Original Article

Soluble receptor for advanced glycation end products and its role in cardiovascular risk assessment in hyperglycemia – A study in North India

Aparna Gupta[1], Parul Goyal[2], Smita Roy[2], Pratip Jana[1], Ajay Chauhan[3], Sarita Jilowa[4], Yashasvi Panghal[2]

[1]Department of Biochemistry, Lady Hardinge Medical College and Associated Hospitals, University of Delhi, New Delhi, India, [2]Department of Biochemistry, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, Guru Gobind Singh Indraprastha University, New Delhi, India, [3]Department of Medicine, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, Guru Gobind Singh Indraprastha University, New Delhi, India, [4]Department of Radiology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, Guru Gobind Singh Indraprastha University, New Delhi, India

Abstract

Introduction: Advanced glycation end products (AGEs) and their cellular receptors (RAGEs) play an important role in the pathogenesis of type 2 diabetes mellitus and its progression to cardiovascular disease (CVD). A marker of the AGE-RAGE axis, soluble RAGE (sRAGE), was examined in this study in various glycemic states as well as in low- and high-CVD-risk patients. **Methods:** In this cross-sectional study, 25 adults were recruited into each of the "Normoglycemic", "Prediabetic", and "Diabetic" groups based on American Diabetes Association 2019 HbA1c% level criteria. Using online American Heart Association Atherosclerotic CVD (AHA ASCVD) risk calculator and guidelines, patients were classified into "Low" and "High" risk categories. Serum sRAGE was assayed using sandwich ELISA technology. Serum markers necessary for calculation of homeostatic model assessment for insulin resistance (HOMA-IR) and atherogenic index of plasma (AIP) were spectrophotometrically estimated. Carotid intima-media thickness (CIMT) was analyzed using B-mode carotid ultrasonography. **Results:** Mann–Whitney U analysis showed that sRAGE, AIP, HOMA-IR, CIMT, and %10-year CVD risk values were significantly different in the two ASCVD risk categories. Spearman test showed a significant correlation between sRAGE and other markers. ROC curve analysis demonstrated a higher area under the curve for sRAGE than other known parameters to differentiate between ASCVD risk categories. Finally, odds ratio analysis showed that sRAGE had higher odds of detecting high CVD risk than AIP or CIMT. **Conclusions:** Our study has demonstrated the possible role of sRAGE in CVD development and suggests that they may serve as screening markers for future CVD risk.

Keywords: Advanced glycation end products, atherosclerotic cardiovascular risk score, diabetes mellitus, prediabetes, soluble RAGE

Introduction

Advanced glycation end products (AGEs) and their receptors (RAGEs) play a key role in the pathogenesis of diabetes mellitus and cardiovascular disease (CVD). This study explores the association of soluble RAGE (sRAGE) with

Address for correspondence: Dr. Pratip Jana, H – 91, 1st Floor, Sector 25, Jal Vayu Vihar, Gautam Budh Nagar, Noida – 201 301, Uttar Pradesh, India.
E-mail: drpratip.jana@gmail.com

Received: 06-08-2024 **Revised:** 24-10-2024
Accepted: 26-10-2024 **Published:** 25-04-2025

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1356_24

How to cite this article: Gupta A, Goyal P, Roy S, Jana P, Chauhan A, Jilowa S, *et al*. Soluble receptor for advanced glycation end products and its role in cardiovascular risk assessment in hyperglycemia – A study in North India. J Family Med Prim Care 2025;14:1325-32.

markers of glycemic status like HbA1c% and homeostatic model assessment of insulin resistance (HOMA-IR) and compares its levels among diabetics, prediabetics, and normoglycemic controls. Furthermore, sRAGE levels were also compared among the American Heart Association – Atherosclerotic CVD (AHA ASCVD) score stratified low- and high-risk groups of patients. Finally, its association with the atherogenic index of plasma (AIP) and carotid intima-media thickness (CIMT) was also assessed.

Material and Methods

This cross-sectional, observational study was conducted from January 1, 2021 to May 31, 2022 at the central laboratory of the Department of Biochemistry, in collaboration with the Department of Medicine and Radiodiagnosis of a tertiary care teaching hospital in New Delhi, India. Approval for this study was granted by the Institutional Ethical Committee.

Due to diminished patient footfalls during the COVID-19 pandemic, a convenient sampling method was used. Based on the fasting and postprandial blood glucose as well as HbA1c % levels (as recommended by ADA 2019), the glycemic status of each patient was assessed. Recruited patients were categorised into three study groups, which are "Normoglycemic patients" (HbA1c level <5.7%), "Prediabetic patients" (5.7% < HbA1c level <6.5%), and "Diabetic patients" (HbA1c level ≥6.5%). Twenty-five consenting adult treatment naïve patients were enrolled in each group to constitute a total of 75 participants for this study. Additionally, using the online AHA ASCVD Risk calculator, the percentage risk of developing CVD in the next 10 years was calculated. As per the AHA risk stratification guidelines, patients were classified into low risk (if 10-year risk < 5%) and high risk (if 10-year risk ≥5%).[1] Subjects with a previous history of diabetes, hypertension, overt cardiovascular events, inflammatory arthropathy, or use of diabetic or anticancer drugs were excluded from the study. A detailed medical history with anthropometric measurements and food and lifestyle habits was taken.

