Scandinavian Cardiovascular Journal

ISSN: 1401-7431 (Print) 1651-2006 (Online) Journal homepage: informahealthcare.com/journals/icdv20

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To cite this article: Al Bayraktar, Uğur Canpolat, Edis Demiri, Ayşegül Ulgen Kunak, Necla Ozer, Serdar Aksoyek, Kenan Ovunc, Adem Ozkan, Okan Bülent Yildiz & Enver Atalar (2015) New insights into the mechanisms of diastolic dysfunction in patients with type 2 diabetes, Scandinavian Cardiovascular Journal, 49:3, 142-148, DOI: 10.3109/14017431.2015.1039571

To link to this article: https://doi.org/10.3109/14017431.2015.1039571

Published online: 29 Apr 2015.

Scandinavian Cardiovascular Journal, 2015; 49: 142–148

informa
healthcare

ORIGINAL ARTICLE

New insights into the mechanisms of diastolic dysfunction in patients with type 2 diabetes

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Abstract

Background. Little is known about the role of advanced glycation end products (AGEs) and their receptor (RAGE) in diabetic cardiovascular complications. Therefore, we aimed to evaluate the association of serum soluble RAGE (sRAGE) levels and left ventricular (LV) diastolic dysfunction in patients with type 2 diabetes. *Methods*. Our study consisted of 40 patients with type 2 diabetes and 40 age- and sex-matched healthy control group. Subjects with age ≥ 50 years old and any cardiovascular risk factors or conditions were excluded from the study. Serum sRAGE levels determined by enzyme-linked immunosorbent assay and LV diastolic dysfunction were evaluated according to current American Society of Echocardiography guidelines. *Results*. Baseline characteristics were similar between groups except body mass index, waist–hip ratio, and fasting glucose levels. Serum sRAGE level was significantly lower in diabetic group compared with control group (676 ± 128 vs. 1044 ± 344, $p < 0.05$). Diastolic dysfunction was observed in 50% of diabetic patients (40% grade I and 10% grade II). Correlation analysis showed that serum sRAGE was negatively correlated with duration of diabetes, septal E'/A', lateral E'/A', and average E/E'. In multivariate regression analysis, serum sRAGE level was strongly associated with diastolic dysfunction in patients with type 2 diabetes. *Conclusion*. Our study showed that serum sRAGE level was significantly lower in type 2 diabetic patients aged < 50 years old. Also, sRAGE has negative correlation with the duration of diabetes and it was significantly associated with the presence of diastolic dysfunction in type 2 diabetes.

Key words: *diastolic dysfunction, sRAGE, type 2 diabetes*

Introduction

Left ventricular (LV) diastolic dysfunction may occur early in the course of the diabetes mellitus (DM) in about 23–75% of the patients, even in the absence of any underlying comorbidity (1–4). Metabolic alterations in myocardium, myocardial fibrosis, cardiac autonomic neuropathy, insulin resistance, and small vessel disease have been proposed to develop in diabetic patients and are the mechanisms that lead to diabetic cardiomyopathy (5,6). The advanced glycation end products (AGEs) via binding their receptors (RAGEs) initiate signal pathways which affect the myocardial function, by the release of growth factors and additional RAGE ligands, formation of reactive oxygen species (ROS), angiogenesis, and endothelial dysfunction (7–9). Naturally occurring soluble RAGE (sRAGE) splice variants have been identified and could potentially act as endogenous inhibitors of RAGE activity (10–12). Because of these characteristics, the sRAGE could represent a naturally occurring competitive inhibitor of the signaling pathways induced by the interaction of AGEs with its cellular receptor; by functioning as a decoy, sRAGE contribute to the removal of circulating

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(Received 31 August 2014; revised 28 March 2015; accepted 7 April 2015)

ISSN 1401-7431 print/ISSN 1651-2006 online
DOI: 10.3109/14017431.2015.1039571

RAGE ligands (12). Although LV diastolic dysfunction has largely been studied in DM, the association of sRAGE with LV diastolic dysfunction in DM has not been studied before. Therefore, in this study we aimed to evaluate the relationship between serum sRAGE levels and LV diastolic dysfunction in relatively young asymptomatic and uncomplicated patients with type 2 DM.

