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Serum Level of Soluble Receptor for Advanced Glycation End Products in Acute Coronary Syndrome and Chronic Stable Angina Patients

Abstract – Acute coronary syndrome (ACS) and chronic stable angina (CSA) have different pathophysiological features and prognoses. Hence, a biomarker that can discriminate between ACS and CSA is crucial. Soluble receptor for advanced glycation end product (sRAGE) involved in vascular inflammation shows potential as the emerging diagnostic marker of ACS. Thus, this research examined the difference in serum level of sRAGE in ACS and CSA patients and investigated the association between sRAGE and plaque instability biomarkers like placental growth factor (PIGF). The serum levels of sRAGE and plaque instability biomarkers were measured from 13 ACS [47 years (26)] and 19 CSA patients [51 years (26)] using enzyme-linked immunoassay. The association between serum level of sRAGE and plaque instability biomarkers was determined by a correlation study. Serum level of sRAGE and PIGF were significantly higher in ACS [sRAGE: 3541 pg/mL (2153.8 pg/mL), p<0.000], [PIGF: 51.91 (31.94) pg/mL, p=0.001] compared to CSA patients [sRAGE: 1268 (1510) pg/mL], [PIGF: 17.28 (22.41) pg/mL]. Binomial logistic regression analysis revealed sRAGE and PIGF as possible predictors of ACS, p<0.05. The serum level of sRAGE was higher in ACS patients and could be the potential dual-biomarker with PIGF in cardiovascular disease (CVD) patients.

Keywords – *Acute coronary syndrome, biomarker, cardiovascular disease, chronic stable angina, PIGF, sRAGE*

1 INTRODUCTION

Accumulation of plaque inside the coronary arteries results in hemodynamic obstruction and angina pectoris symptoms (1). As stated by World Health Organization (WHO), cardiovascular disease (CVD) is the number one cause of death worldwide, accounting for 17.9 million deaths, of which one-third of these were premature deaths of people under 70 years old (2). The presence of established cardiac biomarkers, including cardiac troponin I (cTnI) and MB-isoform of creatine kinase (CK-MB), are only beneficial to diagnose myocardial infarction after irreversible cardiac damage (3). According to the etiology of atherosclerosis which is the dominant cause of CVD, inflammation plays a prominent role in deteriorating vascular system followed by the diagnosis of acute coronary syndrome (ACS) and chronic stable angina (CSA). Therefore, inflammatory biomarkers have a beneficial prospect of diagnosing CVD at the early stage of disease whereby several inflammatory mechanisms are involved before the fatal plaque erosion and rupture (4).

In recent years, the circulating soluble receptor for advanced glycation end product (sRAGE) has been reported as an emerging inflammatory biomarker for the early diagnosis of cardiovascular disease (5–8). The sRAGE, found in human serum, is the product of the proteolytic cleavage of the native membrane receptor for advanced glycation end product (RAGE) mediated by disintegrins and matrix metalloproteinase (MMP) (6, 8–10). The cleavage is the result of the binding of RAGE to its ligands such as advanced glycation end product (AGE), S100 protein family, high mobility group box-1 protein (HMGB1), and amphoterins (11,12). Furthermore, the binding of RAGE to its ligands leads to the activation of RAGE and subsequent release of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), cytokines, and adhesion molecules (10, 12–15). sRAGE reflects the RAGE activity, which has emerged as a central regulator of vascular inflammation and atherosclerosis. It is associated with endothelial dysfunction, increased oxidized low-density lipoprotein, and oxidative stress (9).

The sRAGE competes with membrane-bound RAGE to bind to the ligands, including AGE, S100, and HMGB1 protein (16). Interestingly, sRAGE, which lacks in the cytosolic and transmembrane domain, has caused the downstream signaling of the inflammatory cascade to be impossible (17). Therefore, the release of sRAGE into circulation and the induction of oxidative stress contribute to the inflammatory process in CVD. Thus, the serum level of sRAGE can serve as a marker for the development and progression of cardiovascular disease (8). Given that approximately one-third of the patients with CVD are associated with sudden death, prevention should be given priority, and the need to discover early biomarkers should be emphasized (18,19).

