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Receptor for advanced glycation end products polymorphisms in coronary artery ectasia

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ABSTRACT

Background: Although the implication of receptor of advanced glycation endproducts (RAGE) has been reported in coronary artery disease, its roles in coronary artery ectasia (CAE) have remained undetermined. Furthermore, the effect of *RAGE* polymorfisms were not well-defined in scope of soluble RAGE (sRAGE) levels. Thus, we aimed to investigate the influence of the functional polymorphisms of *RAGE* -374T > A (rs1800624) and G82S (rs2070600) in CAE development.

Methods: This prospective observational study was conducted in 2 groups selected of 2452 patients who underwent elective coronary angiography (CAG) for evaluation after positive noninvasive heart tests. Group-I included 98 patients with non-obstructive coronary artery disease and CAE, and Group-II (control) included 100 patients with normal coronary arteries. SNPs were genotyped by real-time PCR using Taqman® genotyping assay. Serum sRAGE and soluble lectin-like oxidized receptor-1 (sOLR1) were assayed by ELISA and serum lipids were measured enzymatically.

Results: The frequencies of the *RAGE* -374A allele and -374AA genotype were significantly higher in CAE patients compared to controls ($p < 0.001$). sRAGE levels were not different between study groups, while sOLR1 levels were elevated in CAE ($p = 0.004$). In controls without systemic disease, -374A allele was associated with low sRAGE levels ($p < 0.05$), but this association was not significant in controls with HT. Similarly, sRAGE levels of CAE patients with both HT and T2DM were higher than those no systemic disease ($p = 0.02$). The -374A allele was also associated with younger patient age and higher platelet count in the CAE group in both total and subgroup analyses. In the correlation analyses, the -374A allele was also negatively correlated with age and positively correlated with Plt in all of these CAE groups. In the total CAE group, sRAGE levels also showed a positive correlation with age and a negative correlation with HDL-cholesterol levels. On the other hand, a negative correlation was observed between sRAGE and Plt in the total, hypertensive and no systemic disease

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ADA, American Diabetes Association; AGE, advanced glycation end products; ALT, alanine aminotransferase; ARBs, angiotensin II receptor blockers; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CAD, coronary artery disease; CAE, coronary artery ectasia; CCB, calcium channel blockers; CI, confidence interval; DM, diabetic; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal-regulated kinase; FBG, fasting blood glucose; HDL, high density lipoprotein; HL, hyperlipidemic; HMGB1, high mobility group box 1; HT, hypertensive; HWE, Hardy-Weinberg equilibrium; ICAM-1, intercellular adhesion molecule-1; LDL, low density lipoprotein; ND, non-diabetic; NL, normolipidemic; NT, normotensive; MMP, matrix metalloproteinase; OLR1, oxidized low-density lipoprotein receptor 1; OR, odds ratio; Ox-LDL, Oxidized-LDL; PCR, polymerase chain reaction; PPAR, peroxisome proliferator-activated receptor; RAGE, receptor of advanced glycation endproducts; SNP, single nucleotid polymorphism; sOLR1, soluble lectin-like oxidized receptor-1; sRGAE, soluble receptor of advanced glycation endproducts; T2DM, type 2 diabetes mellitus; TG, triglyceride; TSH, thyroid stimulating hormone; VCAM-1, vascular cell adhesion molecule-1.

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control subgroups. Multivariate logistic regression analysis confirmed that the -374A allele ($p < 0.001$), hyperlipidemia ($p < 0.05$), and high sOLR1 level ($p < 0.05$) are risk factors for CAE. ROC curve analysis shows that RAGE -374A allele has AUC of 0.713 (sensitivity: 83.7 %, specificity: 59.0 %), which is higher than HLD (sensitivity: 59.2 %, specificity: 69.0 %), HT (sensitivity: 62.4 %, specificity: 61.1 %) and high sOLR1 level (≥0.67 ng/ml)) (sensitivity: 59.8 %, specificity: 58.5 %).

Conclusion: Beside the demonstration of the relationship between -374A allele and increased risk of CAE for the first time, our results indicate that antihypertensive and antidiabetic treatment in CAE patients causes an increase in sRAGE levels. The lack of an association between the expected -374A allele and low sRAGE levels in total CAE group was attributed to the high proportion of hypertensive patients and hence to antihypertensive treatment. Moreover, the RAGE -374A allele is associated with younger age at CAE and higher Plt, suggesting that -374A may also be associated with platelet activation, which plays a role in the pathogenesis of CAE. However, our data need to be confirmed in a large study for definitive conclusions.

1. Introduction

Coronary artery ectasia (CAE) is defined as the dilatation of the diameter of coronary arteries more than 1.5 fold to the normal adjacent segments in which the morphology of the lesion is either diffuse and/or local (Swaye et al., 1983, Markis et al., 1976). The main characteristics attributed to CAE are foam cell production as a result of lipid accumulation, fibrous cap formation, and disruption of musculo-elastic elements of the vascular wall (Lin et al., 2008). Therefore, it has been emphasized that histological characteristics of the ectatic arterial wall were similar to atherosclerotic lesions but the loss of musculo-elastic arterial wall that weakens and dilates vessels is noted to be specific to CAE (Markis et al., 1976; Boles et al., 2010). Vascular remodeling has been suggested as a response to local plaque growth in CAE and degradation of extracellular matrix by matrix metalloproteinases (MMPs) as well as proteolytic enzymes e.g. serine proteinases involved in the pathological process (Antoniadis et al., 2008; Devabhaktuni et al., 2016). Various inflammatory mediators have also been shown to play a role in CAE supported by numerous studies detecting higher levels of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin (Turhan et al., 2005; Yilmaz et al., 2006), IL-6 (Tokgozoglu et al., 2004; Li et al., 2009; Triantafyllis et al., 2013), and TNF-α (Aydin et al., 2009; Boles et al., 2018). It has also been proposed that increased levels of inflammatory cells such as leukocytes, neutrophils, monocytes (Li et al., 2009), and neutrophil to lymphocyte ratio (Ikenaga et al., 2014; Sarli et al., 2014; Yilmaz et al., 2016) may contribute to CAE pathogenesis.

The underlying etiology of CAE was reported as atherosclerosis for 50 % of cases (Yetkin and Waltenberger, 2007; Dahhan, 2015), followed by congenital diseases, inflammatory diseases e.g. Kawasaki disease, and other causes including heritable connective tissue disorders, percutaneous coronary interventions, and drug use (Dahhan, 2015). Despite the frequent coexistence of atherosclerosis and CAE and the histopathological similarities between the two manifestations, the existence of congenital and isolated CAE that is acquired and not attributed to atherosclerosis represents the differences and complexity of CAE pathogenesis (Yetkin and Waltenberger, 2007; Dahhan, 2015). Furthermore, type 2 diabetes mellitus (T2DM), a well-known risk factor for coronary heart disease was found to be inversely associated with CAE ((Pinar Bermúdez et al., 2003); Androulakis et al., 2004) by promoting negative remodeling of the arterial wall through elevated production of AGEs in the extracellular matrix (Ozturk et al., 2018).

Oxidized low density lipoprotein (ox-LDL) particles and advanced glycation end products (AGEs) which are formed by oxidative and glycosylation reactions have been implicated in atherosclerotic lesions and cardiovascular diseases, involving oxidative stress and endothelial dysfunction (Del Turco and Basta, 2012; Alique et al., 2015). The receptor for AGEs (RAGE) is one of the pattern-recognition receptors located on the cell surface that bind not only AGEs but also various proinflammatory ligands such as amyloid β-peptide, S100/calgranulins, high mobility group box 1 (HMGB1) (Bierhaus et al., 2005). These interactions lead to activation of the several signaling cascades including extracellular signal-regulated kinase- (ERK) 1/2 and JAK/STAT signaling pathways, subsequently inducing the downstream transcription factor NF-κB which upregulates the expression of genes related to inflammation (e.g. adhesion molecules, cytokines), thrombosis, vasoconstriction, and cell survival as well as the RAGE itself (Bierhaus et al., 2005). The proteolytic cleavage of RAGE and ox-LDL receptor 1 (OLR1) results in their respective soluble forms, the soluble RAGE (sRAGE) which blocks the RAGE signaling and therefore has been suggested as a decoy for AGEs (Hanford et al., 2004; Bierhaus et al., 2005), and soluble OLR1 (sOLR1) which is induced by proinflammatory cytokines (Hofmann et al., 2020). The beneficial effect of sRAGE administration on atherosclerotic lesions was shown in ApoE-null diabetic mice and associated with decreased progression of the disease (Bucciarelli et al., 2002). Another in vivo experiment involving the usage of exogenous sRAGE on aged rats found a decreasing effect on endothelial dysfunction related to aging (Hallam et al., 2010). A study of human subjects by Burke and colleagues examining the postmortem atherosclerotic plaques demonstrated an increased expression of RAGE in diabetic patients (Burke et al., 2004). Mahajan et al. (2009) also revealed that peripheral blood mononuclear cells obtained from nondiabetic patients with premature CAD had an increased RAGE expression.