A detailed medical history with anthropometric measurements and food and lifestyle habits was taken. After 12 h overnight fasting, venous blood samples were drawn from each patient in yellow-capped serum separator tubes (SSTs), vacutainers with sodium fluoride and disodium EDTA additives, and vacutainers with dipotassium EDTA (BD vacutainers; Becton, Dickinson and Company, USA). Blood in SSTs was allowed to clot, followed by serum separation by centrifugation at 3500 rpm for 15–20 minutes in the DLAB DM0636 laboratory centrifuge (DLAB Scientific Inc., California, USA).

Spectrophotometric estimation of routine biochemical parameters like plasma glucose, serum total cholesterol, and serum HDL-C was done using the hexokinase, cholesterol oxidase–peroxidase, and enzymatic inhibition methods, respectively, on a Beckman Coulter AU 680 automated clinical chemistry analyzer (Beckman Coulter Inc., Danaher Corporation, California, USA). Plasma HbA1c% was estimated by quantitative immunoturbidimetric assay (based on the reflectance photometry technique) on a Vitros 5600 automated clinical chemistry analyzer (Ortho Clinical Diagnostics, New Jersey, USA). Serum fasting insulin was assessed on a Vitros ECiQ automated electrochemiluminescent immunoassay analyzer (Ortho Clinical Diagnostics, New Jersey, USA). Patient samples were only processed if both daily internal and monthly external quality checks were within acceptable limits.

Insulin resistance was calculated using the homeostatic model assessment for insulin resistance (HOMA-IR), the formula for which is as follows:[2]

$$\text{HOMA - IR} = \frac{\text{F.B.G.}\left(\text{mmol / L}\right)\text{x Fasting Serum Insulin}\left(\mu\text{IU / mL}\right)}{22.5}$$

The atherogenic index of plasma was calculated using the formula:

$$\text{AIP} = \text{Log}_{10}\left(\frac{\text{TG (mg / dL)}}{\text{HDL - C (mg / dL)}}\right)$$

Estimation of CIMT was done via B-mode ultrasonography using GE Healthcare Voluson Ultrasound System (General Electric Company, Boston, New York USA).

Finally, sRAGE was measured based on the principle of double antibody sandwich technology enzyme linked immunosorbent assay (ELISA) by the Shanghai Coon Koon BioTech Co. Ltd., Human Soluble Receptor for Advanced Glycation End Products (SRAGE) ELISA Kit.

Statistical analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± SD. Normality of data was tested by Shapiro–Wilk test. The data were entered in MS EXCEL spreadsheet, and analysis was done using the licensed version of Statistical Package for Social Sciences (SPSS) version 21.0. (IBM Corp., Chicago, USA). A two-tailed value of $P < 0.05$ was considered statistically significant.

Results

Demographic details of the 75 patients (aged 50.32 ± 6.60 years) who were selected for this cross-sectional study are as described in Table 1:

The distribution of patients based on their glycemic status as well as ASCVD risk categories is detailed in Table 2 and graphically demonstrated in Figure 1.

Chi-square test between AHA ASCVD risk category and glycemic status showed significant association between them, with a Chi-square test value of 9.091, $P = 0.011$ ($\phi = 0.348$, Cramer's V = 0.348, $P = 0.011$).

The mean distribution of sRAGE levels in the three study groups based on glycemic status is depicted in Figure 2.

The mean sRAGE levels in the two ASCVD risk categories have also been depicted in the bar chart as shown in Figure 3.

Shapiro–Wilk test determined that the data did not follow normal distribution, and therefore, all nonparametric tests were used. Mann–Whitney U and Wilcoxon W tests showed that the sRAGE, AIP, HbA1c%, HOMA-IR, CIMT, and % 10-year CVD risk values were significantly different in the two ASCVD risk categories, as shown in Table 3.

Spearman rank correlation was done, where sRAGE showed significant negative correlation with AIP ($\rho = -0.456$, $P < 0.001$), HbA1c% ($\rho = -0.493$, $P < 0.01$), HOMA-IR ($\rho = -0.549$, $P < 0.001$), CIMT ($\rho = -0.573$, $P < 0.01$), and % 10-year CVD risk ($\rho = -0.493$, $P < 0.01$).