Previous findings have demonstrated the role of sRAGE as the potential biomarker for the early diagnosis of CVD, but their conclusions contradict (8,20–24). In one study, a low sRAGE level was associated with endothelial dysfunction and was correlated with a higher prevalence of cardiovascular risk factors (6,25). Falcone and colleagues reported lower sRAGE plasma levels in ACS patients than CSA patients, probably due to the higher production of oxygen radicals in acute events, mediated by uninhibited RAGE interaction to its ligands due to low level of sRAGE (23). On the other hand, Basta *et al.,* proved that sRAGE was higher in ACS patients due to the injury of the coronary artery (19). This finding was similar with several other groups of the researcher, which supported the postulation of increased secretion of sRAGE in acute inflammatory settings (13,26). The contradictory findings could be due to the incomparable condition between studies, including time point of blood sample collection, age of patients, the diabetic status, and statin consumption (5). Thus, in this study, selection and recruitment of patients were performed carefully to ensure no significant differences of factors mentioned above that could interfere with the serum level of sRAGE.

As there is no consensus on the level of sRAGE in CVD and hence, this study aimed to investigate the difference in serum level of sRAGE in two distinct groups of CVD patients, which are acute coronary syndrome (ACS) and chronic stable angina (CSA), by using quantitative sandwich enzyme immunoassay technique as described in the previous study (8). Our previous work had established several plaque instability biomarkers to distinguish ACS from CSA patients (27). In this study, we determined whether serum level of sRAGE correlates with any plaque instability biomarkers, which were myeloperoxidase (MPO), placental growth factor (PIGF), and soluble CD40 ligand (sCD40L). Plaque instability biomarkers were included in this study as they are involved in vascular inflammation, platelet activation, and inflammatory instigation, which are crucial in promoting plaque instability.

2 MATERIALS & METHODS

2.1 Patient Recruitment

A comparative cross-sectional study was conducted on 13 ACS patients who underwent angioplasty and 19 CSA patients who underwent elective angioplasty. Patients were recruited from Hospital Universiti Sains Malaysia and National Heart Institute after informed consent was given. Before implementation, ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia and the National Heart Institute [(USMKK/PPP/JEPeM[205.3.(3)].

Power and Sample Size Calculation (PS Software version 3.1.2) was used to calculate the sample size in this study. By using two means formula, sample size with power 80%, alpha 0.05, confidence interval of 95%, difference of interest of 369 pg/mL, and standard deviation (SD) of 304 pg/mL (14), thus, the minimum sample size of 12 per group was obtained. By considering the drop-out rate of 10%, the final sample size for each group (ACS and CSA) was set at 13 patients per group. In this study, 13 ACS and 19 CSA patients were recruited after informed consent.

2.2 Clinical Data Analysis

General and laboratory data from the medical records of these patients were retrieved. In addition, age, gender, presence of hypertension, hyperlipidemia, diabetes mellitus, number of lesions after assessed by angioplasty, total cholesterol level, triglyceride level, Low-Density Lipoprotein (LDL) cholesterol level, High-Density Lipoprotein (HDL) level, and C-Reactive Protein (CRP) level were assessed for this study.

2.3 Blood Sampling Protocol

In this study, 10 mL of whole blood was drawn from the peripheral vein at the antecubital fossa of the patients 48 hours after onset of symptoms. The blood was collected into a plain tube and was left at room temperature ($25 \pm 0.5°C$) for 30 minutes to allow blood clotting. Then, the clot was removed by centrifugation at 2000 x *g* for 10 minutes.

Following the centrifugation, the supernatant (serum) was transferred to a microcentrifuge tube and was stored at -80°C before analysis.