Methods

Study subjects

In this cross-sectional study, a total of 40 patients with type 2 DM and 40 age- and gender-matched healthy control subjects were enrolled between April 2012 and March 2013. Patients were included if they met the following inclusion criteria: asymptomatic (have no heart disease symptoms like chest pain, dyspnea, palpitation, etc.), aged between 18 and 50 years, sinus rhythm, without major cardiovascular risk factors, normal LV systolic function, and no myocardial ischemia, assessed by normal results on treadmill exercise test. Patients with coronary artery disease (CAD), hypertension, valvular heart disease, hepatic or renal failure, thyroid dysfunction, pulmonary disease, Alzheimer disease, malignancy, connective tissue diseases, inflammatory disease, poor echocardiographic image, and using any anti-inflammatory or anti-arrhythmic drugs were excluded from the study.

The local ethics committee approved the study protocol and collection of samples for the analysis of biomarkers after receiving informed consent. The study was in compliance with the principles outlined in the Declaration of Helsinki. The general protocol for each patient immediately after enrollment included collection of baseline clinical and demographic characteristics, laboratory and echocardiographic data have also been recorded.

Anthromorphometric measures

Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). To measure the waist circumference, the tape was placed horizontally around the midpoint between the lower rib margin and the iliac crest, at the level of the umbilicus. The hip circumference was measured at such a point to yield the maximum circumference over the buttocks, with the tape held in a horizontal plane.

Laboratory measurements

Blood samples were drawn after a 12-hour overnight fast and were kept at −80°C for subsequent assay. The concentrations of serum sRAGE were determined using a commercially available enzyme-linked immunosorbent assay kit (Quantikine, Total sRAGE assay R&D Systems, Minneapolis, USA) in duplicate according to the manufacturer's protocol, with intra-assay coefficient of variation of 3.6%.

Transthoracic echocardiography

Echocardiographic measurements were performed with the subjects in partial left decubitus, and continuous electrocardiogram (ECG) monitoring, by digital ultrasound machine (Vivid 5; GE Vingmed Ultrasound AS, Horten, Norway). All echographic acquisitions were digitally stored from at least three consecutive heartbeats for offline analysis (EchoPAC; GE Vingmed Ultrasound AS), which was performed at our tertiary center hospital by one investigator. All measurements and evaluation of LV diastolic function were performed according to the criteria proposed by the American Society of Echocardiography guidelines (13,14).

Analysis of diastolic functions

Diastolic functional parameters in patients and controls were assessed according to the current recommendations of the American Society of Echocardiography and the European Association of Echocardiography (15).

Diastolic functional parameters

Pulsed Doppler assessment of mitral inflow was performed in apical 4-chamber view, with the sample volume placed at the level of valve tips. The following measurements of global LV diastolic function were determined: peak velocities of E and A waves (m/s) and their ratio, deceleration time of E wave (ms), isovolumic relaxation time (ms)—measured as the time interval occurring between the end of systolic output flow, and the transmitral E wave onset—by placing pulsed Doppler sample volume between outflow tract and mitral valve.

Tissue doppler imaging

Apical 4-chamber view was used to measure the early and late annular velocities from the lateral and septal corners of the mitral annulus by pulsed tissue Doppler imaging.

To determine diastolic dysfunction and its grades, E/A, deceleration time (DT), isovolumetric relaxation time (IVRT), E', and E/E' measurements were used. In patients with mild diastolic dysfunction

(grade I), the mitral E/A ratio is <0.8, DT is >200 ms, IVRT is >100 ms, annular E′ is <8 cm/s, and the E/E′ ratio is <8 (septal and lateral). In patients with moderate diastolic dysfunction (grade II), the mitral E/A ratio is 0.8–1.5 (pseudonormal) and decreases by $>50\%$ during the Valsalva maneuver, the E/E′ (average) ratio is 9–12, and E′ is <8 cm/s.

Statistical analysis

The analysis was performed by SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium). Normally distributed data are expressed as mean ± standard deviation. Data deviating from normality are expressed as median (interquartile range), and categorical variables are expressed as percentages. Baseline data in the DM group and control group were compared using unpaired t tests for continuous variables and chi-square tests for categorical variables. Linear regression analyses and partial correlation test by Pearson's method were done to assess the univariable relations. Univariate and stepwise multivariate linear regression analyses were performed to weigh the independent effects of potential determinants on serum sRAGE levels. Furthermore, univariate and multivariate logistic regression analyses were performed to assess the independent association of potential parameters with the presence of LV diastolic dysfunction. Entry into the multivariate regression model required a p value of <0.10 at univariate regression model. All statistical tests were two-tailed and statistical significance was accepted if the P value was <0.05, except for multivariate regression analyses. In this case, statistical significance was formulated using 0.05/the number of included variables.

