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Soluble form of a receptor for advanced glycation end products (sRAGE) as a biomarker

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1. ABSTRACT

There is a growing body of evidence that advanced glycation end products (AGEs) and their receptor (RAGE) system are implicated in various disorders, including vascular complications in diabetes, cardiovascular disease, neurodegenerative diseases, inflammatory and autoimmune disorders, and cancer growth and metastasis. Indeed, the engagement of RAGE with AGEs elicits oxidative stress generation and evokes inflammatory and thrombogenic responses, thus playing an important role in these devastating disorders. Moreover, since administration of a recombinant soluble form of RAGE (sRAGE), has been shown to block the AGE-RAGE signaling pathway in animal models, exogenously administered sRAGE may capture and eliminate circulating AGEs, thus protecting against the AGE-elicited tissue damage by acting as a decoy receptor for AGEs. Recently, sRAGE has been identified in humans. However, there are a few comprehensive papers about the regulation and role of sRAGE in humans. Therefore, in this paper, we review the kinetics, regulation and pathophysiological role of sRAGE in humans. We further discuss the potential clinical utility of measuring sRAGE in various disorders as a biomarker.

2. INTRODUCTION

Reactive derivatives from non-enzymatic glucose-protein condensation reactions, as well as lipids and nucleic acids exposed to reducing sugars, form a heterogeneous group of irreversible adducts called "AGEs (advanced glycation end products)". AGEs were originally characterized by a yellow-brown fluorescent color and an ability to form cross-links with and between amino groups, but the term is now used for a broad range of advanced products of the glycation process (also called the "Maillard reaction"), including N-carboxymethyllysine (CML) and pyrraline, which show neither color nor fluorescence and do not cross-link proteins (1-5). The formation of AGEs *in vitro* and *in vivo* is dependent on the turnover rate of the chemically modified target, the time available, and the sugar concentration. The structures of the various cross-linked AGEs that are generated *in vivo* have not yet been completely determined. Because of their heterogeneity and the complexity of the chemical reactions involved, only some AGEs have been structurally characterized *in vivo* (1-5). The structural identity of AGEs that could mainly mediate their biological actions also remains unknown.

Under the hyperglycemic conditions elicited by diabetes, the glycation process begins with the conversion of reversible Schiff base adducts to more stable, covalently-bound Amadori rearrangement products. Over the course of days to weeks, these Amadori products undergo further rearrangement reactions to form the irreversibly-bound moieties known as AGEs. AGEs could contribute to the aging of proteins and to the pathological complications of diabetes (1-5). Further, there is accumulating evidence that AGEs and their receptor (RAGE) system are implicated in various disorders, including cardiovascular disease, neurodegenerative diseases, inflammatory and autoimmune disorders, and cancer growth and metastasis (6-14). Indeed, the AGE-RAGE interaction elicits oxidative stress generation and subsequently evokes inflammatory and thrombogenic reactions in a variety of cells, thus playing an important role in the development and progression of these devastating disorders (6-14).

Recently, administration of a recombinant soluble form of RAGE (sRAGE) consisting of the extracellular ligand-binding domain, has been shown to not only suppress the development of atherosclerosis but also to stabilize established atherosclerosis in diabetic apolipoprotein E-null mice (15,16). The blockade of the AGE-RAGE axis by administration of sRAGE also ameliorates neuronal dysfunction and reduces the development of acellular capillaries and pericyte ghosts in experimental diabetic retinopathy (17). Furthermore, recently, Kaji *et al.* have also shown that attenuation of the RAGE axis with injection of sRAGE inhibits retinal leukostasis and blood-retinal barrier breakdown in the diabetic RAGE-transgenic mice which are accompanied by decreased expression of vascular endothelial growth factor (VEGF) and intercellular cell adhesion molecule-1 (ICAM-1) in the retina (18). These observations suggest that exogenously administered sRAGE may capture and eliminate circulating AGEs, thus protecting against the AGE-elicited tissue damage by acting as a decoy for AGEs.