2.4 Assay for Serum sRAGE Concentration

According to the manufacturer's instructions, the serum level of sRAGE in two groups of patients, ACS and CSA, were measured by sandwich ELISA using Quantikine® ELISA Human RAGE Immunoassay (R&D Systems, USA). Quantikine® ELISA Kit Controls, Control Set 832 (R&D Systems, USA) were used to construct the standard curve, and blank control was reagent diluent alone. Absorbance was detected at 450 nm and was read with a reference wavelength set at 570 nm using a Multiskan FC microplate reader (Thermo Scientific, USA). The optical density for each point was the average of duplicate samples. The sRAGE concentrations were determined from the linear equation generated from Microsoft Excel by creating a standard curve of adjusted optical density against the standard concentration of sRAGE.

2.5 Assay for Plaque Instability Biomarkers

Several potential plaque instability biomarkers were included in this study: MPO, PIGF, and sCD40L. The measurement of sCD40L and PIGF was performed using Quantikine® Human sCD40L Immunoassay (R&D Systems, USA) and Quantikine® Human PIGF Immunoassay (R&D Systems, USA) accordingly based on the manufacturer's protocol. Meanwhile, the quantitation of MPO was performed using an in-house ELISA assay as described by Fong and colleagues (27).

2.6 Statistical Analysis

The Statistical Package for Social Science (SPSS) version 24.0 was used to analyze the data. Continuous variables were expressed as mean ± standard deviation (normally distributed data) or median (Interquartile range) (non-normally distributed data). Categorical variables were expressed as frequency (percentage). Independent t-test for normally distributed data and Mann Whitney test for non-normally distributed data were performed to determine the significant difference of parameters between two groups. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Pearson's or Spearman's correlation tests were performed to investigate the association between continuous variables. Binomial regression analysis was carried out to predict the probability that observation falls into one of the categories of the dichotomous dependent variable based on one or more independent variables, which can be continuous or categorical. The statistical test was considered significant when the two-sided *p*-value was less than 0.05.

3 RESULTS

3.1 Demographic and Clinical Characteristics

Demographic and clinical characteristics of ACS and CSA patients are shown in Table 1. A total of 13 ACS and 19 CSA patients were recruited in this cross-sectional study (age: 47 (26) versus 51 (26), p=0.684). Among the ACS patients, 11 were diagnosed with ST-elevation myocardial infarction (STEMI), while only two patients had non-ST elevation myocardial infarction (NSTEMI). None of the unstable angina (UA) patients were recruited in this study. The diagnosis of hypertension, hyperlipidemia, and diabetes mellitus was based on medical and laboratory records. Meanwhile, the number of lesions at coronary arteries was assessed by certified cardiologists during the angioplasty procedure. In addition, the biochemical parameters of patients were retrieved from the record.

3.2 Significant Difference of Serum Level of sRAGE in ACS and CSA Patients

The sRAGE was detected in both ACS and CSA patients' serum. As shown in Figure 1A, serum level of sRAGE was significantly higher in ACS patients compared to CSA patients (n=13, median 3541 pg/mL (IQR 2153.8) vs. n=19, 1268 (1510) pg/mL, p<0.000) tested with Mann Whitney test.

3.3 Differences of the Serum Level of Plaque Instability Biomarkers in ACS and CSA Patients

We analyzed three plaque instability biomarkers: MPO, PIGF, and sCD40L. Mann Whitney test revealed only serum level of PIGF was significantly higher in ACS patients compared to CSA patients (n=13, 51.91pg/mL (31.94) vs. n=19, 17.28 (22.41) pg/mL, p=0.001) (Figure 1B). No significant differences were found between ACS and CSA patients for the serum level of MPO and sCD40L (Figure 1C and 1D).

