Receptor of advanced glycation end products and cardiovascular risk in elderly with type 2 diabetes mellitus

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Abstract

The interaction of Advanced Glycation End products (AGEs) and their specific receptor, Receptor for Advanced Glycation End products (RAGE) play an important role in diabetes and vascular complications. Engagement of RAGE by AGEs leads to activation of cellular signaling pathways and vascular dysfunction. The soluble RAGE (sRAGE) acts as a decoy receptor for AGEs. The aim of this study was to evaluate the soluble RAGE in elderly subjects with T2DM and its relationships with glycoxidative, inflammatory and cardiovascular risk markers. The serum AGEs, sRAGE, interleukine-6 (IL-6), lipid profile, glycemic status, uric acid, creatinine and cardiovascular risk markers were determined in elderly subjects with type 2 diabetes mellitus (T2DM, N=72, 75±4 years old) and aged-match healthy subjects (N=15, 76±3 years old). Significant higher levels of AGEs and AGEs/sRAGE ratio concomitantly with significant lower levels of sRAGE were pointed out in elderly subjects with T2DM as compared to control. The values of AGEs/sRAGE ratio were significantly positively associated ($P<0.05$) with atherogenic, inflammatory and cardiovascular risk markers and significantly negatively with anti-atherogenic lipoproteins ($P<0.05$). The multivariate regression analyses showed that atherogenic index was an independent predictor of sRAGE levels and AGEs/sRAGE ratio values. The associations of soluble RAGE and the AGEs/sRAGE ratio with atherogenic and inflammatory markers could reflect the protective role of soluble variants of RAGE in atherosclerosis and diabetes vascular complications.

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Introduction

The interaction of the Receptor for Advanced Glycation End products (RAGE) with its ligands, especially the Advanced Glycation End products (AGEs) is involved in human aging and age-associated pathology, such as: metabolic, cardiovascular, and neurodegenerative diseases.[1-3]

RAGE, a multiligand transmembrane receptor is present on vascular, neuronal, muscular, epithelial or endothelial cells. RAGE is expressed at low levels in tissues in homeostasis, but highly upregulated at sites of tissue damage. The activation of RAGE by AGEs may cause endothelial dysfunction, enhance oxidative stress, stimulate pro-inflammatory and pro-thrombotic processes, being the main cause of vascular complications in diabetes.[1,4]

Soluble RAGE (sRAGE) found in systemic circulation has two isoforms: the cleaved receptor (cRAGE) and the endogenous secretory receptor (esRAGE). The cRAGE, the major component of sRAGE, is generated by proteolytic cleavage of full length RAGE mediated by metalloproteinases and disintegrins. Matrix metalloproteinases 9 (MMP9) and a disintegrin and metalloproteases 10 (ADAM10) are mainly involved in proteolytic ectodomain release of RAGE.[3,5] The esRAGE is formed by alternative splicing from a truncated RAGE mRNA.[5] Recent studies have found important associations between sRAGE or esRAGE levels with the disease status. Increased levels of circulating soluble RAGE were detected in acute phase of tissue damage and even in early stages of diseases.[4,6] Thus, in type 2 diabetes mellitus (T2DM) subjects, soluble RAGE levels were associated with cardiovascular risk, coronary artery disease or plaque vulnerability.[7-10]

Chronic hyperglycemia, dyslipidemia, glycoxidation processes and oxidative stress are implicated in aging, insulin resistance, impaired glucose metabolism, diabetes and cardiovascular complications.[11] AGEs, the main products of glycoxidation, may cause tissue damage via enhance oxidative stress, crosslinking formation and activation of RAGE. The interaction between AGEs and full length RAGE contributes to enhanced expression of RAGE and cellular activation leading to tissue damage. The soluble isoforms of RAGE have an important cellular protective role by binding AGEs, reducing RAGE expression and thus slowing cellular activation.[4,11,12]

Despite the numerous studies, there is still limited information on the involvement of AGEs-RAGE-sRAGE axis in elderly with impaired glucose metabolism. The aim of this study was to evaluate the soluble RAGE in elderly subjects with T2DM and its relationships with glycoxidative, inflammatory and cardiovascular risk markers.