Recently, sRAGE has been identified in mice and humans (19-23). Based on the data in sRAGE-administered animals, it is conceivable that sRAGE may also work as a decoy receptor for AGEs. However, since AGEs up-regulate RAGE expression levels in various tissues and that sRAGE could be mainly generated from proteolytic cleavage of membrane-bound RAGE by the actions of sheddase, a disintegrin and metalloproteinases 10 (ADAM 10) (6, 24-26), it is also possible that sRAGE may reflect tissue RAGE expression and the severity of target organ damage. Accordingly, whether sRAGE is a biomarker that could reflect tissue damage or a protective one against injury may be dependent on the disease types. As far as we know, since there are a few comprehensive papers about the regulation and role of sRAGE in humans (27-30), we review here the kinetics, regulation and pathophysiological role of sRAGE in humans. We further discuss the potential clinical utility of measuring sRAGE in various disorders as a biomarker.

3. sRAGE, DIABETES AND ITS VASCULAR COMPLICATIONS

Diabetic vascular complications are one of the leading causes of end-stage renal failure, acquired blindness, a variety of neuropathies and cardiovascular disease (CVD), which could account for disabilities and high mortality rates in patients with both type 1 and type 2 diabetes (31). Various hyperglycemia-induced metabolic and hemodynamic derangements, including increased formation of AGEs, enhanced reactive oxygen species (ROS) generation, activation of protein kinase C (PKC), stimulation of the polyol pathway and the renin-angiotensin system (RAS), are thought to contribute to the pathogenesis of vascular complications in diabetes (31). However, a clinical study, the Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) Research, has shown that the reduction in the risk of progressive retinopathy and nephropathy resulting from intensive therapy in patients with type 1 diabetes persisted for at least several years, despite increasing hyperglycemia (32,33). In addition, intensive therapy during the DCCT resulted in decreased progression of intima-media thickness (IMT) and subsequently reduced the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57 percent 11 years after the end of the trials (34). Further, a recent follow-up study of United Kingdom Prospective Diabetes Study (UKPDS) also has shown that benefits of an intensive therapy in patients with type 2diabetes are sustained after the cessation of the trial (35). In this study, despite an early loss of glycemic differences between intensive and conventional therapy, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause (legacy effects) were observed during 10 years of post-trial follow-up (35). These observations indicate that intensive therapy to control blood glucose has long-term beneficial effects on the risk of diabetic retinopathy, nephropathy, CVD and death in patients with both type 1 and type 2 diabetes, thus strongly suggesting that so-called ‘metabolic memory’ causes chronic damage in diabetic vessels that are not easily reversed, even by subsequent, relatively good control of blood glucose.

Although the exact pathophysiological mechanisms responsible for a legacy effect of the intensive glycemic control or metabolic memory are unclear, biochemical nature of AGEs, *that is*, gradual accumulation of AGEs under hyperglycemic conditions that are subsequently slowly degraded with intensive glycemic control, is compatible with the concept ‘metabolic memory’ (1-6). Further, AGEs and/or diabetic conditions can up-regulate RAGE expression in various cell types and subsequently induce sustained activation of transcriptional factor nuclear factor-kappaB (NF-kappaB) (6, 36-38). Under diabetic conditions, the AGE-RAGE-induced oxidative stress generation could further potentiate the formation and accumulation of AGEs (15). Therefore, these positive feedback loops between AGEs and RAGE-downstream pathways could make a vicious cycle, thus providing a mechanistic basis for understanding the

concept of 'metabolic memory' in vascular complications in diabetes.

