ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 27(1): 133-137, 2022
DOI: 10.5505/ejm.2022.59219

Choroidal Thickness and Serum Asymmetric Dimethylarginine Levels in Patients with Systemic Sclerosis

Umut Dağ[1], Selahattin Balsak[2*]

[1]*Gazi Yaşargil Eğitim ve Araştırma Hastanesi (bölüm, il, ülke)*
[2]*Batı Hastanesi (bölüm, il, ülke)*

ABSTRACT

In addition to skin and visceral organ involvement, various ocular manifestations have also been described in patients with systemic sclerosis (SSc) or scleroderma. In recent years, optical coherence tomography (OCT) has been introduced into use as a beneficial imaging method in determining macular changes and in measuring choroidal thickness. Asymmetric dimethylarginine (ADMA) is a marker investigated in critical patients due to its proven reductive effect on nitric oxide synthesis. The present study aimed to evaluate serum ADMA levels and changes in choroidal thickness in SSc patients.

The study included 20 adult SSc patients and 23 age- and sex-matched healthy subjects. Patients who had diabetes mellitus, hypertension, hypercholesterolemia, coronary heart disease, advanced-stage heart failure, renal failure, and a history of medication use and smokers and alcohol consumers were excluded. Patients' demographic characteristics and medical histories were recorded. Choroidal thickness was measured using OCT in the right and left eyes of the patients and controls. ADMA levels were measured in the serum samples.

The mean choroidal thickness was lower in the SSc group than in the control group; however, the difference reached the level of statistical significance only in nasal measurements (251.7±78.6 μm for the SSc patients and 279.2±50.7 μm for the control group; p=0.044). The ADMA level was found to be significantly higher in the SSc group than in the control group (0.545±0.130 μMol/L and 0.130±0.155 μMol/L, respectively; p=0.034).

Based on the study outcomes, the serum ADMA level was significantly elevated in the SSc patients in the period when choroidal changes were not evident yet. A better understanding of the data about SSc etiopathogenesis and the role of ADMA in this process would make a contribution to the studies performed to develop new treatment strategies.

Keywords: choroidal thickness; asymmetric dimethylarginine; systemic sclerosis; optical coherence tomography; ocular manifestations

Introduction

Systemic sclerosis (SSc) or sclerodermais an autoimmune connective tissue disorder of unknown etiology, which is characterized by vascular system injury, tissue fibrosis, and cutaneous collagen deposition (1). Immunological imbalance, environmental factors, genetic factors, and oxidative stress play a role in the pathogenesis of SSc (1). Different incidence and prevalence rates have been reported among geographical regions depending on the differences incase definitions and methodology. In many reports, the prevalence of SSc falls between 38 and 341 cases per million (2). The peak incidence of SSc is observed between the ages of 30 and 60 years; moreover, the disease is 6-9 times more frequent in females (2, 3).

Among autoimmune rheumatic diseases, SSc has the highest disease-related morbidity and mortality rates (2, 4); the reason for this is life-threatening organ involvement such as interstitial lung disease, pulmonary arterial hypertension, heart failure, severe gastrointestinal involvement, and renal crisis (2). In addition to skin and visceral organ involvement, various ocular manifestations have also been described in SSc patients. Ocular manifestations may involve the followings: anterior segment (eyelid, conjunctiva, sclera, cornea, iris, and glaucoma), posterior segment (retina, choroid), and orbit and extra-ocular muscles (5). Main ocular changes associated with SSc have been reported as dry eye and choroidal changes (3). Optical coherence tomography (OCT) has been introduced into use as a useful imaging technique for determining macular changes

***Corresponding Author:** Selahattin Balsak, Diyarbakır Gazi Yaşargil Egitim ve Arastırma Hastanesi Goz Hastalıkları Kliniği, Uçkuyular Mahallesi Elazıg Yolu Uzeri 10. km, 21010, Kayapınar, Diyarbakır, Turkey,
E-mail: selahattinbalsak@gmail.com, Phone: +905059981810
ORCID ID: Umut Dağ: 0000-0002-7866-7898, **Selahattin Balsak:** 0000-0002-2269-474X
Received: 24.11.2020, **Accepted:** 13.08.2021

and measuring choroidal thickness. OCT provides high-resolution cross-sectional information about various pathological features of the macula (6).

