EPICARDIAL ADIPOSE TISSUE THICKNESS AND SYSTEMIC SCLEROSIS

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ABSTRACT

Aim*: Microvasculopathy and endothelial damage are obvious features of systemic sclerosis (SSc) and increases risk of cardiovascular disease. Epicardial adipose tissue (EAT) is localized beneath the visceral pericardium and has been shown to be closely related with coronary artery disease (CAD). The aim of this study was to investigate the thickness of EAT in SSc patients who had no previous or current history of cardiac involvement.*

Methods*: Thirty patients with SSc and 30 healthy controls (HC) were included to the study. Measurement of EAT was evaluated using echocardiography and Doppler imaging technique.*

Results*: EAT thickness was significantly higher in SSc group compared to HC (6.2±0.9 mm vs. 5.3±0.6 mm, p=0.01) and it was correlated with disease severity score (r=0.45, p=0.01) in SSc patients.*

Conclusion*: This is the first study, showing a significantly higher EAT thickness in patients with SSc. We believe that further studies are needed to clarify the role of epicardial adipose tissue thickness in patients with SSc.*

Key words*: Scleroderma, Systemic Sclerosis, Epicardial Adipose Tissue Thickness, Microvascular Dysfunction, Coronary Artery Disease.*

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by inflammation, vasculopathy and fibrosis of the skin and major organs, including heart and lung. Systemic sclerosis occurs worldwide, although its reported prevalence varies significantly in different countries[1,2,3]. The estimated incidence of systemic sclerosis in the United States is 20 cases per million population, and its prevalence has been estimated at 276 cases per million population, although the reported prevalence varies depending on the methodology used and the targeted population[1,2,4]. Ethnic and geographical clustering may contribute to the variability in terms of frequency. However, it appears that there is higher frequency among black individuals[5,6,7,8]. The heart involvement can be manifested by myocardial disease, conduction system abnormalities, arrhythmias or pericardial disease and influences prognosis of patients by shortening survival[9]. Endothelial damage and inflammation play an important role in the pathogenesis of atherosclerosis[10] and shown to accelerate in some connective tissue diseases. The association between inflammation and subclinical atherosclerosis was clearly demonstrated in rheumatoid arthritis and systemic lupus erythematosus[11]. Endothelial dysfunction and vasospastic attacks have been precisely revealed as major pathogenic features of SSc. Although vasospasm induced reversible myocardial perfusion abnormalities were shown in earlier studies[12-14], the real prevalence of coronary artery and macrovascular disease in SSc patients remains unclear.

Epicardial adipose tissue (EAT) is a metabolically active visceral fat deposit found around the heart, between the myocardium and pericardium[15]. The biochemical, physiological and biomolecular features of epicardial adipose tissue and the likelihood paracrine interactions within the heart have

been described in previous studies[15-16]. The embryological origin of EAT is resemble to intraabdominal visceral adipose tissue[17]. Previous reports indicated EAT to be a important risk factor for coronary artery disease than adipose tissue located in other parts of body and may have critical role in the development of coronary artery disease (CAD)[16-18-19]. Sade et al. reported that EAT was significantly increased in women with microvascular dysfunction[20]. As a result of these information, we hypothesized that EAT thickness could be a marker for CAD and microvascular dysfunction in SSc patients. In this study EAT thickness has been evaluated in SSc patients who had no manifest sign of cardiac involvement.

Materials and methods

30 consecutive SSc patients (Female/Male: 29/1) and 30 age and sex matched healthy controls (HC) (Female/Male: 28/2) were included in this cross-sectional and observational study. Patients with SSc diagnosis according to preliminary criteria of the American College of Rheumatology and LeRoy were selected by active search in the period January 2012 to August 2012[21-22]. All participants gave written informed consent. Exclusion criteria were being younger than 18 years of age and having personal history of CAD, infectious or inflammatory conditions.

