3.3)	1.00
Hypertension n (%)	5 (16.7)	5 (16.7)	1.00
Smoking n (%)	5 (16.7)	5 (16.7)	1,00
Total cholesterol (mg/dl)	189.1 ± 56.4	186.1 ± 39.8	0.81
LDL cholesterol (mg/dl)	113.5 ± 45.7	109.9 ± 33.0	0.73
HDL cholesterol (mg/dl)	48.3 ± 7.9	50.1 ± 10.6	0.48
Triglyceride (mg/dl)	135.2 ± 57.8	134.8 ± 61.6	0.98

The maximum and mean CIMT measurements were statistically significantly higher in the patients with scleroderma compared to the controls, as shown in Table 2 and Fig. 1 and 2.

Table 2. Carotid intima-media thickness of the scleroderma and control groups

	Scleroderma (n=30)	Control (n=30)	p value
Maximum CIMT (cm)	0.076 ± 0.013	0.054 ± 0.009	< 0.001
Mean CIMT (cm)	0.070 ± 0.011	0.048 ± 0.008	< 0.001

The rheumatologic and inflammatory markers in the patients with scleroderma are summarized in Table 3. A positive moderate correlation was observed between the inflammatory markers, hsCRP and sedimentation, and mean CIMT (r=0.48, p<0.001 for hsCRP; r=0.50, p=0.007 for sedimentation). Anticentromer antibody was negative in all patients, and antiScl was positive in all patients except two so they were not included in the statistical evaluation.

Diffuse type scleroderma was detected in 20 patients and localized scleroderma in 10 patients. The maximum and mean CIMT values were higher in the diffuse group as the result of assessments made for these subgroups (Table 4, Fig. 3 and 4). In addition, duration of disease was significantly longer in patients with diffuse type compared to patients with localized type [mean (SD): 13.00 (4.14) years; median (IQR) 12.50 (6.50) years in diffuse type; mean (SD): 8,50 (6.19) years; median (IQR) 7.50 (8.75) years in localized, p=0.024]. Similarly, triglyceride levels were also higher in patients with diffuse type [mean (SD): 154.00 (58.34) mg/dl; median (IQR) 140.00 (60.00) mg/dl in diffuse type; mean (SD): 97.80 (35.25) mg/dl; median (IQR) 89.50 (57.50) mg/dl in localized, p=0.011]. No significant difference was found between the two groups regarding the other conventional risk factors for atherosclerosis and inflammatory markers.

Table 3. Rheumatologic and inflammatory markers (n=30 in the scleroderma group)

	Mean ± SD	Median	IQR
hsCRP (mg/L)	4.9 ± 5.4	0.97	1.63
Sedimentation (mm/h)	23.2 ± 18.24	19.00	17.00
ANA	2.2 ± 0.76	2.0	1.0
RF (IU/ml)	12.6 ± 8.33	10.1	2.5

SD: Standard deviation; IQR: interquartile range; hsCRP: high sensitive C-reactive protein; ANA: antinuclear antibody; RF: rheumatoid factor

Table 4. CIMT values in diffuse and localized scleroderma

	Diffuse type		Localized type		p
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Maximum CIMT	0.082 ± 0.011	0.080 (0.020)	0.066 ± 0.008	0.070 (0.010)	0.001
Mean CIMT	0.074 ± 0.010	0.073 (0.017)	0.062 ± 0.009	0.065 (0.015)	0.011

IQR: Interquartile range; CIMT: carotid intima media thickness; SD: standard deviation

Discussion

Atherosclerosis is a multifactorial and multistage disease. There is chronic inflammation in all stages of the disease, which continues until the plaque ruptures (19). CAD risk increases in inflammatory diseases such as RA and SLE. CAD is responsible for mortality in patients with RA. Cerebrovascular diseases are the

second most common factor responsible for mortality in patients with RA (20). Subclinical atherosclerosis risk was high in RA independently from conventional risk factors (10). In a 2006 study conducted with 57 Indian patients with RA who did not have CAD, conventional risk factors and CAD risk equivalents, CIMT measured from bifurcation of the common carotid artery was significantly higher in patients compared to controls, and it was concluded that subclinical atherosclerosis was more frequent in these patients (10).