sRAGE can generate from cleavage of cell surface full-length RAGE by sheddase or novel splice variants of RAGE as a C-truncated splice isoform of endogenous secretory RAGE (esRAGE) (19-23). Most of the sRAGE (*ca.* 80%) is derived from the cleavage of membrane-bound RAGE, and esRAGE only occupies about 20% of sRAGE (19-23,26). We, along with others, have shown that sRAGE levels are elevated in patients with type 1 and type 2 diabetes and that serum sRAGE levels are positively, rather than inversely, associated with AGE levels in both non-diabetic and diabetic subjects (39-44). Age-, sex- and body mass index-adjusted AGE levels are significantly increased in proportion to the increasing levels of sRAGE in non-diabetic subjects as well (44). These findings suggest that sRAGE could not efficiently capture and eliminate circulating AGEs *in vivo* by working as a decoy receptor for AGEs. Since AGEs are positive regulators of cell expression of RAGE (6,36,37), our present observations suggest that sRAGE levels may reflect tissue RAGE expression and be elevated in parallel with serum AGE levels as a counter-system against the AGE-elicited tissue damage, even in a non-diabetic general population without apparent cardiovascular disease or renal disease. The concept that sRAGE levels may be elevated in response to serum AGE levels and reflect tissue RAGE expression in diabetes is supported by the following observations; (1) RAGE belongs to the same immunoglobulin superfamily as ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) and that serum levels of soluble forms of ICAM-1 (sICAM-1) and VCAM-1 (sVCAM-1) are elevated in patients with diabetes as biomarkers of endothelial injury by reflecting overexpression of these adhesion molecules in endothelial cells (ECs) (45), (2) Angiotensin II (Ang II) increases RAGE mRNA levels in ECs and subsequently stimulates sRAGE formation *in vitro* (25). Treatment with telmisartan, an Ang II type 1 receptor blocker (ARB), not only inhibits the Ang II-elicited sRAGE generation by ECs, but also decreases serum levels of sRAGE in patients with essential hypertension (25), (3) AGEs up-regulate RAGE expression in various types of cells and that RAGE is up-regulated in atherosclerotic plaques in diabetes, diabetic nephropathy and retinopathy (6,36,37,46-48), (4) Vitreous levels of sRAGE are increased in proliferative retinal diseases by reflecting enhanced RAGE expression in epiretinal membranes of the eyes (48), and (5) Although exogenously administered sRAGE was shown to block the harmful effects of AGEs in animals by acting as a decoy receptor (15-18), it is questionable that endogenous sRAGE could also exert the same biological effect because serum levels of sRAGE in humans are 1000 times lower than needed for the binding AGEs (29,49,50).

The findings that sRAGE levels are positively associated with circulating AGEs and could reflect tissue RAGE expression led us to examine whether sRAGE levels may be a novel biomarker of vascular injury and/or target organ damage in patients with diabetes. To address these issues, we examined whether circulating sRAGE levels were elevated in type 2 diabetic patients, compared with non-diabetic healthy subjects, and explored the association between sRAGE levels and coronary artery disease (CAD) in diabetic subjects. As a result, we found that serum sRAGE levels were significantly higher in type 2 diabetic patients than in non-diabetic age- and sex-matched control subjects and that the presence of diabetes was a sole independent determinant of sRAGE in our subjects (41). Furthermore, serum sRAGE levels were significantly elevated in diabetic patients with CAD, compared to those without CAD, and one of the independent determinants of CAD in patients with diabetes. In addition, we have recently found that serum levels of sRAGE are positively correlated with inflammatory biomarkers such as tumor necrosis factor-alpha (TNF-alpha), sVCAM-1 and monocyte chemoattractant protein-1 (MCP-1) in type 2 diabetic patients (51-53). Moreover, circulating levels of AGEs and sRAGE were the independent determinants of serum MCP-1 levels in patients with type 2 diabetes. Taken together, these observations suggest the possibility that circulating sRAGE level is a novel biomarker of vascular inflammation and target organ damage in both type 1 and type 2 diabetic patients. In support of this, Tan *et al.* reported that serum sRAGE levels and circulating AGEs were correlated with each other and positively associated with the severity of nephropathy in type 2 diabetes (42). Yan *et al.* also reported that sRAGE levels were significantly higher in type 2 diabetic patients with CAD, compared with those without CAD (54). Further, EURODIAB Prospective Complications Study revealed that patients of type 1 diabetes with CVD had higher levels of sRAGE than those without CVD or any microvascular complications and that endothelial damage, renal dysfunction and low-grade inflammation could partially account for the associations between sRAGE and prevalent CVD (55). In this study, sRAGE levels tended to be higher in the presence and across the levels of severity of albuminuria and retinopathy as well (55). In addition, a recent 12-year follow-up study published in the meeting of EASD 2009 showed that higher plasma sRAGE levels were associated with incident cardiovascular morbility and mortality as well as all-cause mortality in type 1 diabetes (56).