Baseline characteristics of the patients including; age, gender, smoking status, diabetes or hypertension history, disease duration since the onset of the first non-Raynaud's symptoms and disease subset (diffuse, limited or sine scleroderma) were recorded. Hypertension was defined as repeated SBP measurements at least 140mmHg, repeated DBP measurements at least 90mmHg or chronic treatment with antihypertensive medications according to criteria of European Society of Cardiology. Diabetes was recorded when it was reported by the patient and appeared in their medical records or if the patient was receiving regular treatment with oral hypoglycemic agents or insulin. Patients who were using tobacco products on admission and those quitted smoking within the last year were considered as smokers

Echocardiography

All patients underwent complete transthoracic examination including two dimensional, color flow and pulsed doppler, tissue doppler imaging as well as epicardial fat thickness measurement with a GE-Vingmed Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway) using a 2.5-3.5 MHz transducer. All examinations were performed by an experienced cardiologist, unaware of patient's clinical information.

Epicardial fat thickness was evaluated on the free wall of right ventricle from the parasternal long axis view, using aortic annulus as an anatomic reference. Epicardial fat thickness, identified as an echo-free space between the pericardial layers on 2-dimensional echocardiography, was measured perpendicularly in front of the right ventricular free wall at end-diastole, for 3 cardiac cycles[23-24]. (Figure 1). The average value comprising three cardiac cycles of each echocardiographical view was used for the statistical analysis. Although MRI is the gold standart diagnostic method for measuring epicardial fat thickness,we did not use because of economic reasons and ethic rules.

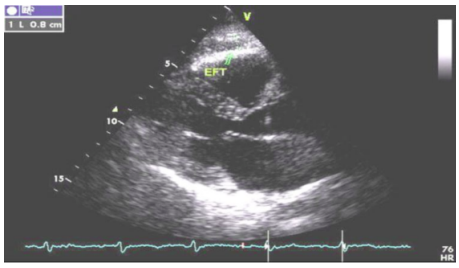

Figure 1: Mesaure of Epicardial Adipose Tissue Thickness(green arrow).

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 16.0 for Windows(SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.) .All data were expressed as mean ± standard deviation (SD). $P<0.05$ indicates statistical significance. Comparisons between means were made using non-parametric student t- test. Relationship between two continuous variables was examined by using Pearson correlation test.

Results

The mean age was 46.7±11.0 and 43.5±9.7 years in SSc patients and HC, respectively ($p>0.05$). The mean disease duration was 7.38±4.82 years in SSc patients. Twenty of them were treated with immunosuppressive agents (11 azathioprine,5 methotrexate, 2 mycofenolate mofetil, 2 cyclophosphamide). Most of patients were taking low dose

steroids (prednisone, <5 mg daily). All SSc patients had Raynaud phenomenon, 13 of 30 had digital ulcers. No difference was found among the groups in terms of having diabetes mellitus, hypertension, hyperlipidemia and smoking history.

The baseline characteristics of the SSc patients were highlighted in table 1.

Age (years)		46.7±11.0
Disease duration (years)		7.38±4.82
Disease subset	Limited n(%)	21 (70)
	Diffuse n(%)	4 (13.3)
	Overlap n(%)	5 (16.7)
Digital ulcer n(%)		13 (43.3)
Interstitial lung disease n(%)		18 (60)
Pulmonary hypertension n(%)		8 (26.7)
Gastrointestinal involvement n(%)		17 (56.7)
Rodnan skin score		11.8±9.05
Disease activity score* (mean±SD)		1.74±1.59
Disease severity score** (mean±SD)		4.69±3.17
Erythrocyte sedimentation rate (mm/h) (mean±SD)		26.3±17.0
C reactive protein (mg/dl) (mean±SD)		0.89±2.01
Concominant diseases n(%)	Diabetes mellitus	3 (10)
	Hypertension	3 (10)
Smoking history		3 (10)

Table 1: Demographic characteristics of scleroderma patients.
Data are expressed as meanşSD or count (percentage) for categorical variables SSc disease activity scale (25), ** SSc disease severity scale (26)*

In echocardiographic evaluation, EAT thickness was found higher in SSc patients than HC (6.2±0.9 mm vs. 5.3±0.6 mm, respectively, p=0.01).

None of the variables including lung or gastrointestinal involvement, hypertension, diabetes mellitus and smoking history were related to EAT (p>0.05). On the other hand, patients with digital ulcer had higher EAT thickness than without, but this difference has not reached statistical significance (0.66±0.07 vs. 0.60±0.09, respectively, p=0.07).

Disease related predictors of EAT thickness were examined by correlation analysis in SSc patients. EAT thickness was only correlated with disease severity score (17) (r=0.45, p=0.01) (table 2).