Table 1. Clinical and laboratory characteristics of ACS and CSA patients

	ACS (*n*=13)	CSA (*n*=19)	*p* value
Demographic			
Age in years	47(26)	51(26)	0.684
Male, *n* (%)	13 (100)	18 (94.74)	0.821
Malay, n (%)	12 (92.31)	17 (89.47)	0.787
Index event, *n* (%)			
STEMI	2 (15.38)	-	
NSTEMI	11 (84.62)	-	
Clinical parameters			
Hypertension, *n* (%)	7 (53.85)	13 (68.42)	0.473
Hyperlipidemia, *n* (%)	8 (61.54)	11 (57.89)	1.000
Diabetes mellitus, *n* (%)	4 (30.77)	11 (57.89)	0.460
Number of lesions	1 (1)	3 (1)	0.014*
Biochemical parameters			
Total cholesterol (mg/dL)	5.10 (1.35)	4.40 (1.90)	0.147
Triglycerides (mg/dL)	1.70 (0.81)	1.90 (1.00)	0.238
LDL cholesterol (mg/dL)	3.53 (1.40)	2.70 (1.50)	0.099
HDL cholesterol (mg/dL)	1.25 (0.23)	1.00 (0.40)	0.147
CRP (mg/dL)	22.03 (22.61)	7.70 (13.63)	0.071

Note: ACS: acute coronary syndrome; CSA: chronic stable angina; UA: unstable angina; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRP: C-reactive protein. [a]Values are represented as either median (IQR) or frequency (%). Numerical data were presented as median (IQR) and analyzed using the Mann-Whitney test, while categorical data were analyzed using the Pearson Chi-Square test. *p < 0.05 as significant

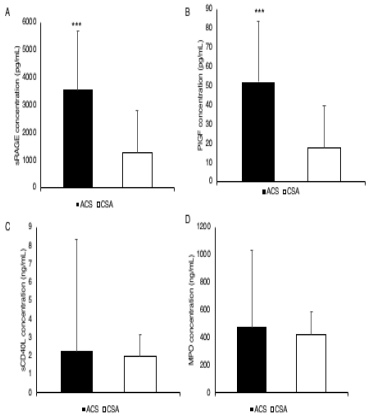

Figure 1. Comparison of serum level of sRAGE and three plaque instability biomarkers (PIGF, sCD40L, and MPO) in ACS and CSA patients. Bar graphs represent median (IQR), ***p<0.001 with n=32. ACS: acute coronary syndrome, CSA: chronic stable angina

3.4 Correlation Analysis

The relationship between serum level of sRAGE and plaque instability biomarkers was studied using correlation analysis. Spearman analysis showed no significant direct correlation (p>0.005) between serum level of sRAGE and all plaque instability biomarkers (Table 2). However, in CSA patients, serum level of sRAGE was negatively correlated with PIGF, p=0.018 (Table 3).

Table 2. Correlation analysis between serum level of srage and plaque instability biomarkers in all patients (n=32)

		Spearman's rho correlation coefficient	*p*-value
sRAGE	PIGF	0.108	0.556
	sCD40L	0.048	0.795
	MPO	0.007	0.969

Table 3. Correlation analysis between serum level of srage and pigf in acs and csa patients

		Spearman's rho correlation coefficient	*p*-value
sRAGE-PIGF	In all patients	0.108	0.556
	In ACS patients	-0.203	0.505
	In CSA patients	-0.537	0.018*

Note: *p < 0.05 as significant

3.5 Logistic Regression

Binomial logistic regression was performed to ascertain the effect of serum level of sRAGE and PIGF on the likelihood of ACS or CSA patients. The logistic regression model was statistically significant, p<0.05. The model explained 86% (Nagelkerke R^2) of the variance in CVD patients and correctly classified 91% cases. An increase in serum levels of sRAGE and PIGF were associated with the likelihood of ACS in CVD patients (Table 4).

Table 4. Logistic regression analysis of ACS and CSA patients

Factors	Univariate regression	
	OR (95% CI)	*p* value
sRAGE	0.997 (0.993 – 1.000)	0.048*
PIGF	0.842 (0.712 – 0.995)	0.043*