The -374T > A polymorphism (5′UTR, rs1800624), being one of the functional single nucleotid polymorphisms (SNPs) of the *RAGE* gene, was shown to suppress the transcriptional activity of the *RAGE* gene (Hudson et al., 2001). Another functional SNP, G82S is localized on the second N-glycosylation region of the *RAGE* gene reported to increase the ligand binding affinity, upregulate the intracellular signaling pathways and the subsequent proinflammatory responses (Hoffmann et al., 2002, Osawa et al., 2007). Although polymorphisms that alter the function of RAGE were reported to be associated with CAD and T2DM, (González et al., 2013; Liu and Qiu, 2013), its role in CAE has yet to be elucidated. Thus, the objective of this study was to determine whether functional polymorphisms of -374T > A (5′UTR, rs1800624) and G82S (C > T, rs2070600) in the *RAGE* gene are associated with CAE risk. The serum levels of soluble forms of both receptors, sRAGE and sOLR1, were also analyzed for their potential role as a biomarker in CAE.

2. Materials and methods

2.1. Study population and selection criteria

One hundred ninety-eight patients were selected for the study among 2452 patients who were admitted to the Institute of Cardiology of Istanbul University-Cerrahpasa, Department of Cardiology for elective coronary angiography from June 2018 to May 2019 (Fig. 1). Following the clinical evaluation made by the same clinic, the inclusion criteria for a total of 98 CAE patients were: chest pain, positive cardiac stress test, ischemia diagnosis by either myocardial perfusion scintigraphy or presumed to have clinically stable angina pectoris, and diagnosis with CAE in one or more arteries. Hypertension (HT) was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or the use of an antihypertensive drug. Of the hypertensive CAE group which

comprised 61.2 % of patients, whose 53.2 % were receiving angiotensin-converting enzyme inhibitors (ACEi), followed by angiotensin II receptor blockers (ARBs) with 32.3 %, calcium channel blockers (CCB) with 9.7 %, and β-blockers with 4.8 %. The control group included 100 patients who showed positive exercise tests, no typical ischemic symptoms and angiographically normal coronary arteries. Patients with ischaemic heart disease were excluded from the control group. Thirty-seven percent of the control group were hypertensive whose 62.9 % were under ACEi treatment, followed by 25.7 % for ARBs, 5.7 % for CCBs, and 5.7 % for β-blockers. T2DM patients were diagnosed as recommended by the American Diabetes Association (ADA) criteria (Handelsman et al., 2015). Hyperlipidemia (HLD) was defined as total cholesterol levels of > 200 mg/dL, dyslipidemia history, and/or use of lipid-lowering medication.

Exclusion criteria were implemented on the following clinical conditions: <1.5 times or no dilatation of native coronary segment

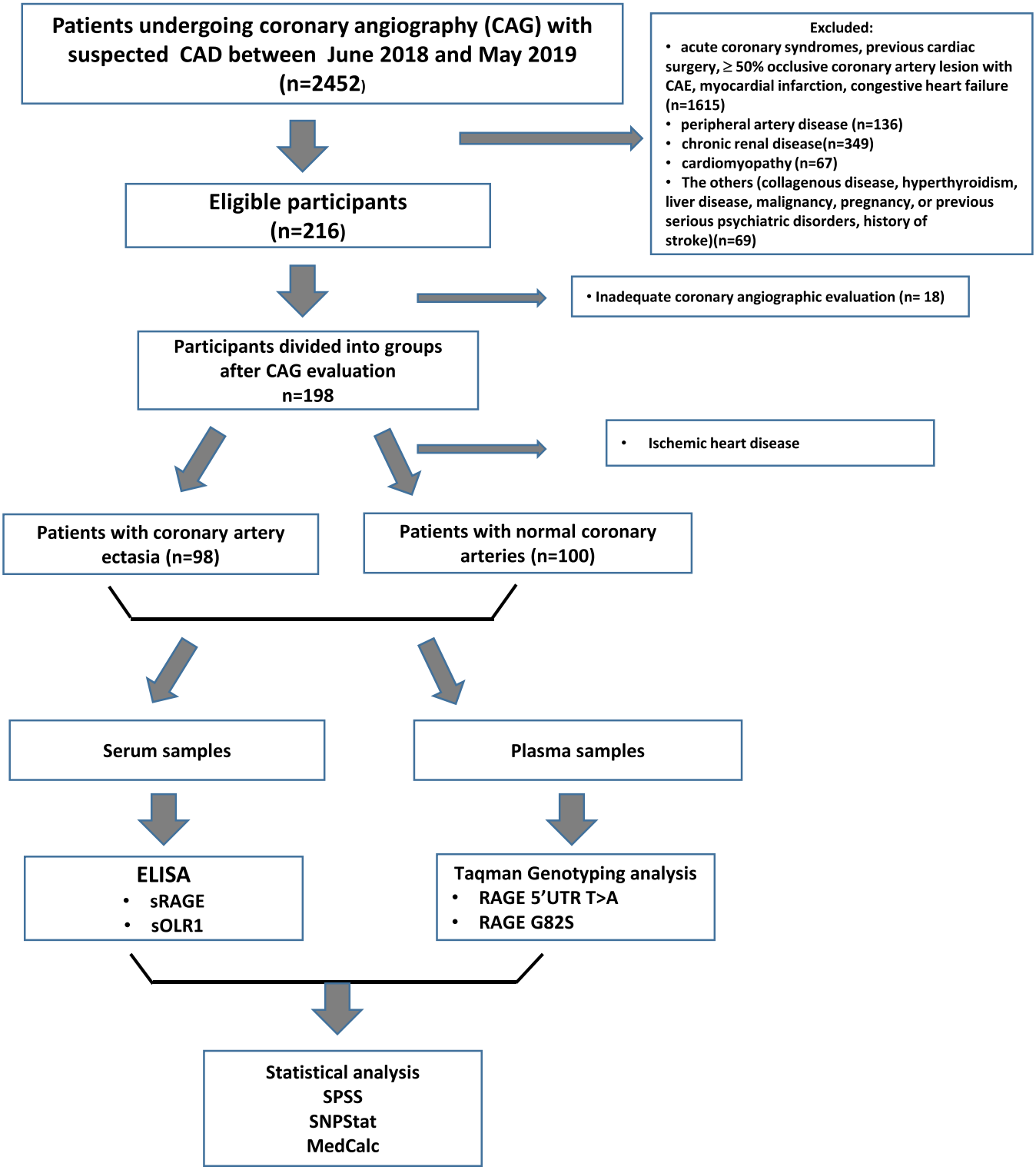

Fig. 1. Flow chart of study inclusion, exclusion, and applied methodology.

compared with normal coronary segment, acute coronary syndromes, cardiomyopathy, congestive heart failure, history of stroke, ≥ 50 % occlusive coronary artery lesion with CAE, myocardial infarction, peripheral artery disease, previous cardiac surgery, chronic kidney disease, collagenous disease, hyperthyroidism, liver disease, malignancy, pregnancy, or previous serious psychiatric disorders. Patients who had previously undergone a coronary revascularization procedure e.g. percutaneous coronary intervention were also excluded due to the procedure itself may result in CAE. The study participants were age- and sex-matched. The mean age of the CAE patients group was 62.41 ± 10.50 (mean ± SD) and the mean age for the control group was 60.27 ± 9.59. The study was approved by the Ethics Committee of the Istanbul University, Istanbul Faculty of Medicine, and complied with the Declaration of Helsinki for medical research involving human subjects (Approval number: 2018/691). All participants gave written informed consent before participating in the study.