Cardiovascular morbidity and mortality are higher in SLE, an inflammatory disease, compared to controls. A study showed that atherosclerosis risk is high in patients with SLE (21). Cardiovascular event prevalence was between 6% and 10% and yearly incidence was 1.5% in prospective cohort studies (22,23). Another case-control study showed that MI risk was high in patients with SLE (24). CIMT was high in patients with SLE who had cardiovascular findings compared to the ones who did not have cardiovascular risk factors and the control group. Inflammation is considered to have a role in atherosclerosis development in patients with SLE. Elevated CRP was associated with atheroma plaque and high CIMT in a cohort composed of 214 patients with SLE (25). C3 elevation was associated with the size of atheroma plaque and coronary artery calcification and was evaluated as an indicator showing that inflammation increases CVD risk in patients with SLE (26).

Similarly, macrovascular disease and subclinical atherosclerosis risk are suggested to be high in patients with scleroderma in whom inflammatory activity is high. A meta-analysis was published on this subject recently. The meta-analysis included 14 CIMT and 7 FMD studies. This analysis showed that the patients with scleroderma had increased atherosclerosis compared to healthy controls (27).

Figure 1. Maximum carotid intima-media thickness in the patients with scleroderma and control groups.

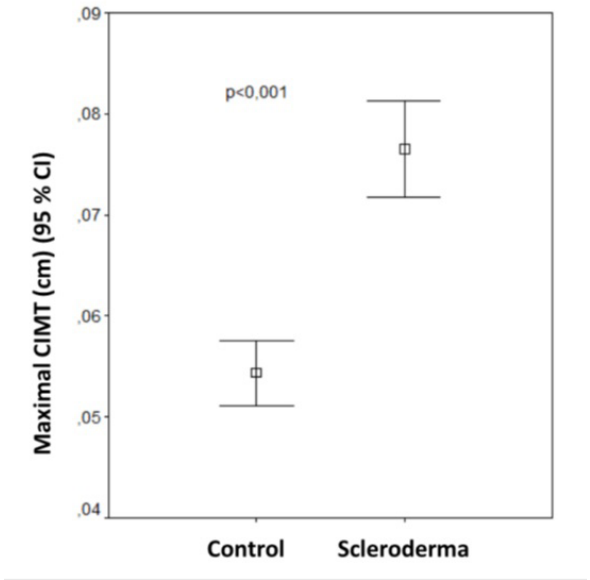


Figure 2. Mean carotid intima-media thickness in the patients with scleroderma and control groups.

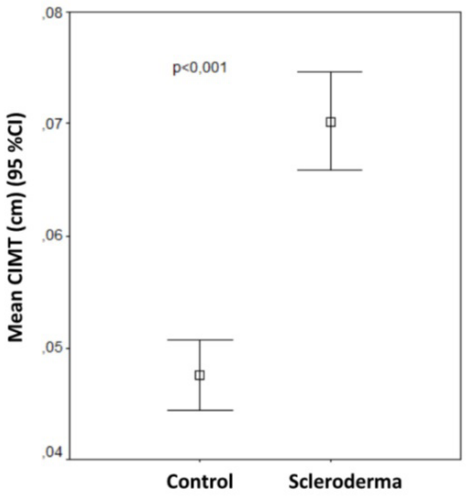


Figure 3. Maximum carotid intima media thickness (CIMT) in diffuse and localized scleroderma.