Materials and Methods

Study population

The study was performed on 87 patients (25 men and 62 women), with age between 70 and 80 years old, hospitalized at *Ana Aslan* National Institute of Gerontology and Geriatrics (NIGG), Bucharest, Romania. Type 2 diabetes mellitus was diagnosed according to the American Diabetes Association criteria.[13] 72 elderly subjects (75±4 years old) were included in diabetes group. The age-matched control subjects (N=15, aged 76±3 years old) were enrolled from healthy individuals present at the geriatric outpatients department. Exclusion criteria were: renal failure, chronic inflammatory, liver and hematological diseases, malignancy, as well as the treatment with insulin, lipid lowering drugs and antioxidants. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of *Ana Aslan* NIGG. All the selected participants in this study gave their written informed consent.

After overnight fasting, blood samples were collected from all selected elderly patients and serum was prepared by centrifugation at 3500 rpm, for 15 minutes at 4°C, according to standard procedures. Serum aliquots were stored at –70°C until analysis for soluble RAGE and glycoxidative and inflammatory biomarkers.

Metabolic parameters

The metabolic parameters: fasting serum glucose (G), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), uric acid and creatinine levels were determined by standard methods using the Thermo Fisher Diagnostic System (USA) analyzer. The results were expressed in mg/dL serum. Glycated hemoglobin A1c (HbA1c) was assessed by the high performance liquid chromatography method with ion-exchange using the Biorad Variant II equipment, and was expressed in % (HbA1c).

Advanced glycation end products

Serum AGEs were assessed by the level of AGEs-associated autofluorescence recorded at 440 nm emission wavelength upon excitation at 350 nm, as previously described.[14] The measurements were done on Perkin Elmer Spectrofluorimeter (LS 50 B, Germany). Fluorescence intensity was expressed in relative fluorescence units (RFU). The coefficient of variation (CV) for replicate measurements was <5%.

Soluble receptor for advanced glycation end products

Serum sRAGE levels were determined by quantitative sandwich enzyme immunoassay, using human Quantikine ELISA kit (R&D Inc., Minneapolis, MN, USA), on ChemWell analyzer (Awareness Technology INC, USA). Serum levels of sRAGE were expressed in pg/mL. Intra-assay coefficient of variability was 6.2% and inter-assay coefficient of variability was 8.2%.

Interleukin-6

IL-6 serum concentrations were determined by the immunoenzymatic method using Quantikine ELISA kit from R&D Inc., Minneapolis, MN, USA. The assays were done on ChemWell analyzer and IL-6 levels were expressed in pg/mL. The coefficients of variability were 4.2 for intra-assay and 6.4 for inter-assay.

Cardiovascular risk markers

The cardiovascular risk markers were evaluated by the following ratios: total cholesterol/high density lipoprotein cholesterol (TC/HDL-C), low density lipoprotein cholesterol/HDL-C (LDL-C/HDL-C) and triglycerides/HDL-C (TG/HDL-C). The atherogenic index (Ai) was evaluated by the logarithmically transformed ratio of TG/HDL-C.[15]

Statistical analysis

Data are presented as means ± standard deviation (SD) for continuous variables. The results were statistically compared between groups by using two-tail Student's unpaired *t* test. The relationships between soluble RAGE and metabolic, glycoxidative, inflammatory and cardiovascular risk markers were assessed by Pearson's two-tailed bivariate correlation test. Subsequently, multivariate linear regression analysis was performed for assessing the determinants of AGEs-RAGE axis. The statistical analysis was performed with SPSS software version 15 (SPSS Inc., Chicago, IL, USA). The statistical significance was considered at P values lower than 0.05.

Results

The metabolic biochemical parameters and clinical characteristics of elderly subjects included in this study were presented in Table 1. Systolic and diastolic blood pressure, fasting glucose, HbA1c and uric acid levels were significantly higher (P<0.001 and P<0.05, respectively) in T2DM elderly subjects, as compared to the control group. Also, significantly increased serum atherogenic lipid levels (TC, LDL-C, TG; P<0.001)) and significantly decreased anti-atherogenic HDL-C levels (P<0.01) were found in T2DM subjects as compared to age-matched control. The serum creatinine values were in normal limits for both groups. Evaluation of cardiovascular risk markers represented by TC/HDL-C, LDL-C/HDL-C and TG/HDL-C ratios revealed significantly increased values (P<0.001) in T2DM group compared to control group. Also, elderly with T2DM had significantly higher values (P<0.001) of atherogenic index as compared to healthy subjects (Table 1).