Note: *p < 0.05 as significant

4 DISCUSSION

In this study, we aimed to measure the serum level of sRAGE in two main groups of CVD patients, *i.e.*, ACS and CSA. Though several previous studies have been conducted on sRAGE in ACS and CSA, the findings were contentious whether the level of sRAGE is elevated or reduced in ACS compared to CSA (28). This study revealed that the serum level of sRAGE in ACS patients was significantly higher compared to CSA patients. This finding is corroborated by several previous studies (8,9,14). The study by Falcone *et al*., (2005) is among the earliest study on sRAGE, and they reported that serum level of sRAGE was lower in CSA patients due to the antagonistic role of sRAGE in competing with the cell surface receptor to prevent the adverse effect of RAGE signaling (14). Our finding hypothesized that severely high inflammation in ACS disrupts the decoying function of sRAGE, which may subsequently lead to the high concentration of unbound sRAGE detected in the circulation. This hypothesis is supported by several recent studies, which stated that sRAGE level in the circulation serves as a marker for the development and progression of cardiovascular disease, particularly during the inflammatory process of coronary atherosclerosis (8,9). Another study also supported the hypothesis that suggested an increased level of S100 protein led to severe inflammation, which produces an elevated serum level of unbound sRAGE in ACS (13).

Severe inflammation during ACS that eventually causes the inability of sRAGE to antagonize the RAGE-ligands binding is supported by several studies. A study by Basta and colleagues (2011) concluded that myocardial injury during the acute ischemic event in ACS increases RAGE ligand known as High Mobility Group Box 1 protein (HMGB1). HMGB1 protein interacts with RAGE and perpetuates a cascade of inflammation and thus, stimulates the higher release of sRAGE into the bloodstream in ACS patients compared to normal controls (19). As sRAGE is proteolytically cleaved by MMP from the native membrane of the cell surface receptor of RAGE, it is postulated that severe inflammatory episodes in unstable plaque may induce higher expression and production of MMP in macrophages of ACS patients (29). As a consequence of the overproduction of MMP, the cleavage of RAGE will also undoubtedly result in the increased level of sRAGE circulating in ACS patients.

Based on our findings and several hypotheses made by previous studies, it can be deduced that a higher serum level of sRAGE reflects a severe inflammatory episode in ACS. Due to an increase in RAGE-ligands binding, which eventually leads to the generation of MMP and other inflammatory cytokines, a higher concentration of sRAGE is released after being proteolytically cleaved by the MMP. Thus, the endless positive feedback loop between RAGE, its ligands, and sRAGE exerted a deleterious effect on the unstable plaques, which resulted in plaque rupture and thrombosis, the two critical events during myocardial infarction.

The complexity of the pathogenesis of CVD causes myriad complications, ranging from asymptomatic to stable angina to acute ischemic events (18). Current management of CVD is mainly focused on the treatment of the later stage of post-infarction, which can be intervened invasively using angioplasty or coronary artery bypass surgery and prescription of pharmacologic agents such as nitroglycerin and clopidogrel. However, very little attention has been given to early detection of CVD before infarction happens due to the unfeasibility of the available diagnostic tool and biomarker that can prophesy the likelihood of irreversible cardiac damage. As the release of sRAGE into circulation reflects the inflammatory episodes in CVD patients, which led to the destabilization of plaque and manifestation of myocardial infarction upon plaque rupture, sRAGE has the potential to be the biomarkers of early CVD (5,6,14,23). Furthermore, sRAGE have been previously associated with N-terminal prohormone of brain natriuretic peptide (NT-proBNP), which is one of the established cardiac markers suggesting the role of sRAGE as a marker of augmented RAGE-AGE signaling activity that contributes to worsened cardiac dysfunction (28).

Another important finding was the significant difference in serum levels of PIGF in ACS and CSA patients. This result matched those observed in earlier studies where elevated plasma levels of PIGF in ACS patients were associated with adverse cardiac outcomes in the long-term follow-up and may have the potential to extend the prediction and prognostic information obtained from the conventional biomarkers (30,31). Although correlation analysis revealed a significant relationship between sRAGE and PIGF only in CSA patients, this provides an insight into a possible interaction that may happen physiologically between these two biomarkers. As it is still a challenge to prove a single biomarker that is the gold standard in predicting CVD in terms of sensitivity and specificity (32), a dual-biomarker

strategy may help identify CVD patients prone to develop ACS earlier.