2.2. Coronary angiography protocol and CAE classification

Coronary angiography (CAG) with either radial artery or femoral artery approach was performed for each patient using a CAG device (Integris BH 5000, Philips, The Netherlands) (Scanlon et al., 1999). The Judkins technique was utilized with 6-French (Fr) and 7-Fr catheters. Coronary angiograms were assessed and classified as suggested by Markis and colleagues (Markis et al., 1976) by two experienced interventional cardiologists. The definition of CAE was made as a dilation of a coronary artery segment ≥ 1.5 times that of the diameter of the adjacent normal segment. Following CAG, patients with CAE categorized according to the Markis classification: Type I, which involves diffuse ectasia of two or three vessels; Type II, which involves diffuse disease in one vessel and focal disease in another vessel; Type II, which involves diffuse ectasia in only one vessel; and Type IV, which involves focal or segmental ectasia (Markis et al., 1976).

2.3. Genetic analysis

2.3.1. Sample collection and DNA isolation

Peripheral blood samples which were collected from 12-hour fasting subjects between 8 and 10 am were drawn into EDTA-containing tubes and plain tubes, then transported with dry iced packages to the Molecular Medicine Laboratory of Istanbul University within 30 min. Total DNA was isolated according to the protocol of the commercial kit (PureLink Genomic DNA Mini Kit, Cat. No: K182002, Thermo Fisher Scientific, USA). DNA concentration and purity were determined using the NanoDrop 2000 Spectrophotometer (Thermo Fisher Scientific, USA). The DNA samples with approximately a ratio of optical density (OD) at 260 nm and 280 nm of 1.8 were included in the study.

2.3.2. Genotyping for RAGE polymorphisms

Real-time PCR was performed for *RAGE* SNPs 5′UTR -374T > A (rs1800624) and G82S C > T (rs2070600) with the LightCycler® 480 (Roche Diagnostics). The reaction mix was prepared with the master mix reagent (TaqMan® Universal Master Mix II (UNG)), FAM, and VIC-labeled hydrolysis probes (40X TaqMan® SNP Genotyping Assays, Thermo Fisher Scientific) and RNase/DNase free molecular grade water. Thermal cycling was carried out under the following conditions: pre-incubation at 50 °C for 2 min, polymerase activation at 95 °C for 2 min, 40 cycles of denaturation at 95 °C for 15 s and annealing/extension at 60 °C for 1 min, and finally cooling at 40 °C for 30 s. Genotypes were determined automatically by the real-time PCR instrument through endpoint genotyping as the fluorescence signal emitted from FAM or VIC dyes during allele amplification (Table 1).

2.4. Biochemical analysis

After the transfer of blood sample collection to the Molecular Medicine Lab, serum samples were obtained from immediate centrifugation of the blood samples in the plain tubes at 3000 rpm for 10 min, then aliquoted and stored at −80 °C until the time of analysis. Quantitative measurements of sRAGE and sOLR1 were done using commercial enzyme-linked immunosorbent assay (ELISA) kits (BioVendor-Laboratorní medicína a.s., Brno, Czech Republic, and USCN Life Science Inc., Wuhan, China, respectively) and executed according to the manufacturer's instructions. Both ELISA kits employ the sandwich ELISA principle. Fasting serum lipid levels were measured enzymatically.

Table 1
SNP sequences and selected bases in hydrolysis probes.

SNP Name	Rs No	VIC-Labeled Base	FAM-Labeled Base
-374T > A	rs1800624	A	T
Sequence	CCAGACTGTTGTCTGCAAGGGTGCA**[A/T]** TTGGGCCTGCATCATGAAGGCAAGG		
G82S	rs2070600	C	T
Sequence	CCGACAGCCGGAAGGAAGAGGGAGC**[C/T]** GTTGGGAAGGACACGAGCCACACTG		

2.5. Statistical analysis

Statistical data were analyzed with SPSS version 20.0 software for Windows (IBM SPSS Statistics, IBM Corporation version 20.0 SPSS Inc., Chicago, IL, USA). The normal distribution of continuous variables was tested using the Kolmogorov–Smirnov (K-S) test and the equality of variances between groups was tested using Levene's test. Continuous variables were compared between the groups using the one-way Anova and Student *t*-test when normally distributed and the non-parametric Kruscal Wallis and Mann–Whitney *U* test in cases of deviation from the normal distribution. The Spearman's rank correlation test was used for the assessment of correlation of the analysed parameters. The Hardy-Weinberg equilibrium (HWE) and the genetic models (co-dominant, dominant, recessive) among the study groups, and linkage disequilibrium and haplotype analysis of *RAGE* [5′UTR -374T > A (rs1800624) and G82S C > T (rs2070600)] variants were calculated with the SNPStats (Catalan Institute of Oncology, Barcelona, Spain) software. Diagnostic values were evaluated using receiver operating characteristic (ROC) curve analysis (MedCalc software). The odds ratio (OR) and 95 % confidence interval (CI) were calculated to determine the relative risks between study groups. Logistic regression was also used to estimate the independent risk factors of CAE. P values below 0.05 were considered statistically significant.

3. Results

3.1. Clinical characteristics

The demographic and biochemical characteristics of CAE patients and the control group are shown in Table 2. The comparison between the CAE group and controls revealed significantly higher levels of serum sOLR1 ($p = 0.004$), triglycerides ($p = 0.011$) in the CAE group, while high density lipoprotein (HDL)-cholesterol levels were found significantly lower in the CAE group ($p = 0.005$). There was no significant difference between the study groups in the remaining metabolic parameters, including age, sex, sRAGE, FBG, HbA1c, total- and low density lipoprotein (LDL)-cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and thyroid stimulating hormone (TSH) levels, hemogram parameters, ejection fraction and prevalence of T2DM ($p > 0.05$).

The prevalence of HT and HLD was significantly higher in CAE patients ($p < 0.001$). Among CAE patients, 17.4 % had HT, 1.2 % had DM, 15.31 % had HLD, 6.12 % had both HT and DM, 17.34 % had both HT and HLD, 6.12 % had both DM and HLD, and 20.41 % had all three conditions. Patients with HT ($p = 0.012$), HLD ($p < 0.001$), or a

Table 2
Baseline characteristics of study groups.

Parameters	Groups		
	CAE (n = 98)	Control (n = 100)	p value
Age (years)	62.41 ± 10.50	60.27 ± 9.59	0.136
Gender (Female/Male)	30/68	41/59	0.128
sRAGE (pg/ml)	1184.28 ± 62.84	1207.44 ± 59.24	0.437
sOLR1 (ng/ml)	0.96 ± 0.07	0.68 ± 0.03	**0.004**
FBG (mg/dl)	115.98 ± 40.66	116.48 ± 56.81	0.943
HbA1c (%)	6.35 ± 1.16	6.11 ± 0.91	0.097
Total-C (mg/dl)	182.68 ± 41.79	183.81 ± 45.54	0.856
HDL-C (mg/dl)	44.03 ± 12.02	49.41 ± 14.56	**0.005**
LDL-C (mg/dl)	126.24 ± 41.32	126.79 ± 40.28	0.925
TG (mg/dl)	166.58 ± 10.01	136.68 ± 7.07	**0.011**
ALT (U/L)	28.04 ± 2.60	22.09 ± 1.30	0.351
AST (U/L)	23.99 ± 1.58	21.23 ± 1.04	0.561
BUN (mg/dl)	16.33 ± 0.50	16.73 ± 0.59	0.886
Creatine (mg/dl)	0.91 ± 0.03	0.87 ± 0.02	0.362
WBC (10^3/μL)	8.39 ± 2.28	7.81 ± 2.49	0.090
Hemoglobin (gr/dl)	13.53 ± 1.79	13.41 ± 1.75	0.610
Hematocrit (%)	39.99 ± 5.03	39.32 ± 6.10	0.399
Platelet (10^3/μL)	236.05 ± 75.85	235.77 ± 67.12	0.978
TSH (μu/ml)	2.18 ± 0.19	2.34 ± 0.14	0.09
EF (%)	56.28 ± 8.31	58.05 ± 6.59	0.098

The continuous variables were compared with the Student *t*-test or Mann–Whitney *U* test as appropriate and the results are shown as mean ± standard deviation (X ± SD) or (X ± SEM). Categorical variables were compared using chi-square test and results are shown as number (%). FBG, fasting blood glucose; HbA1c, hemoglobin A1c; Total-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; WBC, white blood cell; TSH, thyroid stimulating hormone; EF, ejection fraction; T2DM, type 2 diabetes mellitus.

combination of HT and DM ($p < 0.01$), HT and HLD ($p < 0.001$), or all three conditions ($p < 0.001$) have been observed to have a higher risk of CAE than those without these conditions (Table 3).