Receiver operator characteristic (ROC) curve test was done to assess and compare the differentiating power of sRAGE, CIMT, and AIP into the two CVD risk categories. As shown by Figure 4 and Table 4, sRAGE showed higher AUC (0.760, $P < 0.001$) than either CIMT (0.685, $P = 0.006$) or AIP (0.636, $P = 0.045$).

At a cutoff value <13.29 ng/mL, sRAGE had not only a sensitivity of 75% and a specificity of 74.4% but also a positive predictive value of 68.97%, a negative predictive value of 71.74%, and an overall percentage diagnostic accuracy of 70.67% for ASCVD risk stratification.

Furthermore, as shown in Table 5, odds ratio (OR) analysis showed that sRAGE had higher OR (7.36) for detection of high-CVD risk status than CIMT (6.79) or AIP (2.10).

This indicates that sRAGE has better capability of 10-year CVD risk prediction than established biochemical and radiological markers of atherosclerosis such as AIP and CIMT.

Table 1: Demographic details of age and sex distribution in the study population

Sex	*n*	Average Age (in years)
Males	40	50.67±6.97
Females	35	50.06±6.13

Table 2: Patient distribution based on glycemic status and AHA ASCVD Risk Stratification

Glycaemic Status and AHA ASCVD Risk Stratification Crosstabulation	AHA ASCVD Risk Category		Total
	Low Risk	High Risk	
Glycemic Status			
Normoglycemic Patients	18	7	25
Prediabetic Patients	16	9	25
Diabetic Patients	8	17	25
Total	42	33	75

Discussion

The rapid increase in the prevalence of noncommunicable diseases, like type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), is the single largest threat to public health worldwide and especially to the Indian subcontinent, home to more than 1.8 billion people. This not only is due to increasing lifetime exposure to risk factors but is also a function of a marked demographic transition characterized by declining birth and death rates and an increasingly ageing population.[3,4] A 2011 ICMR-INDIAB study found that Indians have the highest incidence rates of prediabetes and diabetes among all major ethnic groups, and the conversion from prediabetes to diabetes occurs more rapidly in this population.[5]

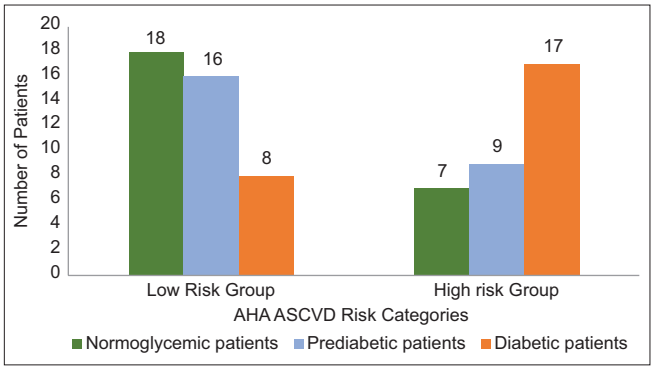

Figure 1: Bar chart showing association of CVD risk category with glycemic status

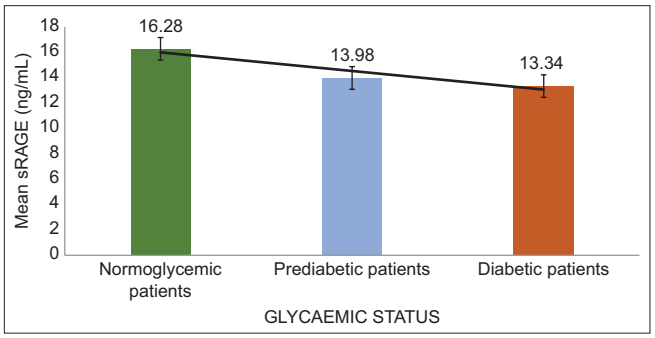

Figure 2: Mean distribution of sRAGE in the three glycemic status categories

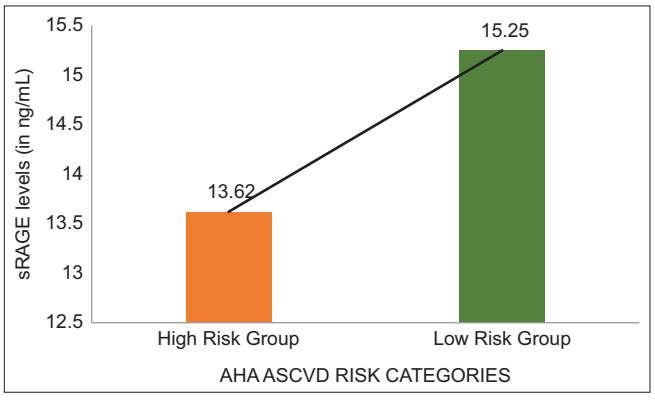

Figure 3: Mean distribution of sRAGE in low- and high-risk ASCVD categories

Table 3: Mann–Whitney *U* and Wilcoxon W test values for sRAGE, AIP, CIMT, and % 10-year risk of CVD development among the ASCVD Risk Categories