Results presented in Table 2 showed relevant changes in the glycoxidative (AGEs) and inflammatory (IL-6) biomarkers in study population. Thus, AGEs and IL-6 levels were significantly increased (P<0.001 and P<0.01) while circulating levels of soluble RAGE were significantly decreased (P<0.001), in T2DM patients *versus* age-matched control subjects.

To further evaluate the involvement of AGEs-RAGE axis in diabetes and cardiovascular risk the ratio of AGEs/sRAGE was

calculated. The results (Table 2) showed significantly higher values of AGEs/sRAGE ratio (P<0.001) in subjects with T2DM than in control group.

The relationships of circulating soluble RAGE with metabolic parameters, biomarkers of glycoxidative and inflammatory status, as well as with cardiovascular disease (CVD) risk markers, were evaluated by Pearson's two-tailed correlations. In elderly subjects with T2DM we pointed out significant negative correlations between serum sRAGE levels with fasting glucose and IL-6 (P<0.05). Although non-significant, negative associations of sRAGE values with AGEs, Ai and CVD risk markers were observed (Table 3).

Stronger associations between the AGEs/sRAGE ratio and metabolic, inflammatory and CVD markers were also found. Results presented in Table 3 showed significant positive correlations of AGEs/sRAGE ratio values with fasting glucose (P<0.01), atherogenic index, IL-6, uric acid, TG and CVD markers: LDL-C/HDL-C and TG/HDL-C (P<0.05). Also, AGEs/sRAGE ratio was significantly negatively correlated with HDL-C (P<0.05).

Multivariate linear regression analysis showed that Ai was the significant determinant of sRAGE (β=–0.744, P=0.046) and AGEs/sRAGE ratio (β=0.815, P=0.006).

Discussions

Recent studies underlined that activation of RAGE and RAGE-dependent signaling pathways are involved in endothelial dysfunction, vascular inflammation, atherosclerosis, metabolic syndrome, diabetes or other disorders.[11,12,16] Moreover experimental studies on diabetic mice have shown that treatment with soluble RAGE significantly reduced atherosclerotic lesion progression.[17] Strong relationships between soluble variants of RAGE and disease state have been found, soluble RAGE being considered as marker of RAGE expression and activation of the AGEs-RAGE axis.[3,18] Also, high levels of soluble RAGE have been associated with healthy human aging and longevity, suggesting the important role of sRAGE in successful aging.[19]

Our study pointed out lower levels of soluble RAGE concomitantly with higher circulating levels of glycoxidation products, AGEs, in elderly with T2DM. These results are in agreement with other studies, which reported decreased sRAGE and/or endogenous secretory RAGE (esRAGE) levels in adult diabetes subjects with good or poor glycemic control.[20,21] Devangelio *et al.*, have

Table 1. Clinical characteristics, metabolic variables and cardiovascular risk markers in control and T2DM elderly subjects.

Parameter	Control group (N=15)	T2DM group (N=72)
Age, years	76±3	75±4 (NS)
Sex, males/females	5/10	20/52
Systolic blood pressure, mm Hg	128±8	143±12***
Diastolic blood pressure, mm Hg	80±7	88±6**
Fasting glucose (mg/dL)	95±9.49	134±37.32***
HbA1c (%)	5.4±0.3	6.7±1.0***
Total cholesterol (mg/dL)	184.33±20.75	236.74±48.00***
LDL-C (mg/dL)	101.83±17.51	152.14±36.15***
HDL-C (mg/dL)	66.25±11.30	52.12±9.69**
Triglycerides (mg/dL)	90.66±24.11	152.13±75.05***
Uric acid (mg/dL)	4.97±0.47	5.37±0.93*
Creatinine (mg/dL)	0.97±0.17	1.05±0.35 (NS)
TC/HDL-C ratio	2.83±0.42	4.71±1.49***
LDL-C/HDL-C ratio	1.57±0.34	3.03±1.02***
TG/HDL-C ratio	1.37±0.31	3.13±1.97***
Atherogenic index	0.12±0.10	0.43±0.22***

Values are means±standard deviation
*P<0.05; **P<0.01; ***P<0.001; P value represents statistical significance *versus* control group; NS, non-significant.
HbA1c, glycated hemoglobin; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus.