Results

Clinical and biochemical characteristics and the presence of LV diastolic dysfunction of the study subjects are presented in Table I. Baseline characteristics were similar between study groups except fasting blood glucose and HbA1c which were significantly higher in diabetics ($p<0.05$). Furthermore, serum sRAGE levels were significantly lower in patients with DM compared with those in healthy control

Table I. Clinical and laboratory characteristics of study subjects ($n=80$).

	Healthy control ($n=40$)	Diabetic patient ($n=40$)	p
Parameters			
Age, years	41.1 ± 8.5	43.2 ± 7.9	0.233
Female gender	24 (60%)	21 (52.5%)	0.499
BMI, kg/m^2	27.2 ± 3.2	30.4 ± 4.7	0.001*
Waist–hip ratio, cm	0.88 ± 0.06	0.92 ± 0.04	0.002*
SBP, mmHg	120 (100–140)	125 (100–140)	0.878
DBP, mmHg	75 (60–85)	75 (60–85)	0.728
Duration of diabetes, years	NA	2 (0.5–9)	
Fasting blood glucose, mmol/l	4.75 ± 0.45	8.16 ± 2.96	0.001*
HbA1c, %	5.0 ± 0.6	7.1 ± 1.6	0.001*
Total cholesterol, mmol/l	5.20 ± 0.83	4.85 ± 0.94	0.079
TG, mmol/l	1.37 (0.44–4.46)	1.45 (0.45–3.73)	0.977
LDL cholesterol, mmol/l	3.2 ± 0.8	3.0 ± 0.9	0.232
HDL cholesterol, mmol/l	1.28 ± 0.38	1.28 ± 0.35	0.957
Serum creatinine, µmol/l	70.7 (46.0–102.5)	69.8 (42.4–96.4)	0.567
Uric acid, µmol/l	280 ± 65	294 ± 77	0.365
ALT, U/L	15 (7–45)	16 (6–48)	0.311
AST, U/L	18 (10–44)	20 (10–38)	0.201
sRAGE, pg/ml	1044 ± 344	676 ± 128	0.001*
Diastolic dysfunction	0	20 (50%)	0.001*
Grade 1	0	16 (40%)	
Grade 2	0	4 (10%)	
E/A	1.3 ± 0.3	1.0 ± 0.3	0.001*
E/E' (Average)	6.4 ± 0.9	7.4 ± 1.0	0.001*

BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HBA1c, Glycated hemoglobin; TG, Triglyceride; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; ALT, Alanine transaminase; AST, Aspartate transaminase; sRAGE, Serum soluble advanced glycation end products.
*$p<0.05$.

group (676 ± 128 pg/ml vs. 1044 ± 344 pg/ml, respectively, $p = 0.001$) (Figure 1). Diastolic dysfunction was observed in 50% of diabetic patients, of those 40% had grade I and 10% had grade II diastolic dysfunction.

In simple correlation analysis, sRAGE levels are negatively correlated with duration of diabetes ($r = -0.32$, $p = 0.04$) (Figure 2), serum triglyceride (TG) level ($r = -0.34$, $p = 0.03$), lateral E' ($r = 0.44$, $p = 0.004$), septal E' ($r = 0.34$, $p = 0.03$), and average E/E' ($r = -0.46$, $p = 0.003$) (Table II).

Multivariate linear regression analysis revealed that duration of diabetes was significantly associated with the serum sRAGE level [β: −0.293, 95% confidence interval (CI): (−0.27.5) to (−0.49), $p = 0.043$] after adjusting for age and mean E/E'. Furthermore, in multivariate logistic regression analysis, serum sRAGE level was independently associated with the presence of LV diastolic dysfunction after adjusting for other parameters including age, BMI, mean E/E', and mitral mean E values (odds ratio: 0.96, 95% CI: 0.94–0.99; $p = 0.028$). The median duration of diabetes in those patients without diastolic dysfunction was 1.5 years, in those with grade I diastolic dysfunction was 3 years, and in those with grade II diastolic dysfunction was 8 years (Figure 3). Also, serum sRAGE level was inversely associated with the grades of diastolic dysfunction (Figure 4).