The study found that CAE involvement was observed in 64.3 % (n = 63) of cases in the right coronary artery (RCA), 44.9 % (n = 44) in the circumflex (Cx) coronary artery, 39.8 % (n = 39) in the left anterior descending artery (LAD), and 10.2 % (n = 10) in left main coronary artery. Of the patients, 64.3 % (63) had one-vessel CAE, and 35.7 % (n = 35) had multi-vessel ectasia. According to Markis classification, 43 (43.9 %) of the patients had type I, 5 (5.1 %) had type II, 37 (37.8 %) had type III, and 13 (13.3 %) had type IV (Table 4).Accordingly, 48 patients (49.0 %) had severe ectasia (type 1 and type 2), while 50 patients (51.0 %) had mild ectasia (type 3 and type 4). The mean Markis score was 2.20.

Table 3
Distribution of systemic diseases in the study groups.

Presence of systemic disease	Groups		
	CAE (n = 98)	Control (n = 100)	p value
HT (%) (total)	60 (61.2 %)	37 (%37)	**0.001** (OR = 2.688, 95 %CI = 1.514–4.775)
HLD (%) (total)	58 (59.2 %)	31 (%31)	**0.001** (OR = 3.227, 95 %CI = 1.799–5.790)
T2DM (%)(total)	33 (33.7 %)	28 (%28)	p > 0.05
HT (only)	17 (51.5 %)	16 (25.8 %)	**p = 0.012** (OR = 1.530, 95 % CI = 1.045–2.240)
T2DM (only)	1 (5.9 %)	5 (9.8 %)	p > 0.05
HLD (only)	15 (48.4 %)	4 (8.0 %)	***p < 0.001**
HT + and HLD+	17 (51.5 %)	6 (11.5 %)	**p < 0.001** (OR = 1.825, 95 % CI = 1.266–2.629)
T2DM + and HLD+	6 (27.3 %)	8 (14.8 %)	p > 0.05
HT+, T2DM+, HLD+	20 (55.6 %)	13 (20.0 %)	**p < 0.001** (OR = 1.754, 95 % CI = 1.188–2.590)
HT-, T2DM-, HLD-	16 (44.4 %)	46 (78.0 %)	**p < 0.001** (OR = 0.221, 95 % CI = 0.113–0.430)

HT, hypertension; T2DM, type 2 diabetes; HLD, hyperlipidemia.
*Fisher's exact test.

3.2. Serum levels of sRAGE and sOLR1 in subgroups by systemic disease

There is some evidence that antihypertensive, antidiabetic and, antihyperlipidemic drugs can affect serum sRAGE levels (Forbes et al., 2005; Nakamura et al., 2005; Santilli et al., 2007; Matsui et al., 2010; Derosa et al., 2014; Wang et al., 2018). Therefore, we analyzed the study groups according to the presence of systemic diseases in subgroups to evaluate the effects of these treatments on sRAGE and sOLR1 levels (Table 5).

Serum sRAGE levels were not different between the total CAE and control groups, nor were different in further analysis of subgroups according to the presence of systemic diseases. However, in the subgroup analysis within the CAE group, serum sRAGE levels were found to be higher in the presence of HT and T2DM than in the absence of any systemic disease ($p = 0.02$). On the other hand, sRAGE levels in the control group did not differ according to the presence or absence of systemic diseases ($p > 0.05$).

There were no significant differences in sOLR1 levels within the CAE group based on the presence of HT, HLD and T2DM comorbidities. However, in the control group, sOLR1 levels of those with all of HT, T2DM and HLD were higher than those with none of these diseases ($p = 0.014$). Additionally, in the absence of systemic diseases, sOLR1 level in the CAE group were higher than in the control group ($p = 0.005$) (Table 5).

3.3. RAGE -374T > A and G82S genotypes and allele distributions

The genotype and allele frequencies of the *RAGE* polymorphisms according to genetic models are summarized in Table 6. Allele frequencies of each polymorphism among the CAE and control groups were in Hardy–Weinberg equilibrium ($p > 0.05$) except for *RAGE* G82S SNP ($p < 0.05$). In genetic models of *RAGE* -374T > A (rs1800624), significant differences were observed between the CAE group and the control group (for TA genotype OR = 0.18, 95 % CI 0.09–0.36 and AA genotype OR = 0.05, 95 % CI 0.02–0.15, $p < 0.0001$ in the codominant model; OR = 0.14, 95 % CI 0.07–0.26 and $p < 0.0001$ in the dominant model; OR = 0.14, 95 % CI 0.05–0.38 and $p < 0.0001$ in the recessive model). The frequency of the -374A allele was significantly higher in the CAE group compared with controls (56 % vs. 23 %; $p < 0.001$) whereas the frequency of the -374T allele was higher in controls then CAE group (77 % vs. 44 %; $p < 0.001$). Accordingly, individuals carrying the minor -374A allele had 3.6 fold increased risk for CAE (95 %CI: 2.243–5.823) while -374T allele carriers had lower CAE risk (risk value: 0.181, 95 %CI: 0.073–0.452).

The analysis of *RAGE* G82S C > T SNP (rs2070600) by genetic models revealed no significant difference between CAE patients and

Table 4
Distribution of *RAGE* 5′UTR −374 T > A genotypes in the CAE group categorized according to Markis classification.

	RAGE 5′UTR −374T > A genotypes		
Number of vessel	**TT**	**AA**	**TA**
1 (n = 63)	11 (17.5 %)	16 (25.4 %)	36 (57.1)
2 (n = 20)	4 (20.0 %)	6 (30.0 %)	10 (50.0 %)
3 (n = 7)	1 (14.3 %)	3 (42.9 %)	3 (43.9 %)
4 (n = 8)	0	2 (25.0 %)	6 (75.0 %)
Markis classification			
Type I (n = 43)	9 (20.9 %)	12 (27.9 %)	22 (51.2 %)
Type II (n = 5)	1 (20.0 %)	1 (20.0 %)	3 (60.0 %)
Type III (n = 37)	6 (16.2 %)	10 (27.0 %)	21 (56.8 %)
Type IV (n = 13)	0	4 (30.8 %)	9 (69.2 %)

Table 5
Comparison of sRAGE and sOLR1 levels in control and CAE subgroups classified by the presence of systemic diseases*.

Parameters	Groups	Presence of systemic diseases						
sOLR1 (ng/ml)		**No systemic disease**	**HT**	**HLD**	**HT + T2DM**	**HT + HLD**	**T2DM + HLD**	**HT + T2DM + HLD**
	CAE	1.06 ± 0.24	0.89 ± 0.17	1.08 ± 0.20	0.88 ± 0.09	0.84 ± 0.13	0.66 ± 0.006	1.03 ± 0.19
	Control	0.62 ± 0.02	0.66 ± 0.04	0.50 ± 0.01	0.58 ± 0.04	0.80 ± 0.14	0.88 ± 0.19	**0.86 ± 0.10[b]**
P value CAE vs. Control		**p = 0.005**	NS	**	NS	NS	NS	NS
sRAGE (pg/ml)	**CAE**	1113.46±195.64	1275.61 ±142.08	989.68 ±123.32	**1981.87 ±308.03 [a]**	1184.60 ±149.29	843.39±64.87	1204.23±106.38
	Control	1185.43±73.40	1476.40 ±214.91	867.71±99.05	1470.77 ±407,58	1136.23 ±176.60	977.13 ±197.39	1124.89±160.57
P value CAE vs. Control		NS	NS	NS	NS	NS	NS	NS

*, In the CAE group, samples with only T2DM were not included in the analysis due to the insufficient number of samples.
**, Due to the insufficient number of samples with only HLD and only T2DM in the control group, sOLR1 and sRAGE levels were not compared between groups.
Data were given as mean ± standard error and p-values were calculated by Mann–Whitney *U* test. HT, hypertensive; HLD, hyperlipidemic; T2DM, diabetic.
[a], CAE subgroup without systemic disease (HT-, T2DM-, and HLD-) vs.CAE subgroup with HT and T2DM, p = 0.02.
[b], Control subgroup with HT+, T2DM+, and HLD + vs.Control subgroup without systemic disease (HT-, T2DM-, and HLD-), p = 0.014.