Parameters	AHA ASCVD Risk category		Mann- Whitney *U* test value	Wilcoxon W test value	*P*
	Low Risk *n*=42	High Risk *n*=33			
sRAGE (ng/mL)	15.25±2.96	13.62±4.49	325.5	886.5	<0.001
AIP	0.61±0.18	0.70±0.20	881.0	1442.0	0.045
HbA1c %	6.13±1.44	7.90±2.77	933.5	1494.5	0.010
HOMA-IR	2.68±1.80	4.64±2.23	1017.5	1578.5	0.001
CIMT (mm)	0.75±0.17	1.01±0.42	947.0	1510.0	0.006
% 10 Year CVD Risk	2.65±1.30	11.93±9.83	1386.0	1947.0	<0.001

Table 4: ROC curve statistics for sRAGE, CIMT, and AIP

Parameters	AUC	Std. Error	*P*	95% Confidence Interval	
				Lower Bound	Upper Bound
sRAGE	0.760	0.058	<0.001	0.646	0.875
CIMT	0.685	0.068	0.006	0.552	0.817
AIP	0.636	0.066	0.045	0.506	0.765

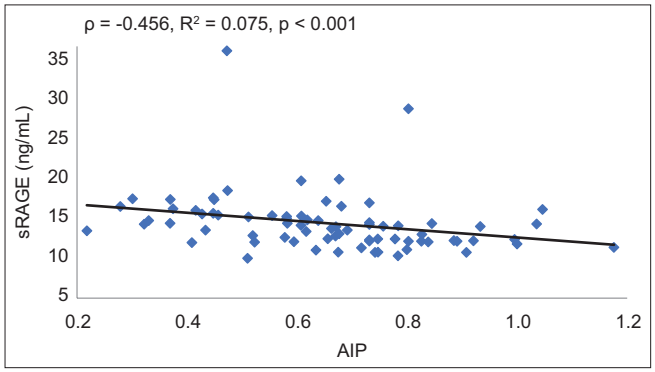

Figure 4: Spearman rank correlation of sRAGE levels with AIP

As T2DM shares several risk factors in common with CVD, such as age, hypertension, dyslipidemia, and obesity to name a few, an increase in the prevalence of diabetes indirectly implicates an escalating risk of CVD as well. According to the World Health Organization, India accounts for one-fifth of the global burden of CVD-related mortalities, seen especially in the younger population. The results of the Global Burden of Disease study have shown that the age-standardized CVD death rate per million population is 272 in India, which is much higher than that of the global average of 235. Despite wide heterogeneity in the prevalence of metabolic risk factors across different geographies, CVD has emerged as the leading cause of death in all parts of India, including poorer states and rural areas.[6,7] Hence, it is imperative that clinical interventions are conducted during the earlier stages of T2DM in order to prevent its progression to CVD.[8]

The cornerstone of preventive cardiology is formulating strategies for CVD risk assessment and reduction. Various international organizations have proposed CVD risk scoring guidelines for pre-emptive risk stratification and management in order to decrease the disease burden and improve health outcomes. In 2013, the American College of Cardiology (ACC) in collaboration with the AHA gave guidelines for assessment of cardiovascular risk with the help of the ASCVD risk calculator. The AHA ASCVD risk score is a calculation of the percentage 10-year risk of developing a cardiovascular ailment, such as acute myocardial infarction or cerebrovascular accident. This risk estimate is dependent on age, sex, race, blood pressure, use of hypertensive medication, glycemic status, smoking habit, total cholesterol levels, and HDL cholesterol levels.[9]

AGEs are a heterogeneous group of bioactive molecules generated under hyperglycemic conditions, oxidative stress, and hypoxia by the nonenzymatic glycation reaction of amine groups of proteins, lipids, and nucleic acids by reducing carbohydrates.[10] AGEs bind to the cellular receptor for AGEs (RAGE). RAGE is a member of the immunoglobulin superfamily of cell surface molecules and is expressed in multiple tissues, including endothelium cells, vascular smooth muscle cells, and monocyte-derived macrophages.[11] This receptor–ligand binding can lead to generation of reactive oxygen species and activation of intracellular signal transduction pathways involved in cytokine production, inflammation, and fibrosis over a prolonged period of time.[12]

A novel marker of the AGE-RAGE axis is sRAGE, which is a RAGE isoform found in serum and is formed by the proteolytic cleavage of membrane-bound RAGE. The relevance of sRAGE is that it competes with cellular RAGE for binding of AGEs and other ligands and therefore may reduce the activation of the RAGE-mediated proinflammatory and profibrotic signaling pathways.[13] This has also been demonstrated in experimental murine models where administration of sRAGE reduced immune and inflammatory responses.[14]