Asymmetric dimethylarginine (ADMA) is an arginine analog and acts as an endogenous inhibitor of nitric oxide (NO) synthase (NOS). Arginine is a NO precursor and has a role in NO formation via NOS. NO is an essential regulator of immune functions and blood circulation of the organs. Recognition of the reductive effect of ADMA on NO synthesis has led the investigators to study the role of ADMA in critical disorders. It has been reported that ADMA level increases in critical diseases and that ADMA is an independent risk factor for cardiac dysfunction, organ failure, and mortality, particularly in intensive care unit (ICU)-hospitalized patients (7).

The present study aimed to evaluate serum ADMA levels and changes in choroidal thickness in patients with SSc. For this purpose, patients with SSc were compared with healthy individuals in terms of serum ADMA levels and macular choroidal thicknesses measured by OCT.

Materials and Methods

Among adult patients who were admitted to the Physical Therapy and Rehabilitation Clinic, 20 patients diagnosed with SSc based on 2 or 3 minor criteria in addition to 1 major criterion were enrolled in the study. The major criterion for diagnosing SSc was the presence of proximal diffuse sclerosis, and the minor criteria were accepted as follows: 1) presence of sclerodactyly 2) presence of digital scars and loss of substance of the finger pads, and 3) presence of bibasilar pulmonary fibrosis (8). Detailed ophtalmological examinatıon of the patients were performed. Their best corrected visual acuity was 8/10-10/10 with Snellen-Scale and IOP was btw 12-18 mmHg. Patients with ocular comorbid disorders that could affect choroidal thickness non-emetrophic (+1.0 , -1.0) patients (since in this case axial length might affect chorodial thickness), those with a history of intra-ocular surgery, and glaucoma were excluded. Patients with diabetes mellitus, hypertension, hypercholesterolemia, coronary heart disease, advanced-stage heart failure, renal failure, and a history of medication and smokers and alcohol consumers were excluded. Age and sex-matched 23 healthy individuals without opthalmological disorders formed the control group. Their best corrected visual acuity was 10/10 with Snellen-Scale and IOP was btw 12-18 mmHg. Informed consent was obtained from all patients and healthy individuals for their participation in the study. The present study was approved by the Local Ethics Committee of Health Sciences University Diyarbakır Gazi Yaşargil Research and Training Hospital (Approval No: 50; date: 25/05/2018).

Demographic characteristics and medical histories of the patients were recorded. Choroidal thickness measurements were performed in the right and left eyes of the SSc patients and controls using EDI-OCT (Spectralis OCT, Heidelberg Engineering, Germany). The measurements were performed in the temporal and nasal regions at a distance of 3mm to the center of the fovea as well as in the central fovea. ADMA levels were measured in the serum samples. Since choroidal thickness varies diurnally, all measurements were performed at the same hour of the day i.e. btw 09:00- 10:00. Also since the chorodial thickness varies with pupil dilatation all measurements were performed prior to pupil dilation.

Statistical Analysis: Statistical analyses were performed using the IBM SPSS for Windows (version 22.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean, median, standard deviation, minimum and maximum for numerical variables. The distribution of the variables was tested by the Kolmogorov-Smirnov test. Independent categorical variables were compared using the Chi-square test. Two-group comparisons of numerical variables were performed using the t-test for normally distributed variables and using the Mann-Whitney U test for non-normally distributed variables. A p-value of <0.05 was considered statistically significant.

Results

The study included 20 patients with SSc (40 eyes) (SSc group) and 23 healthy individuals (46 eyes) (control group). The patient and the control groups were similar in terms of age and sex distribution (Table 1).

The mean choroidal thicknesses and serum ADMA levels in the SSc and control groups are demonstrated in Table 2. The mean choroidal thicknesses were lower in the SSc group than in the control group; however, only the difference in the nasal measurements reached the level of statistical significance. The mean ADMA level was significantly higher in the SSc group than in the control group (Figure 1).

Table 1. Demographic Characteristics of The Patient and Control Groups

	SSc Group (n=20)	Control Group (n=23)	p
Age, year, mean±SD (median)	48.7±18.9 (51)	56.0±11.2 (54)	0.165
Sex, n (%)			
Female	16 (80.0)	12 (52.2)	0.112
Male	4 (20.0)	11 (47.8)	

SSc, systemic sclerosis; SD, standard deviation
Age, year, mean±SD (median) P: Mann-Whitney U test,
Sex P: Chi-square test.