Table 2. Soluble RAGE, glycoxidative and inflammatory biomarkers in control and T2DM elderly subjects.

Parameter	Control group (N=15)	T2DM group (N=72)
sRAGE (pg/mL)	998.08±196.87	685.33±214.91**
AGEs (RFU)	98.57±10.88	116.47±20.20**
AGEs/sRAGE ratio	0.10±0.02	0.18±0.06**
IL-6 (pg/mL)	10.05±5.72	27.29±10.12*

Values are means±standard deviation
*P<0.01; **P<0.001; P, statistical significance *versus* control group.
AGEs, advanced glycation end products; sRAGE, soluble receptor for advanced glycation end products; IL-6, interleukin 6; T2DM, type 2 diabetes mellitus.

shown that the improvement of glycemic control in diabetes subjects after treatment with hypoglycemic drugs has increased the sRAGE levels.[21] In T2DM, the circulating levels of sRAGE may be decreased by the following mechanisms: excessive binding of soluble receptor to elevated AGEs levels and/or impaired of redox cellular balance and other pathways which reduced the endogenous RAGE release.[20,21]

Also, in this study, in elderly subjects with T2DM higher AGEs levels and lower sRAGE levels were found to be associated with dyslipidemia, higher values of atherogenic index, systemic inflammatory marker (IL-6) and cardiovascular risk markers. Moreover, the major determinant of soluble RAGE levels established by regression analysis was the atherogenic index.

The negative associations of soluble RAGE with proatherogenic metabolic and inflammatory biomarkers underline the important functional role of AGEs-RAGE-sRAGE axis in diabetes and vascular complications. Engagement of complete RAGE receptor with AGEs leads to reactive oxygen species (ROS) generation, oxidative and glycoxidative stress increase, reduction of nitric oxide production and bioavailability, enhancement of inflammatory processes and endothelial dysfunction, being involved in accelerated atherosclerosis in diabetes.[14,22,23] Moreover, the RAGE expression is enhanced in diabetic vasculature and sRAGE may be also generated in endothelial cells. Soluble RAGE may competitively inhibit the binding of AGEs ligands to transmembrane RAGE, thereby attenuating atherosclerosis and administration of soluble RAGE may inhibit the progression of atherosclerosis.[17,24]

Higher risk of coronary artery disease has been associated with reduced levels of soluble RAGE.[18] Recent clinical studies have found inverse associations of sRAGE levels with markers of vascular injury, such as: carotid intima-medial thickness[3,18] and vascular cell adhesion molecule-1 (VCAM-1).[20] Therefore, sRAGE has been proposed as biomarker of vascular damage.[23]

Also, our results found out a negative correlation of circulating sRAGE with IL-6 levels in elderly with T2DM, reflecting a proinflammatory effect of reduced levels of sRAGE and increased activity of AGEs-RAGE axis. This association is in line with other previous studies that underlined inverse correlations between soluble variants of RAGE (sRAGE and/or esRAGE) with some systemic inflammatory biomarkers: IL-6, high sensitive C-reactive protein, fibrinogen and S100A12 protein, in subjects with type 2 diabetes.[25,26] Recent clinical studies have emphasized that the AGEs-RAGE axis and RAGE-dependent signaling are related to cardiovascular risk not only in diabetes and reduced soluble RAGE levels are also strongly linked to inflammation in vascular dysfunction.[18,27]

Taking into consideration the deleterious effects of glycoxidation products, AGEs and the beneficial effects of soluble variants of RAGE, we evaluated the ratio of AGEs to sRAGE, viewed as a functional index of both markers. The significantly higher values of AGEs/sRAGE ratio found out in elderly with T2DM and their significant positive associations with atherogenic, inflammatory and CVD risk markers studied: LDL-C/HDL-C, TG/HDL-C underline the relevant contribution of AGEs-RAGE-sRAGE axis in diabetes and its vascular complications. Also, our results have demonstrated that Ai was an independent predictor of AGEs/ sRAGE ratio.