Table 6
Distribution of *RAGE* [5′UTR −374 T > A (rs1800624) and G82S C > T (rs2070600)] genotypes and alleles in the study groups according to genetic models.

Genetic Model(n,%)		**Genotype**	**Patients (n = 98)**	**Controls (n = 100)**	**OR (95 % CI)**	***p-value***	**AIC**	**BIC**
RAGE 5′UTR −374 T > A (rs1800624)	Codominant	TT	16 (16.3 %)	59 (59.0 %)	1 (Reference)	***<0.0001***	233.6	243.5
		TA	55 (56.1 %)	36 (36.0 %)	**0.18 (0.09–0.36)**			
		AA	27 (27.6 %)	5 (5.0 %)	**0.05 (0.02–0.15)**			
	Dominant	TT	16 (16.3 %)	59 (59.0 %)	1 (Reference)	***<0.0001***	238.3	244.9
		TA + AA	82 (83.7 %)	41 (41.0 %)	**0.14 (0.07–0.26)**			
	Recessive	TT + TA	71 (72.5 %)	95 (95.0 %)	1 (Reference)	***<0.0001***	**258.4**	**265.0**
		AA	27 (27.6 %)	5 (5.0 %)	**0.14 (0.05–0.38)**			
	Allele Frequency	T allele	87 (44.0 %)	154 (77.0 %)	*HWE for Patients: 0.22*			
		A allele	109 (56.0 %)	46 (23.0 %)	*HWE for Controls > 0.05*			
RAGE G82S C > T (rs2070600)	−−	CC	91 (92.9 %)	95 (95.0 %)	1 (Reference)	*0.53*	278.1	284.6
		CT	− (%0.0)	− (%0.0)	− (%0.0)			
		TT	7 (7.1 %)	5 (5.0 %)	0.68 (0.21–2.23)			
	Allele Frequency	C allele	182 (93.0 %)	190 (95.0 %)	*HWE for Patients< **0.001***			
		T allele	14 (7.0 %)	10 (5.0 %)	*HWE for Controls< **0.001***			

AIC, Information criteria of Akaike; BIC, Information criteria of Bayesian. The genetic models (co-dominant, dominant, recessive) were calculated with the SNPStats (Catalan Institute of Oncology, Barcelona, Spain) software. HWE, Hardy Weinberg Equilibrium.

controls (p > 0.05). The heterozygous genotype CT of G82S was not observed in both groups. However, in the CAE group, the diabetes rate of was higher in patients with the 82TT genotype, 5 out of 7 patients had diabetes (Fisher exact test, p = 0.041, data not shown).

The distribution of the RAGE -374T > A polymorphism in CAE patients was similar in subgroups categorized by the number of ectatic coronary arteries and Markis classification (Table 4).

3.4. Multivariate regression analysis of RAGE -374T > A

The effects of the risk parameters that we observed on the development of CAE were further evaluated by Binary logistic regression analysis (Table 7). The *RAGE* −374A allele, hyperlipidemia, hypertension, and sOLR1 cut-off levels (equal/higher than 0.67 ng/ml) were chosen as independent variables to evaluate their predictor ability. As a result, binary regression analyses was confirmed that the *RAGE* −374A allele (p < 0.001, 95 % CI: 3.340 – 15.757) hyperlipidemia (p < 0.05, 95 % CI: 0.991 – 4.169) and increased sOLR1 levels (p < 0.05, 95 % CI:0.990 – 4.042) were a risk for CAE, while hypertension did not continue their predictor effects for CAE (p < 0.05).

To assess the diagnostic value of the multivariate logistic regression model, we performed a receiver operating characteristic (ROC) curve analysis (Fig. 1, Table 8). We calculated their sensitivities, specifities, and area under the curve (AUC) to determine their diagnostic accuracies (Fig. 2). The ROC analysis showed that the RAGE -374A allele (sensitivity: 83.7 % and specificity: 59.0 %, AUC = 0.713), HLD (sensitivity: 59.2 %, specificity: 69.0 %, AUC = 0.641), HT (sensitivity: 62.4 %,

Table 7
Multivariate logistic regression by CAE risk.

Independent Variable	**p value**	**OR**	**95 % CI**
***RAGE* -374A Allele**	**0.001**	7.362	3.440–15.757
Hyperlipidemia	**0.05**	2.033	0.991–4.169
Hypertension	0.108	1.798	0.879–3.677
sOLR1 ≥ 0.67 (ng/ml)	**0.05**	2.001	0.990–4.042

Dependent Variable: CAE, OR: Odds Ratio, CI: Confidence Interval.

Table 8
Discriminatory power of independent factors to predict CAE.

Parameters	**AUC (95 % CI)**	**Sensitivity (%)**	**Spesifity (%)**
***RAGE* −374A Allele**	0.713 (0.645 – 0.775)	83.7	59.0
Hyperlipidemia	0.641 (0.570 – 0.708)	59.2	69.0
Hypertension	0.621 (0.550–0.689)	62.4	61.1
sOLR1 ≥ 0.67 (ng/ml)	0.587 (0.510–0.662)	59.8	58.5

CAE, coronary artery ectasia; AUC, area under the ROC curve; ROC, receiver operator characteristic; CI, confidence interval; sOLR1, soluble oxidized- low-density lipoprotein receptor 1.

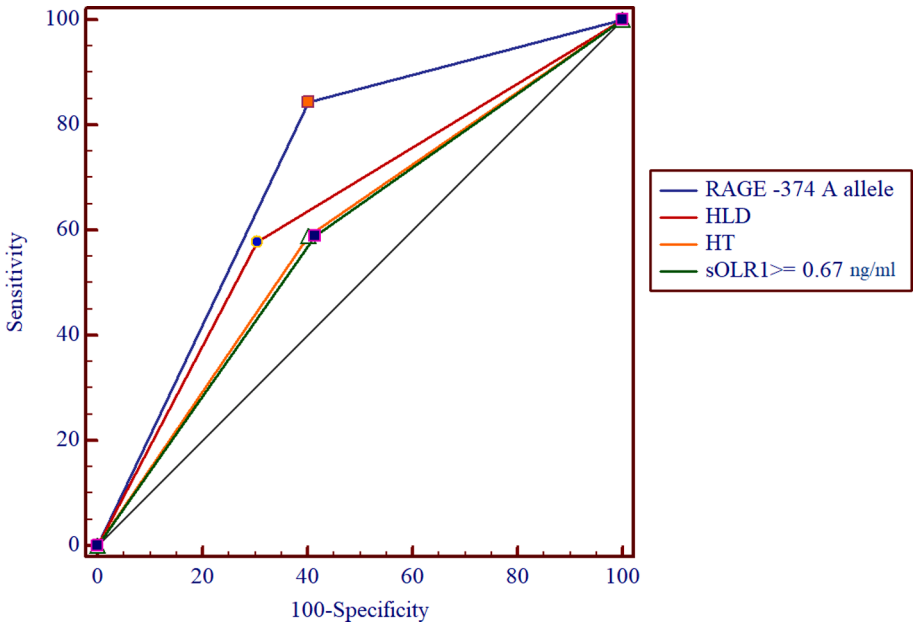

Fig. 2. ROC curve of the multivariate logistic regression model.

specificity: 61.1 %, AUC = 0.621) and sOLR1 cut-off level (≥0.67) (sensitivity: 59.8 %, specificity: 58.5 %, AUC = 0.587) have good diagnostic value for CAE (Table 8).