This tertiary care center-based observational study has two principal findings. First, we have demonstrated an association between hyperglycemia and CVD as shown in Table 2, Figure 1, which was found to be statistically significant with a Chi-square test value of 9.091, $P = 0.011$. Several epidemiological studies have also demonstrated a similar relationship in the general population.[15]

Second, our study has shown an association of sRAGE, a novel marker of the AGE-RAGE axis, with glycemic state and its

Table 5: OR analysis of sRAGE, CIMT, and AIP for predicting CVD risk status

Parameters		AHA ASCVD Risk Stratification		Total	Odds Ratio	95% Confidence Interval	
		Low Risk	High Risk			Lower limit	Upper Limit
sRAGE	Low risk	32	10	42	7.36	2.64	20.56
	High risk	10	23	33			
CIMT	Low risk	35	14	49	6.79	2.34	19.69
	High Risk	7	19	26			
AIP	Low risk	29	17	46	2.10	0.82	5.41
	High Risk	13	16	29			

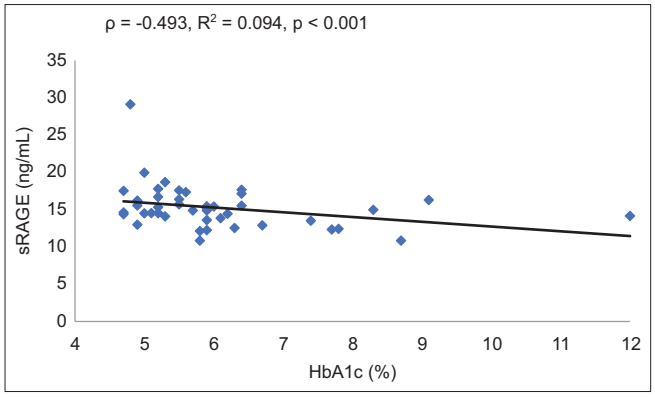

Figure 5: Spearman rank correlation of sRAGE levels with HbA1c%

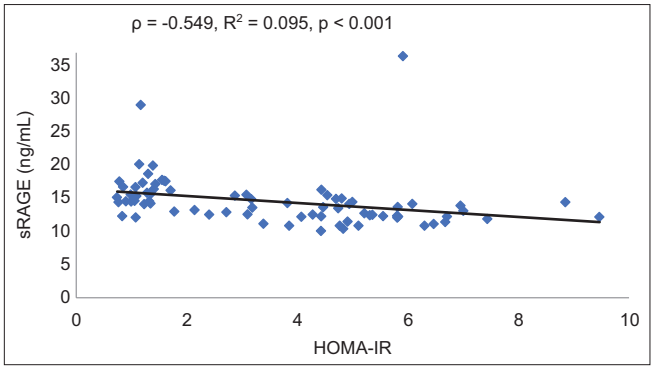

Figure 6: Spearman rank correlation of sRAGE levels with HOMA-IR

conventional markers as well as with CVD risk and markers of its assessment. AGE-RAGE interaction induces harmful effects by activating NF κ-B pathway, leading to increased oxidative stress and inflammatory mediators.[16] Human vascular cells express several RAGE variant proteins, including three novel human RAGE transcripts encoding truncated soluble forms of RAGE.[17] This C-truncated RAGE fragment is called the human soluble receptor for advanced glycation end products, or sRAGE, formed primarily by proteolytic cleavage of the membrane bound RAGE. It consists of only the extracellular ligand binding domain but lacks the cytosolic and transmembrane domains capable of intracellular signal transduction mechanism. Consequently, after being released into the blood, sRAGE competes with RAGE to bind with AGEs, thereby preventing the activation of their signal transduction pathway, which in turn attenuates ROS-mediated injury by the proinflammatory NF-κB and MAP-K pathways. Therefore, a few studies have not only suggested that the administration of sRAGE is protective against diabetic complications but also postulated that this marker may have an atheroprotective function in the body.[18,19] In our study, we have found a negative association of serum sRAGE levels with hyperglycemia as shown in Figure 2. The estimated sRAGE levels were 13.21 ± 4.93 ng/mL in diabetics, 13.98 ± 1.86 ng/mL in prediabetics, and 16.19 ± 3.31 ng/mL in normoglycemic controls. As shown in Figure 5, HbA1c% was found to be a significant independent factor inversely associated with plasma sRAGE levels in both hyperglycemic and normoglycemic patients ($\rho = -0.493$, $P < 0.001$). These findings have also been corroborated by the study of Basta *et al.*, where plasma sRAGE was found to have an inverse correlation with hyperglycemic state. (4) However, contrary to our findings, some studies showed sRAGE may be raised in diabetes consequent to endothelial cell damage.[20,21]

It has been hypothesized that AGEs and oxidative stress play a role of in the development of insulin resistance.[15,22] sRAGE represents a naturally occurring competitive inhibitor of the signaling pathways induced by the interaction of AGEs with its cellular receptor and contributes to the neutralization of circulating RAGE–ligands.[17] In line with this evidence, our study has demonstrated an inverse association of sRAGE with HOMA-IR ($\rho = -0.475$, $P < 0.001$) as depicted in Figure 6.