Discussion

Our study results showed that serum sRAGE level was significantly lower in type 2 DM and also low levels of sRAGE are significantly associated with the presence of LV diastolic dysfunction in type 2 DM, even in the absence of any cardiovascular disease.

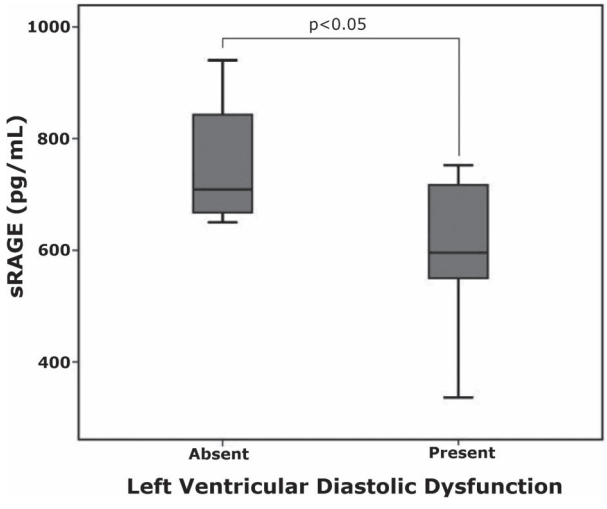

Figure 1. Comparison of serum sRAGE levels according to the presence of diastolic dysfunction in diabetic patients.

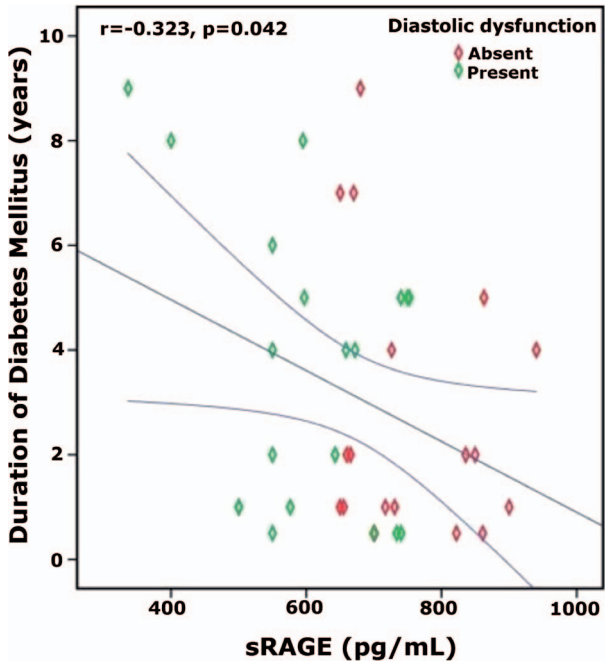

Figure 2. The relationship between sRAGE levels and the duration of diabetes.

It was reported that sRAGE binds to an AGE ligand and may neutralize the AGEs-mediated harmful effect by acting as a decoy. RAGE has gained attention as a modulator of complications associated with DM (16). In a study by Bucciarelli et al. (17), treatment with sRAGE in both euglycemic and diabetic apoE-null mice has stabilized the established atherosclerosis and vascular inflammation without any alteration in lipid levels. Basta et al. (18) found that in diabetic patients, sRAGE levels were significantly lower than those in non-diabetic patients. Furthermore, Koyama et al. (19) reported that endogenous sRAGE levels were lower in type 2 DM and patients with impaired glucose tolerance than those with normal glucose levels (healthy people). Consistent with previous studies, we also found that sRAGE levels were significantly lower in type 2 diabetic patients than those in healthy control group. Furthermore our study showed that sRAGE levels were negatively associated with serum TG level, but had no correlation with BMI or HbA1c levels.