EAT thickness	Age	Disease duration	Disease severity score	Disease activity score	Rodnan skin score
r	0.15	-0.04	**0.40**	0.20	0.16
p value	NS	NS	**0.01**	NS	NS

Table 2: Correlation between epicardial adipose tissue (EAT) and clinical parameters.
Pearson correlation test, r: correlation coefficient

Discussion

In this study, we found significantly higher EAT thickness in patients with SSc compared to control group. To our knowledge, this is the first report demonstrating increased EAT thickness in SSc patients.

Epicardial fat is a particular form of visceral fat and located around the heart, is considered an important cardiovascular risk predictor, due to producing and releasing adipo-cytokines[23-27-28-29]. Epicardial fat seems to affect endothelial function and increase sympathetic system activity by paracrine influence. EAT was significantly increased in women with microvascular dysfunction and individual with a higher detectable carotid atherosclerosis[29,39]. Cetin et al. reported EAT was strongly correlated carotid intima-media thickness[31]. Ahn et al. showed that EAT was thicker in subjects with CAD than in those without, and that it might provide additional information for assessing CAD risk and predicting the extent and activity of CAD[32]. Another study, increased EAT volume and its association with premature cardiovascular disease were reported in systemic lupus erythematosus patients[33].

SSc is characterized by diffuse microvascular pathological process leading to cutaneous and visceral changes and to related clinical manifestations. Endothelial dysfunction and inflammation are most important pathogenic mechanisms in SSc, also recognized as an early marker of atherosclerosis[34]. In old necropsy studies coronary microvascular disease has been documented in SSc patients[35-36]. Carotid intima media thickness of SSc patients was investigated in a few clinical studies; Ho et al. showed increased carotid artery and peripheral vascular disease[37], but no difference was reported in an another study[38].

In a systematic review and meta-analysis reported a relation between accelerated atherosclerosis and autoimmune rheumatic diseases,which

increased cardiovascular risk have shown in a small number of patients with SSc[39].

Similarly, recently published Australian Scleroderma Cohort Study reported 3.2 times more common coronary artery disease (depending on patients' medical records of angina or myocardial infarction) in SSc patients than national health survey[40]. Despite these data, there was no comprehensive prospective study about invasive or noninvasive evaluation of CAD on SSc patients.

In our small cross-sectional study, we have found increased EAT thickness in SSc patients, despite they don't have overt CAD symptoms or signs. This finding can be considered as an indirect indicator of increased coronary artery disease and microvascular dsyfunction in scleroderma patients.

From a clinical perspective, EAT thickness tended to higher in patients with digital ulcer than without in our SSc group. One of the earlier study showed that myocardial perfusion defects was associated with the presence of digital ulcers, this finding might also be consistent with an abnormal vaso-reactivity as a possible pathogenetic mechanism linking cutaneous and myocardial microcirculatory involvement in SSc[41]. In addition, we found positive correlation between EAT thickness and disease severity score. This result supports the hypothesis that inflammation and endothelial damage play an important role in the pathogenesis of cardiovascular disease in SSc.

MRI is the gold standard diagnostic method for measuring epicardial fat thickness. A limitation of our study that, we could not confirm EAT using the standard MRI and CT methods. On the other hand, Echocardiography provide an objective, noninvasive, readily available method and is certainly less expensive than MRI or CT for measuring epicardial fat. Iacobellis et al. validated the measurement of EAT by M-mode and two-dimensional transthoracic echocardiography and showed an excellent correlation between echocardiographical epicardial fat thickness and MRI abdominal or epicardial fat measurements[24].

In this study, we have found increased EAT thickness in SSc and it is correlated with disease severity scale and digital ulcer. This is the first study, displaying a significantly higher EAT thickness in patients with SSc. These findings may enhance the utility of echocardiography as an assessment tool for patient's adiposity and, if confirmed, can assist in the risk stratification of patients with microvascular dysfunction and CAD in SSc.

We believe that further studies are needed to clarify the role of adipose tissue in patients with SSc.