The exact mechanism by which plasma sRAGE levels are decreased in diabetic patients is yet to be fully elucidated. One possibility is that hyperglycemia inhibits sRAGE production directly or via increased cytokines and/or hyperglycemia-induced AGEs. Alternatively, lower sRAGE levels could be due to an increased clearance of AGE ligand/sRAGE complexes.[23]

The lower levels of sRAGE detected in diabetic patients might also indicate an enhanced propensity to diabetic vascular complications, given that RAGE ligands can interact freely with cell-bound RAGE signaling.[24] A meta-analysis done in 2021 by Zahabi *et al.*[25] showed that circulating concentration of sRAGE was significantly associated with an increased risk of CVD mortality. This association was stronger among studies that did not adjust for age, smoking, and chronic disease morbidity. Moreover, numerous other studies have also shown that the sRAGE has an inverse correlation with atherogenic state, which indicates that low sRAGE levels carry a higher CVD risk.[25-29]

In support of this possibility, we found that sRAGE was significantly more (Mann–Whitney U = 325.5, $P < 0.001$) in the low-risk category (15.25 ± 2.96 ng/mL) than in patients belonging to the high-risk group (13.62 ± 4.49 ng/mL) as shown in Table 3 and Figure 3. Our study has also demonstrated that sRAGE showed a significant negative correlation with conventional markers of atherogenicity like AIP (ρ = -0.416, $P < 0.001$) and CIMT (ρ = -0.622, $P < 0.001$) as shown in Figures 4 and 7, respectively. Furthermore, as depicted in Figure 8, sRAGE was inversely correlated with %10-year CVD risk (ρ = -0.493, $P < 0.001$).

These data, together with the inverse association between sRAGE and atherosclerosis previously published, suggest a role for sRAGE in the development of CVD, and therefore, low levels of sRAGE can be a potential novel marker for screening of CVD in prediabetes and diabetes.[30]

For primary care physicians, understanding sRAGE's role has significant potential benefits as it can improve patient care by identifying biomarkers for disease progression and enhance early diagnosis and management of T2DM and CVD-related comorbidities. As our study has shown sRAGE to be a valuable biomarker for CVD progression, with a better OR and AU-ROC curves than a radiological marker like CIMT for detecting higher CVD risk [Table 4 Figure 9 and Table 5], monitoring sRAGE levels enables identification and earlier interventions in patients at higher risk, even in resource-limited primary health centers which do not have B-mode USG setups. This sets the stage for more personalized treatment plans and preventative strategies, such as lifestyle changes or pharmacological interventions.

Furthermore, as research evolves, therapies that modulate sRAGE levels may emerge, offering new treatment options to mitigate disease progression. For primary care physicians, staying informed about these developments will be crucial in delivering comprehensive, evidence-based care that addresses both prevention and treatment of AGE-related diseases leading to better patient outcomes.

This study is not without its limitations, which include a low sample size due to diminished OPD patient footfalls during the COVID-19 pandemic, resulting in less power of statistical analyses of various markers among the three different study groups. Due to the limited number of participants, confounding factors such as family history of T2DM or IHD and dietary and exercise habits could not be eliminated. Moreover, interobservational bias may be present as observer-dependent ultrasonography-based markers like CIMT was used.

After due appraisal of the existing literature, our study is the first of its kind in India which has explored the association of sRAGE, a novel member of the AGE-RAGE axis, in various glycemic states, as well as examining its role as a marker of cardiovascular risk assessment using a user-friendly and easily accessible ASCVD AHA calculator. Therefore, it was not possible to adequately compare the estimated cutoff, sensitivity, and specificity values of sRAGE in this study with similar peer-reviewed Indian studies.