In diabetic patients, the presence of risk factors (like hypertension, dyslipidemia, obesity, smoking, etc.) that can affect ventricular function are known to increase the incidence of diabetic cardiomyopathy. In the absence of these risk factors, the presence of asyptomatic LV diastolic dysfunction might be an early manifestation of diabetic cardiomyopathy. However, to the best of our knowledge, the role of

Table II. Simple correlation analysis of variables associated with serum sRAGE levels.

	r	*p*
Clinical and laboratory parameters		
Age, years	− 0.092	0.578
Female gender	− 0.048	0.770
BMI, kg/m^2	0.102	0.533
Waist–hip ratio	0.166	0.305
SBP, mmHg	0.198	0.221
DBP, mmHg	0.048	0.767
Duration of diabetes, years	− 0.323	0.042*
Fasting blood glucose, mmol/l	0.126	0.438
HbA1c, %	0.239	0.138
Total cholesterol, mmol/l	− 0.054	0.742
TG, mmol/l	− 0.340	0.032*
HDL cholesterol, mmol/l	0.208	0.197
LDL cholesterol, mmol/l	− 0.134	0.411
Uric acid, µmol/l	− 0.220	0.172
Echocardiographic parameters		
Mitral peak E velocity, cm/s	0.051	0.755
Mitral peak A velocity, cm/s	− 0.090	0.579
Mitral peak E/A ratio	0.107	0.509
DT, ms	− 0.105	0.519
IVRT, ms	− 0.14	0.933
Lateral E', cm/s	0.442	0.004*
Lateral A', cm/s	0.032	0.845
Lateral E'/A'	0.315	0.047*
Septal E', cm/s	0.341	0.031*
Septal A', cm/s	− 0.162	0.317
Septal E'/A'	0.406	0.009*
E/E' (Lateral)	− 0.399	0.011*
E/E' (Septal)	− 0.315	0.048*
E' (average), cm/s	0.252	0.116
E/E' (average)	− 0.465	0.003*

BMI, Body mass ındex; DBP, Dıastolıc blood pressure; HBA1C, Glycated hemoglobin; HDL, Hıgh-densıty lıpoproteın; IVRT, Isovolumıc relaxatıon tıme; LDL, Low-densıty lıpoproteın; SBP, Systolıc blood pressure; SRAGE, Soluble advanced glycatıon end products; TG, Trıglyceride.
*$p < 0.05$.

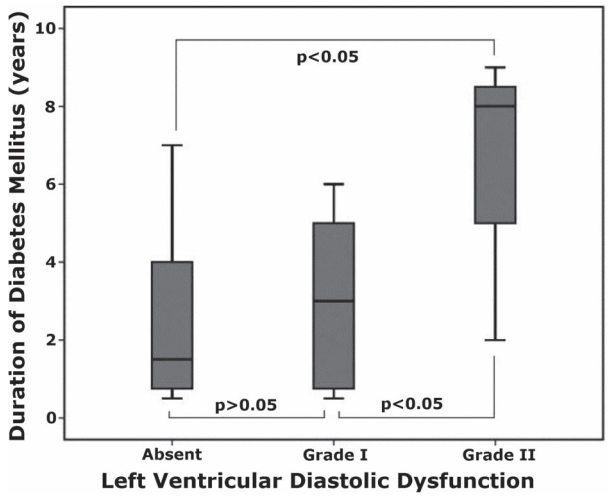

Figure 3. The relation between duration of diabetes and LV diastolic dysfunction.

RAGE in the pathogenesis of diabetic cardiomyopathy is unclear.

The RAGE activation can initiate a number of mechanisms including release of growths factors, additional RAGE ligands, formation of ROS, angiogenesis, and endothelial dysfunction that may adversely affect the cardiac functions (7,8). As a result, AGE cross-linking has specific consequences for cardiac functions. In accordance with this, accumulation of collagen and alteration in myocardial collagen AGEs in the diabetic heart have been demonstrated to decrease myocardial compliance (20,21). It has been found that RAGE blockage normalized LV diastolic stiffness in diabetic mice (22). These data indicate that RAGE activation mediates collagen deposition and AGE formation which leads to increased stiffness of the heart. The indices of LV myocardial contractility were improved in RAGE-blocked diabetic mice, indicating that RAGE is involved in mechanisms related with the contractile properties of the myocytes.