We revealed that MPO and sCD40L were not significantly different between ACS and CSA patients. This result could be due to MPO possess a biphasic pattern of time-course elevation in which it reaches the highest peak of release at 4 and 24 hours after percutaneous intervention and following that shows a marked decrease at 8 and 12 hours (33). However, as this study enrolled patients within 48 hours of symptoms onset, the level of MPO measured may be highly influenced by the time point of blood withdrawal and thus unfavorable to demonstrate the accurate MPO level in ACS and CSA patients. Nonetheless, previous studies regard MPO as the potential predictor of cardiovascular mortality risk due to its involvement in oxidative stress and inflammation contributing to coronary plaque destabilization (34,35).

Furthermore, previous studies showed the association between increased risk of MACE and high concentration of sCD40L in ACS patients (36,37). In contrast, other sCD40L research studies proved no association between sCD40L and the heightened risk of death and recurrent MI (38,39). This discrepancy could be attributable to the aspirin treatment, as aspirin can significantly reduce the level of sCD40L (40). This may provide insight into the similar level of sCD40L measured in our study as both ACS and CSA patients were on various medications and thus may affect the serum sCD40L measurements.

Several caveats must be taken into consideration in the interpretation of our findings. First, our study measured total sRAGE because the detection system used could not discriminate between specific sRAGE splice variants such as C-truncated sRAGE and N-truncated sRAGE isoforms. Second, our results share the same limitation of cross-sectional studies in which the correlations do not imply causality. However, we believe that the relationship between sRAGE and PIGF is biologically plausible. Third, our sample population was only confined to two specific regions in Malaysia, *i.e.*, Kelantan and Kuala Lumpur, and hence, the findings might not be generalizable to the whole of Malaysia.

5 CONCLUSION

This study has shown that serum levels of sRAGE and PIGF in ACS patients were significantly higher relative to CSA patients. This finding suggested that sRAGE and PIGF could be potential dual-biomarkers of ACS. Therefore, a longitudinal cohort study that involves multiple measurements of sRAGE and PIGF at different time points to provide insights into the kinetics of the biomarker is worth venturing to determine the versatility of these potential biomarkers.

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REFERENCES

[1] Agewall S. Acute and stable coronary heart disease: different risk factors. Eur Heart J. 2008 Jul 10;29(16):1927–9.
[2] WHO. Cardiovascular disease. 2018.
[3] Seong AC, Chb MB, Kok C, John M, Cth F. A Review of Coronary Artery Disease Research in Malaysia. 2016;71:42–57.
[4] Armstrong EJ, Morrow DA, Sabatine MS. Inflammatory biomarkers in acute coronary syndromes. Part III: Biomarkers of oxidative stress and angiogenic growth factors. Circulation. 2006;113(8):289–92.
[5] Jensen LJN, Flyvbjerg A, Bjerre M. Soluble Receptor for Advanced Glycation End Product: A Biomarker for Acute Coronary Syndrome. Biomed Res Int. 2015;2015.
[6] Kajikawa M, Nakashima A, Fujimura N, Maruhashi T, Iwamoto Y, Iwamoto A, et al. Ratio of serum levels of ages to soluble form of RAGE is a predictor of endothelial function. Diabetes Care. 2015;
[7] Lindsey JB, Cipollone F, Abdullah SM, McGuire DK. Receptor for advanced glycation end-products (RAGE) and soluble RAGE (sRAGE): cardiovascular implications. Diab Vasc Dis Res. 2009;6(1):7–14.
[8] Villegas-Rodríguez ME, Uribarri J, Solorio-Meza SE, Fajardo-Araujo ME, Cai W, Torres-Graciano S, et al. The AGE-RAGE Axis and Its Relationship to Markers of Cardiovascular Disease in Newly Diagnosed Diabetic Patients. PLoS One. 2016;11(7).
[9] Assiri AMA, Kamel HFM, ALrefai AA. Critical Appraisal of Advanced Glycation End Products (AGEs) and Circulating Soluble Receptors for Advanced Glycation End Products (sRAGE) as a Predictive Biomarkers for Cardiovascular Disease in Hemodialysis Patients. Med Sci. 2018;6(38):1–13.
[10] Brinkley TE, Leng X, Nicklas BJ, Kritchevsky SB, Ding J, Kitzman DW, et al. Racial Differences in Circulating Levels of the Soluble Receptor for Advanced Glycation