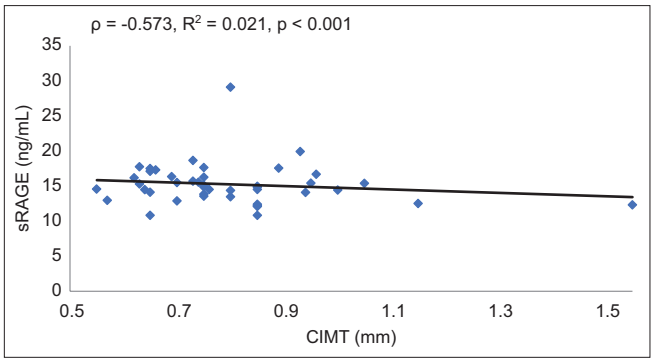

Figure 7: Spearman rank correlation of sRAGE levels with CIMT

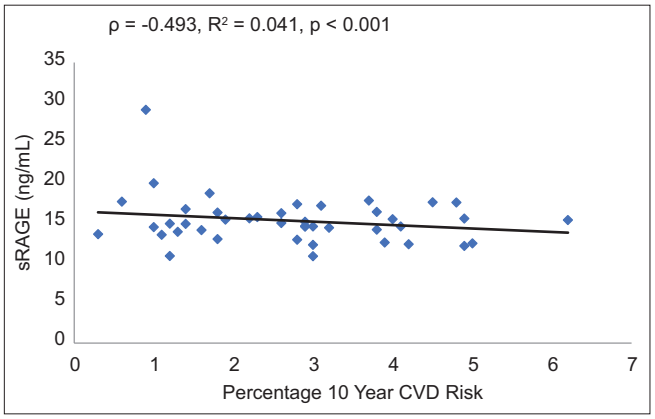

Figure 8: Spearman rank correlation of sRAGE levels with % 10-year CVD risk

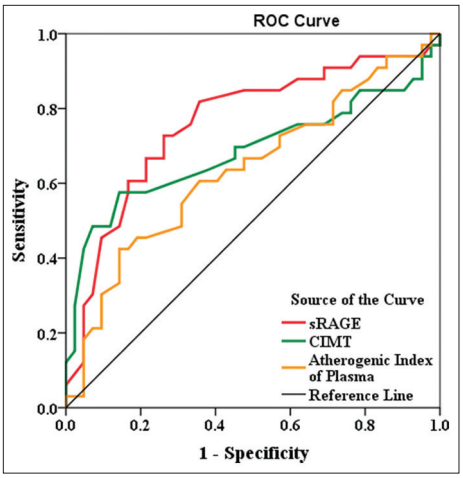

Figure 9: ROC curve to assess diagnostic capacity of sRAGE, AIP, and CIMT for CVD risk stratification

Conclusion

In conclusion, although our study is limited by its low sample size and cross-sectional design, we have demonstrated improvement in 10-year CVD risk prediction by addition of sRAGE, which provides evidence for its role in CVD development beyond conventional inflammatory markers and cardiovascular risk factors. This suggests that it may serve not only as a noninvasive marker for future CVD development but also as a potential

pharmacological target. However, a greater number of studies with a larger sample size and of prospective design are necessary to establish the role of this marker in CVD development and CVD-related mortality.

Ethical approval

The ethical approval of this study was granted by the Institutional Ethics Committee, ABVIMS and Dr RML Hospital, New Delhi, in accordance with GCP-CDSCO/ICMR/Schedule Y (latest amendments) guidelines/ICH-GCP, vide letter no. F. No. TP (MD/MS) (107/2020)/IEC/ABVIMS/RMLH/373.