Table 2. Choroidal Thicknesses and Serum Asymmetric Dimethylarginine levels in The Patient and Control Groups

	SSc Group (n=20)	Control Group (n=23)	p
Choroidal thickness, μm,mean±SD (median)			
Nasal	251.7±78.6 (242.0)	279.2±50.7 (280.0)	0.044
Temporal	248.8±87.4 (256.5)	277.2±58.4 (269.0)	0.077
Central Fovea	271.2±82.3 (272.0)	296.2±57.1 (276.5)	0.102
ADMA, μMol/L, mean±SD (median)	0.55±0.07 (0.54)	0.47±0.09 (0.47)	<0.001

Discussion

The choroid is the highly vascular layer of the eye and is a tissue with the highest blood circulation per weight in the body; thus, the choroid not only plays a significant role in the pathophysiology of various ophthalmological disorders but also is involved in a wide range of systemic diseases. Along with the introduction of OCT into use, the number of studies investigating choroidal thickness and affecting factors has increased (9).

Age and gender are among the important factors affecting choroidal thickness (9). Besides, many disorders/conditions may affect choroidal thickness, which can be listed as diabetes mellitus, hypercholesterolemia, hypertension, smoking, ankylosing spondylitis, Raynaud's phenomenon, Vogt-Koyanagi-Harada syndrome, Behcet's disease, sarcoidosis, metastatic cancers, Sturge-Weber syndrome, sickle cell disease, leukemia, Alzheimer's disease, and migraine (9). In the present study, choroidal thickness was compared between the SSc patients and healthy controls. The patient and control groups were matched in terms of age and sex. Furthermore, patients who had diabetes mellitus, hypertension, hypercholesterolemia, coronary heart disease, advanced-stage heart failure, renal failure, and a history of medication and smokers and alcohol consumers were excluded; thus, confounding effects of these conditions were eliminated.

It has been reported that choroidal thinning is observed in SSc patients due to impaired choroidal perfusion caused by the early involvement of ocular microcirculation (10). Coşkun et al. (11) compared scleroderma patients (n=46) with healthy controls (n=31) in terms of choroidal thicknesses measured from the left eyes. They reported that nasal choroidal thickness (148±51.5 μm vs. 261.9±66.9 μm, p=0.012), temporal choroidal thickness (181.8±62.7 μm vs. 276.5±70.2 μm; p=0.046), and subfoveal choroidal thickness (230.5±66.3 μm vs. 363.2±83.16 μm; p<0.001) were lower in the patients than in the controls. Based on these findings, Coşkun et al. (11) concluded that obstruction of the arterioles and decreased capillary density due to vasculopathy in patients with scleroderma might cause choroidal atrophy. In their study, Esen et al. (12) measured choroidal thickness using OCT in the right and left eyes of 60 SSc patients and30 healthy controls and found the mean values to be significantly lower in the SSc patients than in the healthy controls. Choroidal thicknesses determined by Esen et al. [12]in the SSc patients and controls were 297.77±60.8 μm and 339.8±50.4 μm, respectively, for subfoveal choroidal thickness; 267.32±51.1 μm and 308.65±49.9 μm, respectively, for nasal choroidal thickness, and 270.63±46.3 μm and 309.22±42.4 μm, respectively, for temporal choroidal thickness (p<0.001 for all). Aydin et al. (13) measured the choroidal thickness at five points (subfoveal, 1 mm and 3 mm nasal, and 1 mm and 3 mm temporal from the center of the fovea) in SSc patients (n=34) and healthy subjects (n=31)

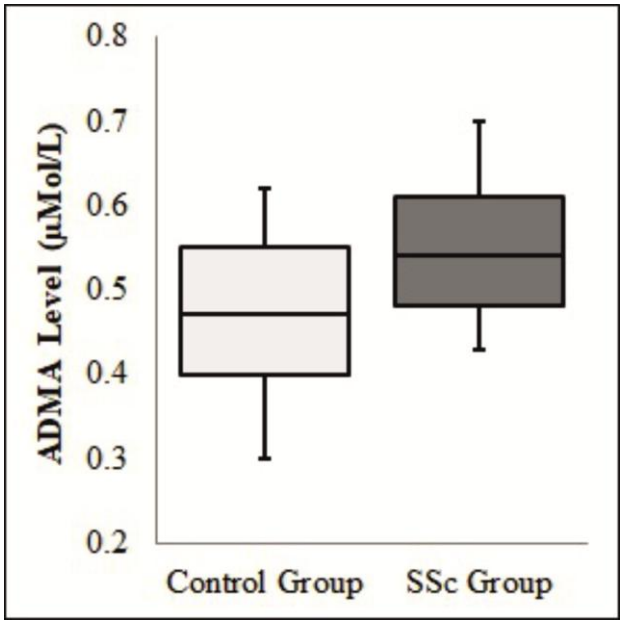

Fig. 1. Serum asymmetric dimethylarginine (ADMA) levels in the systemic sclerosis (SSc) and control groups