3.5. Evaluation of the effects of RAGE polymorphisms on CAE with systemic diseases

Because of the proposed effects of antihypertensive treatments on sRAGE levels in patients with type 2 diabetes (Forbes et al. 2006; Forbes et al., 2005; Nakamura et al., 2005; Matsui et al., 2010; Derosa et al., 2014; Wang et al., 2018), we further analyzed the effects of the *RAGE* -374T > A SNP on serum levels of sRAGE and sOLR1 and other study parameters by dividing the study groups into subgroups according to their hypertensive status (Table 9).

Serum sRAGE levels were higher in both the CAE and control groups in the HT subgroups receiving antihypertensive treatment than in patients without systemic disease (HT, T2DM and HLD) and therefore not receiving relevant medication, but the difference was not statistically significant. In the CAE group, the highest sRAGE levels were observed in HT patients with -374TT genotype. While the -374A allele was associated with lower sRAGE levels compared to the -374TT genotype in the total control group, there was no similar relationship in subgroup analyzes based on the presence of hypertension. This may be due to the low prevalence of HT in the control group and thus the small sample size.

In both the total CAE group and the CAE subgroups hypertensive (alone) and without systemic disease, the -374A allele was associated with younger age ($p = 0.006$, $p = 0.037$, and $p = 0.020$, respectively) and higher Plt values ($p = 0.003$, $p < 0.001$, and $p = 0.042$, respectively). However, this relationship was not present in the control group. However, in both CAE and control groups, *RAGE* -374T > A SNP had no effect on lipid and glycemic parameters and sOLR1 levels. Since there was not enough sample in our study in the subgroups consisting of individuals with only T2DM and only HLD, the effects of *RAGE* -374T > A SNP in the CAE and control groups in the presence of these systemic diseases could not be examined. In addition, due to the small number of minor allele carriers, the effects of the *RAGE* G82S SNP in patient subgroups could not be evaluated.

In the overall CAE group, sRAGE levels showed a weak positive correlation with age (rho (ρ) = 0.232, $p = 0.024$) and a negative correlation with HDL levels (ρ = -0.275, $p = 0.007$). In this group, the −374A allele showed a negative correlation with age (ρ = -0.277, $p = 0.006$) and a positive correlation with platelet count (Plt) (ρ = 0.303, $p = 0.002$). Similarly, in hypertensive CAE, there was a positive correlation between sRAGE and age (ρ = 0.687, $p = 0.005$). Additionally, there was a positive correlation between the -374A allele and Plt (ρ = 0.738, $p = 0.001$), while a negative correlation was observed between the -374A allele and age (ρ = -0.528, $p = 0.029$). In the CAE patients without systemic disease, the -374A allele was negatively correlated with age (ρ = -0.595, $p = 0.015$) and positively correlated with Plt (ρ = 0.517, $p = 0.04$).

In the total control group, a negative correlation was observed between sRAGE level and Plt and -374A allele (ρ = −0.410, $p = 0.001$ and ρ = -0.237, $p = 0.029$, respectively). A negative correlation was observed between sRAGE and Plt in both hypertensive and no systemic disease control subgroups (ρ = −0.657, $p = 0.008$ and ρ = −0.481, $p = 0.003$, respectively). In controls without systemic disease, sOLR1 was also negatively correlated with HDL (ρ = −0.419, $p = 0.011$).

4. Discussion

Although the etiopathogenesis of coronary artery ectasia has not yet been fully elucidated, clinical studies suggest a common pathological mechanism involving atherosclerosis and atherosclerosis risk factors. Inflammation is a common factor contributing to the occurrence of both atherosclerosis and CAE, except for some ectatic cases with non-atherosclerotic conditions (Ozturk et al., 2018). Advanced glycation end products (AGEs) are known to form cross-links with components in the basement membrane of the extracellular matrix. The increased RAGE activation by engaging AGEs are reported to be a contributing factor to microvascular and macrovascular complications in diabetes (Goldin et al., 2006). Although the RAGE activation is also known to be related to vascular inflammation and acceleration of atherosclerosis (Wendt et al., 2006; Choi et al., 2009), its role in CAE pathogenesis has yet to be determined. On the other hand, it is suggested that the soluble form of RAGE (sRAGE), which is described as a “sponge” for AGEs, may have protective functions as it lacks the amino terminus and is unable to activate NF-κB signaling (Bush et al., 2010). The *RAGE* -374A allele is known to suppress the transcriptional activity of *RAGE* gene (Hudson et al., 2001). The expression of the 82S allele of the functional SNP G82S in the *RAGE* gene has been found to be associated with increased ligand

Table 9
Effects of *RAGE* 5′UTR T > A polymorphism on patient characteristics in study groups and subgroups stratified by hypertension.

Parameters	CAE Total group *RAGE* -374T/A SNP		Hypertensives *RAGE* -374T/A SNP		No systemic disease *RAGE* -374T/A SNP	
	TT genotype (n:16)	A allele (AA + TA genotypes) (n:82)	TT genotype (n: 5)	A allele (AA + TA genotypes) (n = 12)	TT genotype (n: 4)	A allele (AA + TA genotypes) (n = 12)
Age (years)	69.06 ± 3.31	**61.11 ± 1.04** [a]	81.0 ± 1.34	**64.92 ± 3.52**[c]	66.75 ± 2.43	**57.50 ± 1.82** [e]
sRAGE (pg/ml)	1115.40 ± 120.77	1197.36 ± 71.35	1674.24 ± 270.78	1130.66 ± 150.53	982.31 ± 120.36	1157.18 ± 259.96
sOLR1 (ng/ml)	1.37 ± 0.32	0.89 ± 0.06	0.75 ± 0.11	0.94 ± 0.22	1.65 ± 0.92	0.86 ± 0.13
FBG (mg/dl)	115.94 ± 12.11	115.99 ± 4.34	101.60 ± 5.65	102.08 ± 3.20	94.25 ± 5.96	98.58 ± 2.99
HbA1c (%)	6.09 ± 0.23	6.40 ± 0.13	6.06 ± 0.14	5.88 ± 0.05	5.65 ± 0.12	5.85 ± 0.05
Total-C(mg/dl)	163.69 ± 10.55	186.39 ± 4.52	138.60 ± 14.00	150.58 ± 13.05	161.50 ± 15.71	169.17 ± 12.58
HDL-C (mg/dl)	43.81 ± 2.73	44.07 ± 1.36	49.60 ± 5.48	45.0 ± 2.94	41.00 ± 2.65	44.50 ± 3.09
LDL-C (mg/dl)	108.75 ± 10.15	129.66 ± 4.51	84.20 ± 15.93	96.58 ± 11.51	111.75 ± 19.09	110.50 ± 12.23
TG (mg/dl)	142.63 ± 21.24	171.26 ± 11.20	101.60 ± 29.85	122.42 ± 17.75	116.75 ± 16.66	162.67 ± 31.89
Plt (10^3/μL)	194.19 ± 9.83	**244.22 ± 8.69**[b]	166.00 ± 9.89	**264.83 ± 17.52** [d]	180.00 ± 7.29	**217.00 ± 10.86**[f]
	CONTROLS					
	Total group ***RAGE* -374T/A SNP**		**Hypertensives** ***RAGE* -374T/A SNP**		**No systemic disease** ***RAGE* -374T/A SNP**	
	TT genotype **(n:59)**	**A allele** **(AA + TA genotypes)** **(n = 41)**	**TT genotype** **(n: 11)**	**A allele** **(AA + TA genotypes)** **(n = 5)**	**TT genotype** **(n: 26)**	**A allele** **(AA + TA genotypes)** **(n = 20)**
Age (years)	58.81 ± 1.19	62.37 ± 1.55	64.64 ± 2.77	68.60 ± 5.57	56.65 ± 2.01	59.95 ± 1.82
sRAGE (pg/ml)	1304.45 ± 78.46	**1068.86 ± 86.17** [g]	1453.09 ± 271.27	1523.02 ± 391.16	1295.65 ± 102.26	1040.77 ± 95.63
sOLR1 (ng/ml)	0.63 ± 0.03	0.75 ± 0.05	0.65 ± 0.05	0.69 ± 0.07	0.59 ± 0.03	0.65 ± 0.04
FBG (mg/dl)	109.12 ± 5.46	127.07 ± 11.31	98.73 ± 4.50	110.80 ± 4.44	93.62 ± 1.45	94.25 ± 2.21
HbA1c (%)	6.07 ± 0.12	6.16 ± 0.14	5.76 ± 0.05	5.92 ± 0.07	5.71 ± 0.05	5.67 ± 0.06
Total-C (mg/dl)	182.41 ± 5.83	185.83 ± 7.35	184.00 ± 12.76	190.40 ± 23.10	173.85 ± 7.85	165.15 ± 7.82
HDL-C (mg/dl)	47.81 ± 1.81	51.71 ± 2.40	50.64 ± 3.61	56.80 ± 4.13	48.38 ± 2.60	52.40 ± 4.43
LDL-C (mg/dl)	126.10 ± 5.16	127.78 ± 6.51	121.00 ± 11.40	125.00 ± 25.83	118.04 ± 7.11	115.80 ± 7.34
TG (mg/dl)	133.10 ± 8.58	141.83 ± 12.13	123.09 ± 16.82	101.20 ± 21.21	125.04 ± 13.54	122.50 ± 9.02
Plt (10^3/μL)	227.00 ± 8.41	248.39 ± 10.85	225.64 ± 20.94	221.20 ± 22.08	212.00 ± 11.88	238.05 ± 13.88