Consent of participation

All patients signed written consent to participate in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. ASCVD Risk Estimator. Available from: https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calulate/estimator/. [Last accessed on 2023 Aug 28].
2. Antuna-Puente B, Disse E, Rabasa-Lhoret R, Laville M, Capeau J, Bastard JP. How can we measure insulin sensitivity/resistance? Diabetes Metab 2011;37:179–88.
3. Shrivastava U, Misra A, Mohan V, Unnikrishnan R, Bachani D. Obesity, Diabetes and Cardiovascular Diseases in India: Public Health Challenges. Curr Diabetes Rev 2017;13:65–80.
4. The Growing Danger of Non-Communicable Diseases Acting Now to Reverse Course. [Internet]. The World Bank Human Development Network.; 2011. Available from: https://shorturl.at/AU0BY.
5. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, *et al*. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study. Diabetologia 2011;54:3022–7.
6. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–34.
7. Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India: Current epidemiology and future directions. Circulation 2016;133:1605–20.
8. Singh VP, Bali A, Singh N, Jaggi AS. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol 2014;18:1–14.
9. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, *et al*. 2013 ACC/AHA Guideline on the assessment of cardiovascular risk. Circulation 2014;129 (25_suppl_2):S49–73.
10. Gryszczyńska B, Budzyń M, Formanowicz D, Wanic-Kossowska M, Formanowicz P, Majewski W, *et al*. Selected atherosclerosis-related diseases may differentially affect the relationship between plasma advanced glycation end products, receptor sRAGE, and uric acid. J Clin Med 2020;9:E1416.
11. Brett J, Schmidt AM, Yan SD, Zou YS, Weidman E, Pinsky D, *et al*. Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. Am J Pathol 1993;143:1699–712.
12. Wang X, Xu T, Mungun D, Zhou C, Zha Z, Lu M, *et al*. The relationship between plasma soluble receptor for advanced glycation end products and coronary artery disease. Dis Markers 2019;2019:4528382.
13. Yamagishi S-ichi. Comment on: Selvin *et al*. sRAGE and risk of diabetes, cardiovascular disease, and death. Diabetes 2013;62:2116-21. Diabetes 2013;62:e26.
14. Wendt T, Harja E, Bucciarelli L, Qu W, Lu Y, Rong LL, *et al*. RAGE modulates vascular inflammation and atherosclerosis in a murine model of type 2 diabetes. Atherosclerosis 2006;185:70–7.
15. Heine RJ, Dekker JM. Beyond postprandial hyperglycaemia: Metabolic factors associated with cardiovascular disease. Diabetologia 2002;45:461–75.
16. Prasad K. Low levels of serum soluble receptors for advanced glycation end products, biomarkers for disease state: Myth or reality. Int J Angiol 2014;23:11–6.
17. Yonekura H, Yamamoto Y, Sakurai S, Petrova RG, Abedin MJ, Li H, *et al*. Novel splice variants of the receptor for advanced glycation end-products expressed in human vascular endothelial cells and pericytes, and their putative roles in diabetes-induced vascular injury. Biochem J 2003;370:1097–109.
18. Nakamura K, Yamagishi S-ichi, Adachi H, Kurita-Nakamura Y, Matsui T, Yoshida T, *et al*. Elevation of soluble form of receptor for advanced glycation end products (sRAGE) in diabetic subjects with coronary artery disease. Diabetes Metab Res Rev 2007;23:368–71.
19. Basta G, Del Turco S, Marchi F, Navarra T, Battaglia D, Mercuri A, *et al*. Elevated soluble receptor for advanced glycation end product levels in patients with acute coronary syndrome and positive cardiac troponin I. Coron Artery Dis 2011;22:590–4.
20. Basta G, Sironi AM, Lazzerini G, Del Turco S, Buzzigoli E, Casolaro A, *et al*. Circulating soluble receptor for advanced glycation end products is inversely associated with glycemic control and S100A12 protein. J Clin Endocrinol Metab 2006;91:4628–34.
21. Nakamura K, Yamagishi S-ichi, Adachi H, Matsui T, Kurita-Nakamura Y, Takeuchi M, *et al*. Serum levels of soluble form of receptor for advanced glycation end products (sRAGE) are positively associated with circulating AGEs and soluble form of VCAM-1 in patients with type 2 diabetes. Microvasc Res 2008;76:52–6.
22. Soldatos G, Cooper ME, Jandeleit-Dahm KAM. Advanced-glycation end products in insulin-resistant states. Curr Hypertens Rep 2005;7:96–102.
23. Renard C, Chappey O, Wautier MP, Nagashima M, Morser J, Scherrmann JM, *et al*. The human and rat recombinant receptors for advanced glycation end products have a high degree of homology but different pharmacokinetic properties in rats. J Pharmacol Exp Ther 1999;290:1458–66.
24. Yonekura H, Yamamoto Y, Sakurai S, Watanabe T,

Yamamoto H. Roles of the receptor for advanced glycation endproducts in diabetes-induced vascular injury. J Pharmacol Sci 2005;97:305–11.

25. Sharifi-Zahabi E, Sharafabad FH, Abdollahzad H, Malekahmadi M, Rad NB. Circulating advanced glycation end products and their soluble receptors in relation to all-cause and cardiovascular mortality: A systematic review and meta-analysis of prospective observational studies. Adv Nutr 2021;12:2157–71.
26. Koyama H, Shoji T, Yokoyama H, Motoyama K, Mori K, Fukumoto S, *et al.* Plasma level of endogenous secretory RAGE is associated with components of the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol 2005;25:2587–93.
27. 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;25:1032–7.
28. Falcone C, Bozzini S, D'Angelo A, Matrone B, Colonna A, Benzi A, *et al.* Plasma levels of soluble receptor for advanced glycation end products and coronary atherosclerosis: Possible correlation with clinical presentation. Dis Markers 2013;35:135–40.
29. Fotheringham AK, Bagger JI, Borg DJ, McCarthy DA, Holst JJ, Vilsbøll T, *et al.* Circulating levels of the Soluble Receptor for AGE (sRAGE) during escalating oral glucose dosages and corresponding isoglycaemic i.v. glucose infusions in individuals with and without type 2 diabetes. Nutrients 2020;12:2928.
30. Hudson BI, Harja E, Moser B, Schmidt AM. Soluble Levels of Receptor for Advanced Glycation Endproducts (sRAGE) and coronary artery disease. Arterioscler Thromb Vasc Biol 2005;25:879–82.