using enhanced depth imaging OCT. Contrary to the above-mentioned studies, no significant difference was determined between the patients and controls in terms of choroidal thickness measurements (13). In the present study, choroidal thicknesses were lower in the SSc group than in the control group; however, the difference reached the level of statistical significance only in the nasal measurements. Differences in the study outcomes might occur due to the differences in the parameters such as disease definition, disease duration, and age groups.

It has been suggested that thinning of the choroidal layer in patients with SSc begins from the outer macular regions (nasal and temporal) (10). In the present study, the nasal choroidal thickness was found to be significantly lower in the patients with SSc than in the controls (251.7±78.6 µm and 279.2±50.7 µm, respectively; p=0.044). No statistically significant difference was determined between the patients and controls in terms of the temporal and central foveal thicknesses.

Free radical NO is a potent vasodilator and is synthesized from L-arginine via NOS. It is thought that NO shows biphasic activity under physiological and pathological conditions and that NO may be both beneficial and harmful depending on concentration and local environment. It has been recently suggested that endogenous levels of ADMA, which is an inhibitor of NOS, play a role in the regulation of NO. Hence, ADMA level is considered a reflection of endothelial dysfunction in many diseases. In summary, it can be suggested that an elevated ADMA level indicates abnormal NO regulation and contributes to endothelial dysfunction (14). The reference range of ADMA level in healthy subjects was investigated by means of a systematic review and meta-analysis after literature review and it was determined to be 0.34-1.10 µMol/L with the use of high-performance liquid chromatography (HPLC) and to be 0.25-0.92 µMol/L with the use of enzyme-linked immunosorbent assay (ELISA) (15).

Asymmetric dimethylarginine has been investigated in various studies as a marker and mediator of endothelial dysfunction (16). Zhou et al. (17) carried out a systematic review and meta-analysis and reported a relationship between ADMA level and all-cause mortality. SSc is one of the diseases in which increased ADMA levels are observed (18,19). In their study, Blaise et al. (20) found the ADMA levels to be higher in the patients with SSc (n=39) than in the controls (n=24) (0.68±0.12 µM and 0.62±0.12 µM, respectively; p=0.06). Dağ et al. (21) also determined higher ADMA levels in the patients with SSc (n=30) than in the controls (n=30) (0.545±0.130 µMol/L and 0.130±0.155 µMol/L, respectively; p=0.034). Dimitroulas et al. (22) determined the mean ADMA levels to be0.35±0.23 µMol/L in the patients with SSc (n=66) and to be 0.25±0.20 µMol/L in the control group (n=30). In addition, in the same study, the ADMA levels were found to be higher in the SSc patients with pulmonary arterial hypertension (n=24) than those without (n=42) (0.44±0.22 µMol/L and 0.26±0.18 µMol/L, respectively; p=0.006); this finding suggested that ADMA might play a role in the pathogenesis of pulmonary arterial hypertension due to the contribution of high ADMA levels to endothelial dysfunction. The ADMA level was found to be also associated with ulcer development in the SSc patients followed-up for three years (23). In the present study, the ADMA level was also found to be significantly higher in the SSc patients than in the controls (0.55± 0.07 µMol/Land 0.47±0.09 µMol/L, respectively; p<0.001).

Currently, there is no specific pharmacological treatment to decrease the ADMA levels and to prevent its harmful effects. It is thought that a better understanding of the mechanism of action of ADMA in various diseases would make a contribution to the development of specific treatments for the relevant diseases (18).

In conclusion, based on the study outcomes, a significant elevation was observed in the ADMA levels of the SSc patients in the period when choroidal changes were not evident yet. We are in the opinion that a better understanding of the etiopathogenesis of SSc and the role of ADMA in this process would contribute to the studies on the development of new therapies.