However, this is the first report confirming the independent association of AGEs/sRAGE ratio and sRAGE with Ai, in elderly with T2DM. Moreover, the AGEs/sRAGE ratio has been found to be an independent predictor of both markers of endothelial dysfunction: flow mediated vasodilation (FMD) and of nitroglycerine-induced vasodilation.[28] Thus, the AGEs/sRAGE ratio could be a more sensitive marker of endothelial dysfunction and atherosclerosis than AGEs or sRAGE. It has been underlined that sRAGE might have a counter-regulatory mechanism which counteracts the vasotoxic effects of AGEs and AGEs-RAGE axis.[22,28]

Experimental studies on diabetic mice showed that the deficiency of full length RAGE receptor has attenuated the development of atherosclerosis and administration of sRAGE has inhibited the progression of atherosclerotic changes and also stabilized atherosclerosis by blocking the RAGE-dependent signaling.[17,29] The blockade of RAGE signaling may reduce the activation of nuclear factor NF-kB and the expression of inflammatory cytokine.[2,22] By binding AGEs levels, soluble RAGE counteracts the deleterious effects of full length RAGE signaling.

Table 3. Correlations between soluble RAGE levels and metabolic, glycoxidative and inflammatory biomarkers and cardiovascular risk markers in elderly patients with T2DM (N=72).

Parameter	sRAGE r	AGEs/sRAGE r
AGEs (RFU)	–0.170	0.546**
sRAGE (pg/mL)	1.000	–0.874**
AGEs/sRAGE ratio	–0.874**	1.000
IL-6 (pg/mL)	–0.224*	0.273*
Fasting glucose (mg/dL)	–0.251*	0.337**
HDL-C	0.124	–0.261*
TG (mg/dL)	–0.146	0.245*
Uric Acid (mg/dL)	–0.097	0.240*
Atherogenic index	–0.149	0.279*
TC/HDL-C ratio	–0.120	0.220
LDL-C/HDL-C ratio	–0.166	0.247*
TG/HDL-C ratio	–0.113	0.252*

r, Pearson's correlation coefficients
*, P<0.05; **, P<0.01
AGEs, advanced glycation end products; sRAGE, soluble receptor for advanced glycation end products; IL-6, interleukin 6; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus.

In elderly with T2DM fasting serum glucose was significantly positively associated with AGEs/sRAGE ratio values and significantly negatively with circulating sRAGE levels. It is well known that chronic hyperglycemia induces increased reactive oxygen species production, enhances oxidative and glycoxidative processes, amplifying the AGEs formation that induces RAGE activation, proinflammatory and procoagulant mechanisms, rising oxidative stress and atherogenesis.[11,20,23] Moreover in experimental studies of atherosclerosis, it has been demonstrated the protective role of RAGE deletion.[29] Recent evidences support the role of sRAGE and esRAGE as biomarkers or endogenous protection factors against RAGE-mediated pathogenesis. Also reduced sRAGE levels have been associated with inflammatory and metabolic pathways that could affect the clinical outcome in subjects with diabetes.[26]

Our results highlight the important role of AGEs-RAGE-sRAGE axis in the link between metabolic and endothelial dysfunction. The associations of soluble RAGE and the AGEs/sRAGE ratio with atherogenic and inflammatory markers could reflect the protective role of sRAGE in atherosclerosis and diabetes vascular complications. Therefore, the assessment of sRAGE and AGEs/sRAGE ratio could be useful biomarkers for the cardiovascular risk assessment and also potential therapeutic targets for prevention and treatment of vascular complications in diabetes.

The study limitations are the reduced number of subjects and a lack of evaluation of endothelial dysfunction and coronary atherosclerosis by using cardiovascular imaging procedures such as: coronary angiography, brachial artery flow mediated dilation or ultrasonographic measurement of the intima media thickness.

Conclusions

The components of AGEs-RAGE axis are associated with cardiovascular risk markers in elderly with type 2 diabetes mellitus. Results highlight the protective role of sRAGE in limiting the deleterious effects of metabolic and glycoxidative stress, thus reducing the cardiovascular risk and inflammation in diabetic elderly.