RAGE mediates the AGE-signaling to MCP-1 and TNF-alpha expression in various types of cells including ECs (57-59). Further, there are several papers to show the positive correlation between serum levels of MCP-1 and TNF-alpha and circulating AGE levels (60,61). These observations suggest that enhancement of the AGE-RAGE axis under diabetic conditions could account for the positive association between sRAGE levels and these inflammatory markers in our patients. Recently, Basta *et al.* reported that plasma sRAGE (measured by the same commercial enzyme-linked immunosorbent assay kit as ours) was inversely associated with the inflammatory marker C-reactive protein (CRP) and hemoglobin A1c which were also independently associated with sRAGE on stepwise regression analysis in their subjects (diabetic patients and controls) (62). However, in their study, CRP was not identified as independent predictors of plasma sRAGE in diabetic patients alone. Therefore, our data to

show the positive association between sRAGE and some inflammatory markers in diabetics are not necessarily discrepant against their findings. Further, recently, sRAGE, but not esRAGE, has been shown to be independently correlated with albuminuria in type 2 diabetic patients (49). sRAGE itself might be capable of triggering inflammatory reactions via binding of Mac-1 and subsequent activation of NF-kappaB, thus being involved in diabetic vascular complications (63).

Although number of patients was very small (one included 30 subjects, and the other 50), there were two papers to show that sRAGE levels were decreased in type 2 diabetic patients (62,64). Devangelio *et al.* reported that sRAGE levels were significantly decreased in type 2 diabetic patients and that HbA1c was inversely and independently associated with sRAGE (64). Basta *et al.* also showed that decreased sRAGE levels in type 2 diabetic patients were associated with the increased CVD risk (62). In addition, Grossin *et al.* reported that although serum sRAGE levels in type 2 diabetic patients and healthy controls were similar, sRAGE levels were significantly decreased in the diabetic patients with renal and retinal complications compared with those without complications (65). At present, we do not know the reasons for the opposite results in type 2 diabetic patients. The difference of subject population (age and duration of diabetes) and ethnicity could account for the discrepancies. Anyway, we should present the possibility of the other side of story, *that is*, sRAGE levels could be inversely associated with the risk of vascular injury in type 2 diabetic patients. However, it is unlikely that decreased *rather than* increased sRAGE level could be a biomarker of vascular complications in diabetes, because as far as we know, there are no papers to show that (1) sRAGE efficiently captures and eliminates circulating AGEs in diabetic patients by working as a decoy receptor for AGEs, (2) sRAGE levels are inversely associated with serum levels of AGEs in diabetics, and (3) sRAGE levels are decreased in type 1 diabetic patients compared with controls. Since interaction of RAGE with the ligand promotes the RAGE shedding (26), sRAGE levels could correlate with high levels of ongoing inflammation in diabetes.

There is still some controversy over the therapeutic modulation of sRAGE. Forbes *et al* reported that treatment of ramipril, an angiotensin-converting enzyme inhibitor (ACEI) restored the decreased plasma levels of sRAGE in diabetic rats (66). Similarly, they also found that there was a significant increase in plasma sRAGE levels in patients who had type 1 diabetes and were treated with an ACEI perindopril (66). As described above, Nakamura *et al.* reported that telmisartan, an ARB, inhibited sRAGE generation by Ang II-exposed ECs and decreased serum levels of sRAGE in patients with essential hypertension (25). Although atorvastatin or rosiglitazone has been shown to increase serum sRAGE levels (67,68), whether modulation of circulating sRAGE levels has a beneficial effect on the progression of diabetic vascular complications is unknown.