Endproducts in Middle-Aged and Older Adults Tina. Metabolism. 2017;70:98–106.
[11] Grauen H, Yndigegn T, Marinkovic G, Grufman H, Mares R, Nilsson J, et al. The soluble receptor for advanced glycation end-products (sRAGE) has a dual phase-dependent association with residual cardiovascular risk after an acute coronary event. Atherosclerosis. 2019;287:16–23.
[12] Mahajan N, Dhawan V. Receptor for advanced glycation end products (RAGE) in vascular and inflammatory diseases. Int J Cardiol. 2013;168(3):1788–94.
[13] Cai XY, Lu L, Wang YN, Jin C, Zhang RY, Zhang Q, et al. Association of increased S100B, S100A6 and S100P in serum levels with acute coronary syndrome and also with the severity of myocardial infarction in cardiac tissue of rat models with ischemia-reperfusion injury. Atherosclerosis. 2011;217(2):536–42.
[14] Falcone C, Emanuele E, D'Angelo A, Buzzi MP, Belvito C, Cuccia M, et al. Plasma levels of soluble receptor for advanced glycation end products and coronary artery disease in nondiabetic men. Arterioscler Thromb Vasc Biol. 2005;25(5):1032–7.
[15] Yan XX, Lu L, Peng WH, Wang LJ, Zhang Q, Zhang RY, et al. Increased serum HMGB1 level is associated with coronary artery disease in nondiabetic and type 2 diabetic patients. Atherosclerosis. 2009;205(2):544–8.
[16] Loomis SJ, Chen Y, Sacks DB, Christenson ES, Robert H, Rebholz CM, et al. Cross-sectional Analysis of AGE-CML, sRAGE, and esRAGE with Diabetes and Cardiometabolic Risk Factors in a Community- Based Cohort Stephanie. Clin Chem. 2017;63(5):980–9.
[17] Reichert S, Triebert U, Navarrete A, Hofmann B, Schaller H, Schlitt A, et al. Soluble form of receptor for advanced glycation end products and incidence of new cardiovascular events among patients with cardiovascular disease. Atherosclerosis. 2017;266:234–9.
[18] Boudoulas KD, Triposciadis F, Geleris P, Boudoulas H. Coronary Atherosclerosis: Pathophysiologic Basis for Diagnosis and Management. Prog Cardiovasc Dis. 2016;58(6):676–92.
[19] Basta, G., Turco, S.D., Marchi, F., Navarra, T., Battaglia, D., Mercuri, A., Mazzone A. & Berti S. Elevated soluble receptor for advanced glycation end product levels in patient with acute coronary syndrome and positive cardiac troponin I. Coron Artery Dis. 2011;
[20] Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al. A soluble form of the receptor for advanced glycation endproducts (RAGE) is produced by proteolytic cleavage of the membrane-bound form by the sheddase a disintegrin and metalloprotease 10 (ADAM10). FASEB J. 2008;22(10):3716–27.
[21] Zheng H, Li Y, Xie N, Huang JL, Xu HF, Luo M. Decreased levels of soluble receptor for advanced glycation end-products in aortic valve calcification patients. Genet Mol Res. 2015;14(2):3775–83.
[22] Bower JK, Pankow JS, Lazo M, Christenson E, Hoogeveen RC, Ballantyne CM, et al. Three-year variability in plasma concentrations of the soluble receptor for advanced glycation end products (sRAGE). Clin Biochem. 2014;47(1–2):132–4.
[23] Falcone C, Bozzini S, Guasti L, D'Angelo A, Capettini AC, Paganini EM, et al. Soluble RAGE plasma levels in patients with coronary artery disease and peripheral artery disease. ScientificWorldJournal. 2013;2013:584504.
[24] Mulrennan S, Baltic S, Aggarwal S, Wood J, Miranda A, Frost F, et al. The role of receptor for advanced glycation end products in airway inflammation in CF and CF related diabetes. Sci Rep. 2015;5:8931.