References

1. 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;6:7-14.
2. Stirban A, Gawlowski T, Roden M. Vascular effects of advanced glycation endproducts: clinical effects and molecular mechanisms. Mol Metab 2013;3:94-108.
3. Yan SF, Ramasamy R, Schmidt AM. Soluble RAGE: therapy and biomarker in unraveling the RAGE axis in chronic disease and aging. Biochem Pharmacol. 2010;79:1379-86.
4. 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.
5. Tam XH, Shiu SW, Leng L, et al. Enhanced expression of receptor for advanced glycation end-products is associated with low circulating soluble isoforms of the receptor in Type 2 diabetes. Clin Sci (Lond) 2011;120:81-9.
6. Santilli F, Vazzana N, Bucciarelli LG, Davi G. Soluble forms of RAGE in human diseases: clinical and therapeutical implications. Curr Med Chem 2009;16:940-52.
7. Fujisawa K, Katakami N, Kaneto H, et al. Circulating soluble RAGE as a predictive biomarker of cardiovascular event risk in patients with type 2 diabetes. Atherosclerosis 2013;227: 425-8.
8. Basta G, Del Turco S, Marchi F, 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.
9. Park HJ, Baek JY, Shin WS, et al. Soluble receptor of advanced glycated endproducts is associated with plaque vulnerability in patients with acute myocardial infarction. Circ J 2011; 75:1685-90.
10. Lu L, Pu LJ, Zhang Q, et al. Increased glycated albumin and decreased esRAGE levels are related to angiographic severity and extent of coronary artery disease in patients with type 2 diabetes. Atherosclerosis 2009;206:540-5.
11. Piarulli F, Sartore G, Lapolla A. Glyco-oxidation and cardiovascular complications in type 2 diabetes: a clinical update. Acta Diabetol 2013;50:101-10.
12. Schmidt AM, Yan SD, Wautier JL, Stern D. Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. Circ Res 1999;84:489-97.
13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34:S62-9.
14. Gradinaru D, Borsa C, Ionescu C, Margina D. Advanced oxidative and glycoxidative protein damage markers in the elderly with type 2 diabetes. J. Proteomics 2013;92:313-22.
15. Dobiasova M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). Clin Biochem 2001; 34:583-8.
16. Yang SJ, Kim S, Hwang SY, et al. Association between sRAGE, esRAGE levels and vascular inflammation: analysis with 18F-fluorodeoxyglucose positron emission tomography. Atherosclerosis 2012;220:402-6.
17. Bucciarelli LG, Wendt T, Qu W, et al. RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice. Circulation 2002;106:2827-35.
18. Falcone C, Emanuele E, D'Angelo A, 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.
19. Geroldi D, Falcone C, Emanuele E. Soluble receptor for advanced glycation end products: from disease marker to potential therapeutic target. Curr Med Chem 2006;13:1971-8.
20. Motawi TMK, Abou-Seif MA, Bader AMA, Mahmoud MO. Effect of glycemic control on soluble RAGE and oxidative stress in type 2 diabetic patients. BMC Endocrine Disorders 2013;13:32.
21. Devangelio E, Santilli F, Formoso G, et al. Soluble RAGE in type 2 diabetes: association with oxidative stress. Free Radic Biol Med 2007;43:511-8.
22. Ramasamy R, Yan SF, Schmidt AM. The diverse ligand repertoire of the receptor for advanced glycation endproducts and pathways to the complications of diabetes. Vascul Pharmacol 2012;57:160-7.
23. Oliveira MIA, de Souza EM, de Oliveira Pedrosa F, et al. RAGE receptor and its soluble isoforms in diabetes mellitus complications. J Bras Patol Med Lab 2013;49:97-108.
24. Park L, Raman KG, Lee KJ, et al. Suppression of accelerated

diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. Nat Med 1998;4:1025-31.
25. Basta G, Sironi AM, Lazzerini G, 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.
26. Nakamura K, Yamagishi S, Adachi H, 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.
27. Selvin E, Halushka MK, Rawlings AM, et al. sRAGE and risk of diabetes, cardiovascular disease, and death. Diabetes 2013;62:2116-21.
28. Kajikawa M, Nakashima A, Fujimura N, et al. Ratio of serum levels of AGEs to soluble form of RAGE is a predictor of endothelial function. Diabetes Care 2015;38:119-25.
29. Soro-Paavonen A, Watson AM, Li J, et al. Receptor for advanced glycation end products (RAGE) deficiency attenuates the development of atherosclerosis in diabetes. Diabetes 2008;57:2461-9.