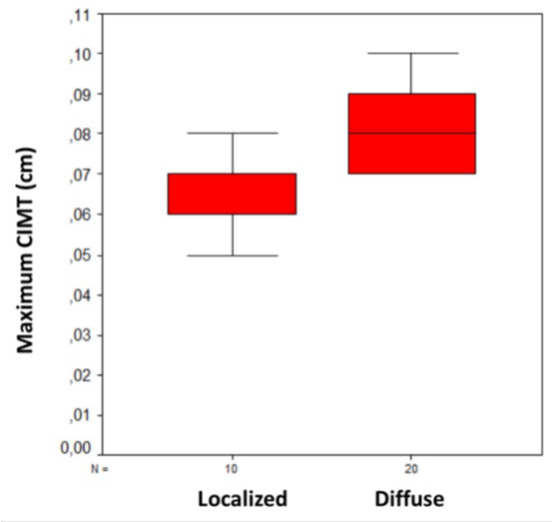
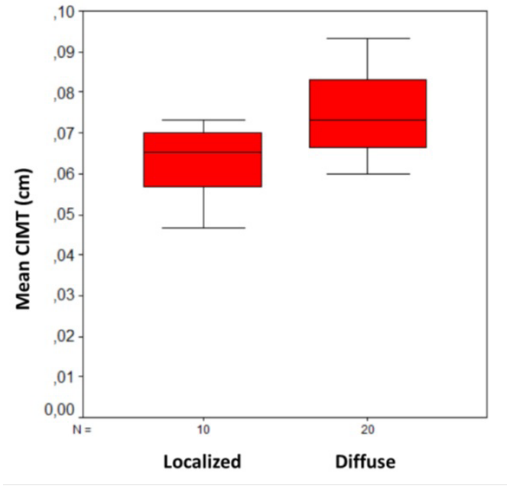


Figure 4. Mean carotid intima media thickness (CIMT) in diffuse and localized scleroderma



However, data on this issue are conflicting. In a study about macrovascular disease in 172 patients with scleroderma with suspicion of CAD, the presence of CAD was evaluated with coronary angiography, and CAD prevalence was reported as less high compared to the general population (14). However, coronary angiography is not sufficient for showing atherosclerosis, because coronary angiography is a diagnostic method that evaluates only coronary artery lumen through administering a contrast medium. Mild plaques, particularly ones that expand outward not inward (positive remodeling), may easily be overlooked on coronary angiography. In addition, reference segments that we evaluate (assume) as normal on coronary angiography may also have atherosclerotic plaques as atherosclerosis shows diffuse involvement. Thus, coronary artery disease prevalence does not provide accurate information when evaluated with coronary angiography.

In a 2007 study conducted in Italy based on the data that macrovascular disease risk is high in patients with scleroderma, 35 patients with scleroderma and 20 controls were evaluated. Endothelial functions and presence of subclinical atherosclerosis were evaluated by measuring FMD and CIMT in the brachial artery. Conventional CAD risk factors were also considered. FMD was impaired and a significant increase was detected in CIMT in the patients with scleroderma, but an association was not detected between impaired CIMT and FMD and conventional risk factors (13). These findings may suggest that early atherosclerosis development occurs more frequently in patients with scleroderma. Although the prevalence of conventional risk factors of atherosclerosis is high in patients with scleroderma, it is not clear how it affects macrovascular disease development or whether accelerates it or not. An association was not detected between conventional risk factors and macrovascular disease in that study. It was hypothesized that the factors such as inflammation, cytokines, and increased lipid oxidation could play a role in the pathogenesis of subclinical atherosclerosis. In addition, an association was not detected between subclinical atherosclerosis and duration, clinical course and laboratory features of scleroderma disease (13).

In a study, high prevalence of intermittent claudication was associated with peripheral arterial disease in patients with scleroderma; however, cardiovascular and cerebrovascular events were detected not to be higher than general population (28). In contrast, impaired FMD and increased CIMT are accepted as significant markers of atherosclerotic disease. In addition, increased FMD and CIMT are used as a strong predictor of cardiovascular disease and cerebrovascular events (29).

Lekakis et al. detected that FMD was impaired and CIMT increased in 12 patients who had primary or scleroderma-related Raynaud phenomenon (30). Szucs et al. observed that FMD was impaired; however, CIMT did not increase in 29 patients with scleroderma (12).