References

1) Flemons WW. Clinical practice. Obstructive sleep 1. Mayes MD. *Scleroderma epidemiology*. Rheum Dis Clin North Am. May 2003; 29(2): *239-54*.
2) Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. *Incidence and prevalence of systemic sclerosis: a systematic literature review.* Semin Arthritis Rheum. Feb 2008; 37(4): *223-35*.
3) Barnes J, Mayes MD. *Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers*. Curr Opin Rheumatol. Mar 2012; 24(2): *165-70*.
4) Ranque B, Mouthon L. *Geoepidemiology of systemic sclerosis*. Autoimmun Rev. Mar 2010; 9(5): *A311-8*.
5) Silver RM, Bogatkevich G, Tourkina E, Nietert PJ, Hoffman S. *Racial differences between blacks and whites with systemic sclerosis*. Curr Opin Rheumatol. Nov 2012; 24(6)*: 642-8*.
6) Reveille JD. *Ethnicity and race and systemic sclerosis: how it affects susceptibility, severity, antibody genetics, and clinical manifestations*. Curr Rheumatol Rep. Apr 2003; 5(2): *60-7*.
7) Gelber AC, Manno RL, Shah AA, Woods A, Le EN, Boin F, et al. *Race and association with disease manifestations and mortality in scleroderma: a 20-year experience at the Johns Hopkins Scleroderma Center and review of the literature*. Medicine (Baltimore). Jul 2013; 92(4): *191-205*.
8. Laing TJ, Gillespie BW, Toth MB, Mayes MD, Gallavan RH Jr, Burns CJ. *Racial differences in scleroderma among women in Michigan*. Arthritis Rheum. Apr 1997; 40(4): *734-42*.
9) Champion HC. *The heart in scleroderma*. Rheum Dis Clin North Am 2008;34:*181-90*
10) Steffens S, Mach F. *Inflammation and atherosclerosis*. Herz 2004; 29: *741-8*
11) Salmon JE, Roman MJ. *Subclinical atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus*. Am J Med. 2008; 121(10 Suppl 1): *3-8*
12) Kahan A, Devaux JY, Amor B, Menkes CJ, Weber S, Nitemberg A, et al. *Nifedipine and thallium-201 myocardial perfusion in progressive systemic sclerosis*. N Engl J Med 1986; 314: *1307-402*
13) Alexander EL, Firestein GS, Weiss JL, Heuser RR, Leitl G, Wagner HN Jr, et al. *Reversible cold-induced abnormalities myocardial perfusion and function in systemic sclerosis*. Ann Intern Med 1986;105: *661-8*
14) Anvari A, Graninger W, Schneider B, Sochor H, Weber H, Schmidinger H. *Cardiac involvement in systemic sclerosis*. Arthritis Rheum 1992; 35: *1356-61*
15) Iacobellis G, Corradi D, Sharma AM. *Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart*. Nat Clin Pract Cardiovasc Med 2005; 2: *536-43*
16) Taguchi R, Takasu J, Itani Y, et al. *Pericardial fat accumulation in men as a risk factor for coronary artery*

disease. Atherosclerosis 2001; 157: *203-9*

17) Marchington JM, Mattacks CA, Pond CM. *Adipose tissue in the mammalian heart and pericardium:structure,foetal development and biochemical properties*. Comp Biochem Physiol B Comp Biochem 1989; 94: *225-32*

18) Gorter PM, de Vos AM, van der Graaf Y, et al. *Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography*. Am J Cardiol 2008; 102: *380-5*

19) Rosito GA, Massaro JM, Hoffmann U, et al. *Pericardial fat,visceral abdominal fat,cardiovascular disease risk factors,and vascular calcification in a community-based sample: the Framingham Heart Study*. Circulation 2008; 117: *605-13*.

20) Sade LE, Eroğlu S, Bozbaş H, Özbiçer S, Hayran M, Haberal A, et al. *Relation between epicardial fat thickness and coronary flow reserve in women with chest pain and angiographically normal coronary arteries*. Atherosclerosis 2009; 204: *580-5*

21) *Subcommittee for Scleroderma Criteria of the American Rheuatism Association Diagnostic and Therapeutic Criteria Committee.Preliminary criteria fort he classification of systemic sclerosis (Scleroderma)*. Arthritis Rheum 1980; 23: *581-90*

22) LeRoy EC, Black C, Fleischmajer R, et al. *Scleroderma (systemic sclerosis): classification, subsets and pathogenesis*. J Rheumatol 1988; 15: *202-5*.