Serum levels of esRAGE are also positively correlated with circulating AGEs such as pentosidine and CML in both type 1 and type 2 diabetes (69,70). esRAGE levels were increased levels in type 2 diabetic patients with decreased renal function, and serum creatinine was one of the independent determinants of esRAGE levels in these patients (69). However, in contrast to the case of sRAGE, esRAGE levels are decreased, rather than increased, in both type 1 and type 2 diabetic patients with microalbuminuria or retinopathy, compared with those without microvascular complications (71-73). Further, esRAGE levels were inversely associated with carotid IMT in both type 1 and type 2 diabetes, and one of the independent risk factors for the progression of carotid atherosclerosis in patients with type 1 diabetes (74,75). In addition, Koyama *et al*. reported that esRAGE levels were decreased in Japanese type 2 diabetic patients compared with non-diabetic subjects and that its low levels were associated with the components of the metabolic syndrome and carotid atherosclerosis (76). Decreased esRAGE levels were associated with inflammation, arterial stiffness and severity of CAD in patients with type 2 diabetes (77,78). These observations were contrary to the above-mentioned findings that sRAGE levels were associated with conventional coronary risk factors, including inflammatory biomarkers, and one of the independent determinants of CAD in diabetic patients. Therefore, the kinetics and pathophysiological role of sRAGE and esRAGE could differ in diabetes. Decreased levels of esRAGE may be associated with co-morbidity such as diabetic microangiopathy and accelerated atherosclerosis in unknown mechanisms other than working as a decoy receptor for AGEs because (1) as mentioned above, esRAGE levels are approximately 3~5-fold lower than sRAGE and are not sufficient to efficiently eliminate circulating AGEs in humans (29,49,50) and (2) there are no reports to show the inverse associations between esRAGE and AGE levels. We should also note that there was a controversy about the associations between decreased esRAGE levels and vascular complications in diabetes. esRAGE levels were reported not to be associated with albuminuria, carotid IMT, peripheral and autonomic neuropathy in type 2 diabetic patients (49,79). Sakurai *et al.* reported that there was no significant difference of esRAGE levels between type 1 diabetic patients and healthy controls (73).

4. sRAGE AND CVD

Plasma CML and sRAGE levels were elevated after percutaneous coronary interventions with stenting, and positively associated with the extent of vascular injury (80). Further, Basta *et al.* reported that plasma sRAGE levels were higher in non-diabetic patients with symptomatic carotid atherosclerosis than those without symptom (81). They also showed that in symptomatic patients, plasma levels of sRAGE were positively associated with CML, and CML and RAGE levels in carotid plaques were correlated with each other (81). These observations suggest that higher levels of sRAGE may be a biomarker of a high degree of vascular inflammation in non-diabetic patients with CAD as well. It is interesting that, as described before, the same authors previously reported that sRAGE levels were inversely associated with

coronary risk factors in type 2 diabetes (62). These findings suggest that the regulation of sRAGE and its association with vascular disease may differ between patients with and without diabetes.

Koyama *et al.* have shown that serum sRAGE levels are increased with advancing New York Heart Association functional class, and higher in patients with cardiac events than in event free patients (82). In their study, sRAGE and serum pentosidine levels were independent risk factors for cardiac events in the multivariate Cox proportional hazard analysis, thus suggesting that serum sRAGE level is an independent prognostic factor for heart failure (82). In addition, elevated plasma levels of sRAGE were positively associated with primary graft dysfunction after lung transplantation as well (83).

Although the above-mentioned observations suggest that increased sRAGE levels is a biomarker of CVD, opposite scenario-*that is*, decreased sRAGE level could be related with CVD, was also presented by some researchers. Indeed, increased CRP and decreased sRAGE levels were observed in non-diabetic patients with angiographically proven CAD, compared with those with coronary risk factors and without CAD (84). In addition, Falcone *et al.* reported that, independent of established vascular risk factors and lipid parameters, the odds ratio for the presence of CAD in non-diabetic male subjects was 6.7 when the lowest quartile of the sRAGE levels (below 766 pg/ml) compared with the highest quartile (85). Further, plasma levels of sRAGE were positively associated with endothelial function and major cardiovascular event-free survival in non-diabetic subjects (86). Meanwhile, we have recently found that sRAGE levels are independently and inversely associated with high mobility group box 1 (HMGB1) levels in an apparently healthy population (87). HMGB1 is one of the ligands for RAGE, and HMGB1 and RAGE interaction promotes chemotaxis and maturation of immune cells, enhances the expression of adhesion molecules, and stimulates the production of cytokines by various types of cells (88). Moreover, sRAGE is absent and HMGB1 levels are higher in diabetic $RAGE^{-/-}/apoE^{-/-}$ mice, compared with diabetic $apoE^{-/-}$ mice (89). These observations suggest that sRAGE may protect against CVD by working as a decoy receptor for circulating HMGB1. Binding affinity of HMGB1 to RAGE is 10-times higher than that of AGEs (50, 90), whereas serum concentration of HMGB1 is 1000-times less than that of AGEs (87,91), thus supporting the concept that circulating HMGB1 *but not* AGEs is a molecular target for sRAGE. Therefore, the differences of kinetics and serum concentrations of the RAGE ligands (ex. AGEs and HMGB1) in various disorders could account for the discrepant results between sRAGE levels and the disease status.