Macedo et al. found a slight increase in the intima-medial thickness of the common carotid artery in patients with scleroderma, but there was no statistical significance compared to the control group (17). However Schiopu et al. showed patients with scleroderma had a higher prevalence of carotid plaque and elevated serum proteins than matched controls (31).

Although data show that subclinical atherosclerosis risk is high in patients with scleroderma, researchers have proposed that these patients should be supported by new studies due to the presence of conflicting results and since data were obtained from a limited number of studies (27,32). Atherosclerosis is a chronic inflammatory disease. Data suggest that early atherosclerosis may develop in some autoimmune rheumatic diseases. The role of classical and non-classical risk factors is also known in these diseases. Scleroderma is characterized by vasculopathy, and microvascular involvement is common. Macrovascular involvement was also reported in some studies. Distal artery disease in fingers is a classical factor in patients with scleroderma. Although conflicting results were reported for CIMT measurement in these patients, data are also available reporting that the prevalence of coronary artery and cerebrovascular disease is not high (14,33).

The presence of non-classical risk factors such as lipoprotein (a), oxidized LDL, and inflammation is also real in addition to the classical risk factors. Moreover, increased vascular injury-related markers such as antibody against oxidized LDL and soluble vascular adhesion molecules are associated with vascular injury in these patients.

The aim of our study was to evaluate the presence of subclinical atherosclerosis in patients with scleroderma through measuring CIMT due to conflicting and complex results. CIMT was compared in patients with scleroderma and a control group. Thirty patients diagnosed with scleroderma and 30 healthy controls were included in the study. Groups were similar regarding age, gender, and risk factors for atherosclerosis. Mean and maximum CIMT values were significantly high in the patients with scleroderma. In addition, a statistically significant relationship was found between mean CIMT and hsCRP and between mean CIMT and the erythrocyte sedimentation rate. This correlation was not shown in previous studies. In our study, subclinical atherosclerosis was more prominent in patients with scleroderma compared to the control group. This may have resulted from the increased inflammatory activity in the patients with scleroderma. In the assessment performed for the subtypes of scleroderma, CIMT was significantly higher in the diffuse type compared to the localized type. Although no difference was detected between the diffuse

and limited groups regarding inflammatory markers, duration of disease was longer and triglyceride was higher in the diffuse type; no difference was detected in the other risk factors for atherosclerosis. These findings suggest that inflammation plays a role in the CIMT increase in patients with scleroderma; however, the difference between diffuse and localized types suggest that long-term disease activity plays a role instead of the grade of inflammation. An important limitation is the small number of patients in the subgroups. The possible difference in levels of inflammatory markers between the subgroups could not be shown. Although the major risk factors for atherosclerosis were similar, finding different triglyceride levels could be due to a phenomenon developing in the small number of cases.

Data about early atherosclerosis are conflicting in patients with scleroderma. This conflict may be explained by multiple factors such as methodological differences, comorbidities, and different ratios of diffuse and localized diseases.

Limitations

Our study is a single center and cross-sectional study and included small patient and control groups. The patient numbers in scleroderma subgroups are not sufficient.

Conclusion

CIMT measurements were statistically significantly higher in the patients with scleroderma compared to the control group. This suggests that subclinical atherosclerosis prevalence increased in the patients with scleroderma. Subclinical atherosclerosis in the patients with scleroderma was associated with increased inflammatory activity in these patients. In addition, CIMT was greater in the diffuse type compared to the localized type.

Supporting these findings with further studies and evaluating whether it has a prognostic value would provide important knowledge about the pathophysiology of rheumatic diseases and atherosclerosis.

Conflicts of interest

The authors declare that there is no conflict of interest.

Financial support

The authors declare that this study has received no financial support.

Ethics approval

The study protocol was approved by the Research Ethics Committee of Ankara University Medical Faculty. Approval number: 128-3583 and date: 21st April 2008.

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