23) Iacobellis G, Assael F, Ribaudo MC, et al. *Epicardial fat from echocardiography:a new method for visceral adipose tissue predicition*. Obes Res 2003; 11: *304-10*

24) Iacobellis G, Ribaudo MC, Assael F, et al. *Echocardiographic epicardial adipose tissue is realeted to anthropometric and clinical parametres of metabolic syndrome:A new indicator of cardiovascular risk*. J Clin Endocrinol Metab 2003; 88: *5163-8*.

25) Valentini G, Silman AJ, Veale D. *Assessment of disease activity*. Clin Exp Rheumatol 2003; 21(3 Suppl 29): *39-41*.

26) Medsger TA Jr, Silman AJ, Steen VD, Black CM, Akesson A, Bacon PA, et al. *A disease severity scale for systemic sclerosis: development and testing*. J Rheumatol 1999; 26(10): *2159-67*.

27) Iacobellis G, Pistilli D, Gucciardo M, Leonetti F, Miraldi F, Brancaccio G, et al. *Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease*. Cytokine 2005; *29: 251-5*.

28) Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS, et al. *Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease*. *Cardiovasc Diabetol 2006; 5: 1*.

29. Sacks HS, Fain JN. *Human epicardial adipose tissue: a review*. Am Heart J 2007; 153: *907-17*.

30) Nelson MR, Mookadam F, Thota V, Emani U, Al Harthi M, Lester SJ, et al. *Epicardial fat:an additional measurement for subclinical atherosclerosis and cardiovascular risk stratification?* J Am Soc Echocardiogr 2011; 24: *339-45*

31) Cetin M, Cakıcı M, Polat M, Suner A, Zincir C, Ardic I, et al. *Relation of epicardial fat thickness with Carotid intima-media thickness in patients with type 2 Diabetes Mellitus*. Int J Endocrinol. 2013; 2013: *769175*.

32) Ahn SG, Lim HS, Joe DY, Kang SJ, Choi BJ, Choi SY, et al. *Relationship of epicardial adipose tissue by echocardiography to coronary artery disease*. Heart 2008; 97(3): *7*.

33) Lipson A, Alexopoulos N, Hartlage GR, Arepalli C, Oeser A, Bian A, et al. *Epicardial adipose tissue is increased in patients with systemic lupus erythematosus*. Atherosclerosis. 2012; 223(2): *389-93*.

34) Le Brocq M, Leslie SJ, Milliken P, Megson IL. *Endothelial dysfunction: from molecular mechanisms to measurement, clinical implications,and therapeutic opportunities*. Antioxid Redox Signal 2008; 10: *1631-74*.

35) D'Angelo WA, Fries JF, Masi AT, Shulman LE. *Pathologic observations in systemic sclerosis (scleroderma): a study of fifty-eight autopsy cases and fifty-eight matched controls*. Am J Med. 1969; 46(3): *428-40*.

36) Follansbee WP, Miller TR, Curtiss El, Orie JE, Bernstein RL, Kiernan JM, et al. *A controlled clinicopathologic study of myocardial fibrosis in systemic sclerosis (scleroderma)*. *J* Rheumatol 1990; 17: *656-62*.

37) Ho M,Veale D, Eastmond C, Nuki G, Belch J. *Macrovascular disease and systemic sclerosis*. Ann Rheum Dis. 2009; 59: *39-43*.

38) Macedo R, Andretta M, Albers C, Skare T, Ribas-Filho J M, Czeczko N G. *Evaluation of carotid artery intima-media complex thickness as a marker of vascular damage secondary to accelerated atherogenesis in progressive systemic sclerosis*. Rev Col Bras Cir 2012; 39(1): *10-14*.

39) Tyrrell PN, Beyene J, Feldman BM, McCrindle BW, Silverman ED, Bradley TJ. *Rheumatic disease and carotid intima-media thickness: a systematic review and meta-analysis*. Arterioscler Thromb Vacs Biol 2010; 30(5): *1014-26*.

40) Ngian G-S, Sahhar J, Proudman S M, Stevens W,Wicks I P, Doornum SV. *Prevalence of coronary heart disease and cardiovascular risk factors in a national cross-sectional cohort study of systemic sclerosis*. Ann Rheum Dis 2012; 71(12): *1980-3*.

41) L Belloli, N Carlo-Stella, G Ciocia, A Chiti, M Massarotti, B Marasini. *Myocardial involvement in systemic sclerosis*. *Rheumatology 2008; 47: 1070-2*.

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