[25] Geroldi D, Falcone C, Emanuele E, Angelo AD, Calcagnino M, Buzzi MP, et al. Decreased plasma levels of soluble receptor for advanced glycation end-products in patients with essential hypertension. 2005;1725–9.
[26] Yoon S, Park S, Park C, Chang W, Cho D, Ko Y, et al. Association of soluble receptor for advanced glycation end-product with increasing central aortic stiffness in hypertensive patients. Pahophysiology Nat Hist. 2012;23:85–90.
[27] Fong SW, Few LL, See Too WC, Khoo BY, Nik Ibrahim NNI, Yahaya SA, et al. Systemic and coronary levels of CRP, MPO, sCD40L and PlGF in patients with coronary artery disease. BMC Res Notes. 2015;8:679.
[28] Wannamethee SG, Welsh P, Papacosta O, Ellins EA, Halcox JPJ, Whincup PH, et al. Circulating soluble receptor for advanced glycation end product : Cross-sectional associations with cardiac markers and subclinical vascular disease in older men with and without diabetes. Atherosclerosis. 2017;264:36–43.
[29] Prasad K. Low Levels of Serum Soluble Receptors for AGEs, biomarkers for disease state, myth or reality. Int J Angiol. 2014;23(1):11–16.
[30] Lenderink T, Heeschen C, Fichtlscherer S, Dimmeler S, Hamm CW, Zeiher AM, et al. Elevated Placental Growth Factor Levels Are Associated With Adverse Outcomes at Four-Year Follow-Up in Patients With Acute Coronary Syndromes. J Am Coll Cardiol. 2006;47(2):307–11.
[31] Heeschen C, Dimmeler S, Fichtlscherer S, Hamm CW, Berger J, Simoons ML, et al. Prognostic Value of Placental Growth Factor in Patients With Acute Chest Pain. JAMA. 2004 Jan 28;291(4):435–41.
[32] Lindahl B. Are there really biomarkers of vulnerable plaque? Clin Chem. 2012;58(1):151–3.
[33] Ramachandra CJA, Ja KPMM, Chua J, Cong S, Shim W, Hausenloy DJ. Myeloperoxidase As a Multifaceted Target for Cardiovascular Protection. Antioxidants Redox Signal. 2020;32(15):1135–49.
[34] Govindarajan S, Raghavan VMM, Rao ACV. Plasma myeloperoxidase and total sialic acid as prognostic indicators in acute coronary syndrome. J Clin Diagnostic Res. 2016;10(8):BC09-BC13.
[35] Liu C, Xie G, Huang W, Yang Y, Li P, Tu Z. Elevated serum myeloperoxidase activities are significantly associated with the prevalence of ACS and high LDL-C levels in CHD patients. J Atheroscler Thromb. 2012;19(5):435–43.
[36] Pusuroglu H, Akgul O, Erturk M, Uyarel H, Bulut U, Akkaya E, et al. Predictive value of elevated soluble CD40 ligand in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. Coron Artery Dis. 2014;25(7):558–64.
[37] Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez MJ, Kaski JC. Soluble CD40 ligand:interleukin-10 ratio predicts in-hospital adverse events in patients with ST-segment elevation myocardial infarction. Thromb Res. 2007;121(3):293–9.
[38] Gremmel T, Frelinger AL, Michelson AD. Soluble CD40 ligand in aspirin-treated patients undergoing cardiac catheterization. PLoS One. 2015;10(8):1–16.
[39] Mehta R, Bassand J, Chrolavicius S, Diaz R, Eikelboom JW, Health H, et al. Dose Comparisons of Clopidogrel and Aspirin in Acute Coronary Syndromes. N Engl J Med. 2010;363(16):1585–1585.
[40] Rondina MT, Lappe JM, Carlquist JF, Muhlestein JB, Kolek MJ, Horne BD, et al. Soluble CD40 Ligand as a Predictor of Coronary Artery Disease and Long-Term Clinical Outcomes in Stable Patients Undergoing Coronary Angiography. Cardiology. 2008;109(3):196–201.