Our study showed that 50% of type 2 diabetic patients at the age of < 50 years were found to had asymptomatic LV diastolic dysfunction. Among them, 40% had grade I diastolic dysfunction whereas 10% had grade II LV diastolic dysfunction. We showed that there was a close relationship between serum sRAGE levels and LV diastolic dysfunction. In their study including 86 well-controlled type 2 diabetic patients, Zabalgoitia et al. (2) found that 47% of the patients had LV diastolic dysfunction (30% with grade I and 17% with grade II diastolic dysfunction). Also, Poirier et al. (1) showed that 60% of 46 type 2 diabetic patients free from CAD, hypertension, and kidney disease had diastolic dysfunction

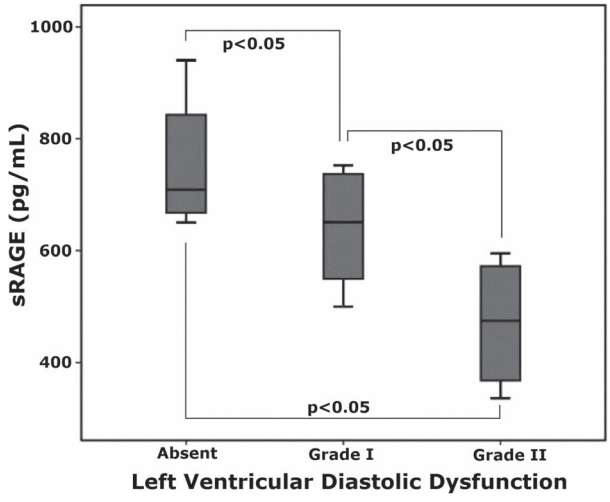

Figure 4. The relationship between sRAGE levels and grades of diastolic dysfunction.

(32% grade I and 28% grade II diastolic dysfunction). In another study, Boyer et al. (4) found that 75% of 57 normotensive type 2 diabetic patients have LV diastolic dysfunction. Patil et al. (23) found that 53% of 127 asymptomatic type 2 diabetic patients had LV diastolic dysfunction, and the prevelance of diastolic dysfunction was positively correlated with the duration of diabetes. Masugata et al. (24) showed that in type 2 diabetic patients there is a close relationship between LV diastolic dysfunction and the duration of diabetes. In the present study, the incidence of LV diastolic dysfunction was 50% and the duration of diabetes was associated with the grade of LV diastolic dysfunction. Nearly the same incidence was shown by Patil et al. and Zabalgoitia et al., whereas in their studies Poirier and Boyer et al. had found higher incidence of diastolic dysfunction. Because of the shorter duration of diabetes history and inclusion of relatively younger patients in our study, the incidence of LV diastolic dysfunction was found to be lower as compared with previous studies.

Our study showed that type 2 diabetic patients aged <50 years free from any cardiovascular and other diseases that may affect LV function had significant inverse correlation between serum sRAGE levels and the presence and grades of LV diastolic dysfunction. Studies showed that in type 2 diabetes, there is a relationship between low sRAGE levels and the presence of atherosclerosis (19,25,26). Also there is a relationship between AGEs and the presence of diastolic dysfunction (27). Moreover, there is a significant relation between low sRAGE levels and the risk of developing cardiovascular disease and mortality (28). Our study showed that serum sRAGE levels are low in type 2 diabetic patients who had LV diastolic dysfunction. Moreover, we showed that lower sRAGE levels are present with the increase in the grade of LV diastolic dysfunction.

Our study has some limitations. First, we perform measurement of total sRAGE, because the detection system used cannot discriminate between specific sRAGE splice variants. Therefore, it should be kept in mind that reduced sRAGE levels measured by this assay may be caused by a reduction of distinct circulating sRAGE isoforms (13). Second, the number of the study subjects was small. Third, our results share the limitations of cross-sectional, observational studies. We evaluate association, not prospective prediction. Therefore, large number of study population and prospective follow-up will be required to confirm our findings and to establish the utility of the measurement of sRAGE levels in daily clinical practice.

In conclusion, to the best of our knowledge, this is the first study that investigates the relationship between serum sRAGE levels and the presence of LV diastolic dysfunction in type 2 diabetic patients aged <50 years. Serum sRAGE levels were significantly lower in type 2 DM. LV diastolic dysfunction was found in 50% of type 2 diabetic patients aged <50 years. These patients had lower serum sRAGE levels than those with normal diastolic functions. Also, there is a significant association of serum sRAGE levels with the grades of diastolic dysfunction.

Acknowledgement

The authors thank to Hakan Çakır for statistical assistance.

Funding/Supporting Institutions

This work was supported by Hacettepe University Scientific Research Projects Coordination Unit [Project No. 6097].

Declaration of interest: The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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