Data were given as mean ± standard deviation and p-values were calculated by Student's *t*-test and Mann Whitney *U* test. FBG, fasting blood glucose; HbA1c, hemoglobin A1c; Total-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; Plt, Platelet; ns, not significant. Bold values indicate statistical significance ($p < 0.05$).
a, $p = 0.006$ A allele vs. TT genotype (Total CAE group).
b, $p = 0.003$ A allele vs. TT genotype (Total CAE group).
c, $p = 0.037$ A allele vs. TT genotype (Hypertensive CAE group).
d, $p < 0.001$ A allele vs. TT genotype (Hypertensive CAE group).
e, $p = 0.020$ A allele vs. TT genotype (No systemic disease CAE group).
f, $p = 0.042$ A allele vs. TT genotype (No systemic disease CAE group).
g, $p = 0.03$ A allele vs. TT genotype (Total Control group).

binding and increased production of inflammatory mediators such as cytokines and MMPs, thereby promoting the inflammatory response (Hofmann et al., 2002, Osawa et al., 2007). Furthermore, Shiu et al. (2012) showed that binding of AGEs to RAGE induces OLR-1 expression. The elevated sOLR1 levels have also been associated with proinflammatory cytokines including TNF-α and IL-6, MMP-2 and MMP-9, carotid plaque inflammation, and proposed as a biomarker for predicting ischemic stroke (Markstad et al., 2019). In addition, high sOLR1 levels have also been associated with vascular diseases including CAE, preeclampsia and coronary slow flow phenomenon in the Turkish population (Balin et al., 2012; Civelek et al., 2015; Tuten et al., 2015; Caglar et al., 2016). Based on these reasons, we studied two functional SNPs of the *RAGE* gene, -374T > A (5′UTR, rs1800624) and G82S C > T (rs2070600), along with serum sRAGE and sOLR1 levels to determine whether they could be associated with a genetic predisposition to CAE and how they could affect the prognosis of the disease. The study found that the RAGE -374A allele was associated with a 3.6-fold increased risk of CAE ($p < 0.001$). In addition, serum sOLR1 levels were higher in CAE patients compared to controls subjects with normal coronary angiograms ($p = 0.004$). Multivariate logistic regression analysis confirmed that the RAGE -374A allele, hyperlipidaemia, and elevated sOLR1 levels were identified as risk factors for CAE. The levels of sRAGE were similar between the CAE and control groups. However, CAE patients with both DM and HT had higher serum sRAGE levels than CAE patients without systemic disease ($p = 0.02$). The -374A allele was linked to younger patient age and higher platelet count in both the hypertensive and non-systemic disease CAE subgroups, as well as in the overall CAE group and with lower sRAGE levels in the control group.

The soluble form of RAGE (sRAGE, the extracellular ligand binding domain of the receptor) has been shown to suppress atherosclerotic progression by blocking the AGE-RAGE signaling pathway and stabilizes the lesion in in vivo diabetic mouse models (Yamagishi and Matsui, 2010). Administration of sRAGE in murine models of type 1 and type 2 diabetes also revealed a diminishing effect on inflammation and atherosclerosis by blocking ligand-RAGE interaction (Ramasamy et al., 2007). Studies suggesting lower plasma sRAGE levels in non-diabetic male patients with CAD compared to healthy controls also support that sRAGE suppresses atherosclerosis (Falcone et al., 2005a; McNair et al., 2011). In contrast to these studies reporting that sRAGE levels are low and AGEs are increased in type 2 diabetes, there are also conflicting results reporting increased sRAGE levels, especially in uncontrolled type 2 diabetes (Steenbeke et al., 2021). For instance, in Japanese patients with type 2 diabetes, serum sRAGE levels were found to be associated with CAD and increased significantly compared to nondiabetic patients, as well as correlated with circulating levels of AGEs (Nakamura et al., 2007, Nakamura et al., 2008). Although the antiatherogenic impact of

sRAGE via competition with RAGE for AGEs binding has been emphasized, increased levels of sRAGE in diabetic patients may not prevent the development of CAD due to much higher levels of AGEs already (Prasad, 2021). In addition, various studies have shown that sRAGE levels in patients with type 2 diabetes increase with aerobic exercises and the use of thiazolidinediones, which are peroxisome proliferator-activated receptor (PPAR) gamma agonists used in the treatment of type 2 diabetes. (Choi et al., 2012; Forbes et al., 2005; Tan et al., 2007). Recently, a bidirectional cross-talk between RAGE and angiotensin II type-1 (AT1), a component of the renin-angiotensin system that regulates the blood pressure, induced by RAGE ligands has been shown and suggested an important role in cardiovascular diseases (Yokoyama et al., 2021). Supportingly, some studies have shown that the use of antihypertensive medications such as ACEis, Angiotensin II reseptör blockers, and calcium channel blockers increase sRAGE concentration, reduce formation of AGEs and attenuates the proinflammatory RAGE signaling (Forbes et al., 2005; Nakamura et al., 2005; Derosa et al., 2014). On the other hand, Matsui et al. reported that nifedipine, a calcium channel blocker (CCB), acts as an anti-oxidative and anti-inflammatory agent against AGEs by suppressing RAGE expression through PPARgamma activation in tubular cells (Matsui et al., 2010). These data suggest that serum sRAGE levels are affected by the use of antidiabetic and antihypertensive drugs. In this study, the higher sRAGE levels observed in CAE patients with both HT and T2DM on antihypertensive and antidiabetic treatment compared to patients without systemic disease (normotensive, normoglycemic and normolipidemic CAE patients) supports that antihypertensive and antidiabetic drugs may have a beneficial effect on serum sRAGE levels ($p = 0.02$).

Moreover, genetic variants in the *RAGE* gene have also been associated with RAGE expression and thus the circulating level of sRAGE (Lim et al., 2017). Therefore, research has mainly focused on the relationships between functional genetic variants of *RAGE* and pathological conditions. Previous reports investigating the effect of *RAGE* gene variations in diabetic patients have suggested a possible protective role against cardiovascular complications for the *RAGE* -374AA genotype and -374A allele. The former was associated with a lower prevalence of cardiovascular disease in type 1 diabetes (Pettersson-Fernholm et al., 2003), and the latter was linked to a lower risk for ischemic heart disease in type 2 diabetes (dos Santos et al., 2005). In addition, several studies found that -374AA genotype was associated with a reduced risk of CAD in nondiabetic subjects, lower risk of vessel stenosis in CAD patients with more 50 % stenosis in at least one vessel, lower prevalence for ischemic stroke, lower incidence of restenosis after coronary stent implantation, and protective against cardiac events in nondiabetic CAD patients (Falcone et al., 2004, Falcone et al., 2005b, Zee et al., 2006, Falcone et al., 2007, Falcone et al., 2008; Aydogan et al., 2012). However, some studies suggested different effect of *RAGE* -374T > A SNP. A *meta*-analysis including 4402 type 2 diabetic patients and 6081 controls in Caucasians also indicated that the -374A allele was associated with CAD in patients (Liu and Qiu, 2013). Similarly, a few studies conducted in the Turkish population revealed that the -374A allele was associated with CAD risk in diabetic patients (Kucukhuseyin et al., 2009, Aydoğan et al. 2012). On the other hand, another *meta*-analysis including 4343 patients and 5402 controls found no association between *RAGE* -374T > A SNP and CAD (Wang et al., 2012).