References

1. Singh D, Parihar AK, Patel S, et al. Scleroderma: An insight into causes, pathogenesis and treatment strategies. Pathophysiology 2019; 26: 103-114.
2. Ingegnoli F, Ughi N, Mihai C. Update on the epidemiology, risk factors, and disease outcomes of systemic sclerosis. Best Pract Res Clin Rheumatol 2018; 32: 223-240.
3. Kreps EO, Carton C, Cutolo M, et al. Ocular involvement in systemic sclerosis: A systematic literature review, it's not all scleroderma that meets the eye. Semin Arthritis Rheum 2019; 49: 119-125.
4. Fett N. Scleroderma: nomenclature, etiology, pathogenesis, prognosis, and treatments: facts and controversies. Clin Dermatol 2013; 31: 432-437.
5. Tailor R, Gupta A, Herrick A, et al. Ocular manifestations of scleroderma. Surv Ophthalmol 2009; 54: 292-304.
6. Chan A, Duker JS, Ko TH, et al. Normal macular thickness measurements in healthy eyes using Stratus optical coherence tomography. Arch Ophthalmol 2006; 124: 193-198.
7. Brinkmann SJ, de Boer MC, Buijs N, et al. Asymmetric dimethylarginine and critical illness. Curr Opin Clin Nutr Metab Care 2014; 17: 90-97.
8. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980; 23: 581-590.
9. Tan KA, Gupta P, Agarwal A, et al. State of science: Choroidal thickness and systemic health. Surv Ophthalmol 2016; 61: 566-581.
10. Ingegnoli F, Gualtierotti R, Pierro L, et al. Choroidal impairment and macular thinning in patients with systemic sclerosis: the acute study. Microvasc Res 2015; 97: 31-36.
11. Coşkun E, Zengin O, Kenan S, et al. Evaluation of choroidal thickness in patients with scleroderma. Eye (Lond) 2016; 30: 588-592.
12. Esen E, Tas DA, Sizmaz S, et al. Evaluating choroidal characteristics in systemic sclerosis using enhanced depth imaging optical coherence tomography. Ocul Immunol Inflamm 2017; 25: 356-362.
13. Aydin E, Atik S, Koc F, et al. Choroidal and central foveal thickness in patients with scleroderma and its systemic associations. Clin Exp Optom 2017; 100: 656-662.
14. Dooley A, Gao B, Bradley N, et al. Abnormal nitric oxide metabolism in systemic sclerosis: increased levels of nitrated proteins and asymmetric dimethylarginine. Rheumatology (Oxford) 2006; 45: 676-684.
15. Németh B, Ajtay Z, Hejjel L, et al. The issue of plasma asymmetric dimethylarginine reference range - a systematic review and meta-analysis. PLoS One. 2017; 12: e0177493.
16. Wieczór AM, Wieczór R, Kulwas A, et al. Asymmetric dimethylarginine and angiogenesis: biological significance. Int Angiol 2018; 37: 431-436.
17. Zhou S, Zhu Q, Li X, et al. Asymmetric dimethylarginine and all-cause mortality: a systematic review and meta-analysis. Sci Rep 2017; 7: 44692.
18. Tain YL, Hsu CN. Toxic dimethylarginines: asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA). Toxins (Basel) 2017; 9: 92.
19. Zhang L, Wan YN, Zhao JH, Wang YJ, Wang YX, Yan JW, Huang XL, Wang J. The association between systemic sclerosis, arginine and asymmetric dimethylarginine. Inflammation 2015; 38: 218-223.
20. Blaise S, Maas R, Trocme C, et al. Correlation of biomarkers of endothelium dysfunction and matrix remodeling in patients with systemic sclerosis. J Rheumatol 2009; 36: 984-988.
21. Dağ Ş, Budulgan M, Dilek B, et al. Relation of asymmetric dimethylarginine and cardiac involvement in systemıc sclerosis. ActaReumatol Port 2014; 39: 228-235.
22. Dimitroulas T, Giannakoulas G, Sfetsios T, et al. Asymmetrical dimethylarginine in systemic sclerosis-related pulmonary arterial hypertension. Rheumatology (Oxford). 2008; 47: 1682-1685.
23. Silva I, Teixeira A, Oliveira J, et al. Endothelial dysfunction and nailfoldvideocapillaroscopy pattern as predictors of digital ulcers in systemic sclerosis: a cohort study and review of the literature. Clin Rev Allergy Immunol 2015; 49: 240-252.