The -374T > A SNP has also been implicated in Kawasaki Disease, an inflammatory condition with vascular complications including CAE (Maggioli et al., 2014). In our study, we detected for the first time a significantly higher frequency of the −374A allele in CAE patients with coronary artery disease in comparison with controls. The −374A allele was associated with a 3.6-fold increase in CAE risk. Logistic regression analysis revealed that carriers of the *RAGE* −374A allele were independently associated with CAE risk along with the conventional CAD risk factor of HLD but not with HT. In the control group, the −374A allele showed a significant association with lower levels of sRAGE compared to the homozygous TT genotype ($p = 0.03$). In addition control subgroup without systemic disease was also observed a non-significant decrease in sRAGE levels in carriers of the -374A allele. These results support Hudson et al.'s (2001) finding that the variant -374A allele causes repression of *RAGE* transcription. On the other hand, the disappearance of the association between the -374A allele and low sRAGE levels in CAE patients, taken together with the increasing effects of antihypertensive and antidiabetic drugs on sRAGE levels ($p = 0.02$), may be due to the particularly high rate of antihypertensive drug use in the CAE group, which may have masked the decreasing effect of the -374A allele on sRAGE levels.

OLR1 has emerged as a potential therapeutic target for CAD in recent studies (Barreto et al., 2021). An in vivo study of OLR1 knockout mice subjected to ischemia for 3 weeks provided reduced cardiac remodeling and smaller infarct size, subsequently improving cardiac function (Lu et al., 2012). In stable CAD patients, increased levels of sOLR1 have been associated with the incidence of major adverse cardiovascular events in a two-year follow-up (Zhao et al., 2019). Our study found high levels of sOLR1 in CAE patients ($p = 0.004$), confirming the study by Balin et al. (2012). These findings strengthen the suggestion that increased sOLR1 levels are a risk not only for CAD but also for CAE, especially with its effects in favor of atherosclerosis.

Proatherogenic conditions such as T2DM, HT, and HLD are known to increase OLR1 expression (Nagase et al., 1997; Kataoka et al., 1999; Chen M et al., 2000; Chen M et al., 2001; Mehta et al., 2006). This is also supported by the high sOLR1 levels ($p = 0.014$) observed in the control group of our study in the association of HT, T2DM and HLD. In addition, a non-significant increase in OLR1 levels was observed in control subjects with HT + HLD and T2DM + HLD compared to those without systemic disease. On the other hand, in the analysis between the subgroups without HT, T2DM and HLD in our study, the high OLR1 levels observed in the CAE group ($p = 0.005$) indicate that OLR1 levels increase in the CAE independently of these comorbidities. The -374A allele, which was found at a high frequency in the CAE group without HT, T2DM and HLD, as well as in the total CAE group and in the subgroups according to systemic diseases, may be associated with increased sOLR1 levels in CAE. In this case, the -374A allele associated with repression of RAGE expression would result in reduced sRAGE levels and consequently increased AGE levels. It is known that AGEs can induce OLR1 expression via RAGE (Shiu et al., 2012). Thus, increased AGE binding to RAGE may lead to increased OLR-1 expression. This relationship may explain the high sOLR1 levels in CAE patients even in the absence of HT, T2DM and HLD. This suggests that the RAGE -374T/A SNP, as well as systemic disorders, may contribute to increased sOLR1 levels in CAE patients.

Another prominent finding of our study is the association of the -374A allele with younger patient age ($p = 0.006$, $p = 0.037$ and $p = 0.020$, respectively) and higher platelet count (Plt) ($p = 0.003$, $p < 0.001$ and $p = 0.042$, respectively) in the total CAE and hypertensive and no systemic disease CAE subgroups. In the correlation analyses, the -374A allele was also negatively correlated with age and positively correlated with Plt in all of CAE subgroups. In the total CAE group, sRAGE levels also showed a positive correlation with age and a negative correlation with HDL levels. On the other hand, a negative correlation was observed between sRAGE and Plt in the total, hypertensive and no systemic disease control subgroups.

Platelet count is inversely associated with age (Le Blanc and Lordkipanidzé, 2019). The association of the -374A allele with younger patient age may be responsible for the high platelet count in CAEs. Platelets are blood cells with the RAGE receptor on their membranes. RAGE expression has been reported to be 3.2 times higher in platelets from older adults compared to younger people (Recabarren-Leiva et al., 2021). Recent studies have shown that platelet stimulation via AGE-RAGE binding leads to an increase in sRAGE expression and secretion, platelet activation and P-selectin expression on the membrane (Gawlowski et al., 2009). Therefore, we propose that increased RAGE expression may contribute to inflammation in CAE through platelet

activation.

At this point, high AGE levels caused by the effect of the -374A allele on low sRAGE may lead to sRAGE expression in platelets and platelet activation. This may explain why circulating sRAGE levels did not decrease in CAE patients despite the high frequency of the -374A allele, which we also attributed to the use of antihypertensive drugs. A *meta*-analysis including 1366 CAE patients and 957 healthy controls from a total of 14 studies reported that increased mean platelet volume was significantly associated with CAE, suggesting that platelets influence the CAE process in addition to their role in inflammatory and thrombotic responses (Moghadam et al., 2018). Supporting this, a study conducted in the Chinese population reported that mean platelet volume was increased in CAE and that CAE patients were at high risk of thrombotic disease (Liang et al., 2019). Therefore, we assume that the RAGE -374A allele may affect the development of CAE by causing an increase in platelet activation.

The present study has some limitations. Firstly, this is a preliminary study consisting of a small number of participants from the Turkish population. Therefore, further studies in a larger size and conducted in different populations are needed for the confirmation of the effect of *RAGE* -374T > A SNP and sOLR1 on CAE risk. However, considering that CAE is a rare form of CAD, it is important to include 98 patients with clinically confirmed CAE in this study. Secondly, we didn't measure the expression of RAGE, which if studied, would provide information on mRNA levels of sRAGE variants (e.g. endogenous secretory sRAGE) formed by alternative splicing of the RAGE gene. Thirdly, since AGE levels could not be measured, the sRAGE/AGE ratio, which would provide a better understanding of the findings, could not be calculated. Fourthly, due to the low frequency of the rare 82S allele in our study groups, its relationship with sRAGE/sOLR1 levels and the risk of CAE could not be analyzed in detail. Finally, platelet activation and platelet aggregation function tests were not performed.

In conclusion, this study shows that the *RAGE* -374A allele and increased sOLR1 levels are risk factors for CAE development. Importantly, the RAGE -374A allele was associated with younger age at CAE. Our findings suggest that this association may also be related to platelet activation, which is involved in the pathogenesis of CAE. However, platelet activation and platelet aggregation function together with sRAGE levels and the RAGE -374T > A SNP should be evaluated in a larger CAE sample to make definitive interpretations. More importantly, the evaluation of the RAGE -374T > A SNP together with its associated parameters may help to fine-tune the medical management of patients with CAE, the treatment of which is still controversial.

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CRediT authorship contribution statement

Ezgi Irmak Aslan: Investigation, Methodology. **Gulcin Ozkara:** Investigation, Validation. **Onur Kilicarslan:** Investigation. **Ozgur Selim Ser:** Investigation. **Cem Bostan:** Data curation, Supervision, Writing – review & editing. **Ahmet Yildiz:** Conceptualization, Formal analysis, Resources, Writing – review & editing. **Ayca Diren Borekcioglu:** Data curation, Methodology. **Oguz Ozturk:** Conceptualization, Data curation, Supervision, Resources, Writing – review & editing. **Ozlem Kucukhuseyin:** Data curation, Methodology, Validation. **Hulya Yilmaz Aydogan:** Funding acquisition, Methodology, Project administration, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gene.2024.148450.

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