5. sRAGE AND HYPERTENSION (HT)

Plasma levels of sRAGE were decreased in patients with essential HT, compared with age- and sex-matched normotensive subjects (92). Further, sRAGE levels were inversely associated with pulse pressure, thus suggesting that sRAGE may be a marker of arterial stiffness in essential HT (92). When we analyzed anthropometric, metabolic and inflammatory variables, including sRAGE in 271 consecutive non-diabetic outpatients with essential HT, 24-hour creatinine clearance ($p<0.0001$, inversely), gamma-glutamyltranspeptidase ($p<0.001$), body mass index ($p=0.007$, inversely), and TNF-alpha ($p=0.024$) were independently associated with sRAGE levels (93). These findings suggest that anthropometric and inflammatory variables and liver and renal function may be the determinants of sRAGE levels in non-diabetic hypertensive patients. The exact reasons for the discrepant results between the two papers, *that is*, an inverse correlation between sRAGE and pulse pressure in one hand and a positive correlation between body mass index and TNF-alpha with sRAGE in the other, are unclear. Difference of patient population, disease activity, and concentrations of serum levels of AGEs and HMGB1 between the two studies could affect the results.

6. sRAGE AND CHRONIC KIDNEY DISEASE (CKD)

Serum AGE, HMGB1, sRAGE, and an endogenous inhibitor of nitric oxide synthase, asymmetric dimethylarginine (ADMA) levels in CKD patients were significantly higher than those in control subjects (94). In addition, AGE and sRAGE levels were correlated with each other, and AGEs and HMGB1 were independently associated with ADMA in non-diabetic CKD patients (94). These findings suggest that elevation of the RAGE ligands may enhance ADMA levels, suggesting the active involvement of AGE/HMGB1-RAGE-ADMA axis in CKD patients.

sRAGE levels were increased in patients with decreased renal function, especially those with end-stage renal failure (95). There was a significant inverse relationship between estimated glomerular filtration rate (eGFR) and serum sRAGE levels (96). However, significant inverse relationships were also found for sRAGE to IMT and plaque number in patients with CKD (96). Further, Gross *et al.* reported that low sRAGE levels were associated with a 2-3 times higher risk for mortality in renal transplant recipients especially after correction for creatinine clearance (97). In addition, low circulating esRAGE is reported to predict cardiovascular mortality in end-stage renal disease patients (98). The pathophysiological significance of these correlations between decreased sRAGE/esRAGE and cardiovascular events in CKD patients will have to await more mechanistic studies.

7. sRAGE AND NEURODEGENERATIVE DISORDERS

Emanuele *et al.* reported that levels of sRAGE were significantly reduced in the plasma of patients with Alzheimer disease compared with that for those with either vascular dementia ($p<0.05$) or with controls ($p<0.001$) (99). Further, circulating sRAGE levels were decreased in patients with mild cognitive impairment (MCI), and could be a marker of exteeme longevity in humans (100,101).

Further, sRAGE levels were significantly decreased in serum of the patients with amyotrophic lateral sclerosis comparing to the control group, although the correlation between the serum sRAGE levels and clinical parameters of the disease was not significant (102). Sternberg *et al.* reported that serum levels of sRAGE were significantly lower in multiple sclerosis (MS) patients compared to levels in healthy controls (103). They also showed the association of sRAGE with disease activity and rate of clinical relapse. These observations suggest that sRAGE may protect against various types of neurodegenerative disorders and that decreased sRAGE level could be a biomarker of these degenerative diseases.

8. sRAGE AND INFLAMMATORY DISEASES

sRAGE levels at baseline significantly correlated with bone/cartilage turnover markers including C-terminal propeptide of type I procollagen, carboxyterminal telopeptide of type I collagen and cartilage oligomeric matrix protein in rheumatoid arthritis (RA) patients, and the decrease of sRAGE levels following hormone replacement therapy paralleled with diminished concentration of these molecules (104). Bone mineral density (BMD) in hip and femoral neck and progression of Larsen score at 1 year were associated with baseline sRAGE levels. The same authors reported that sRAGE levels were decreased in RA patients and that its synovial fluid levels were higher in patients treated with methotrexate, compared without disease-modifying anti-RA treatment (105). sRAGE levels in RA patients were associated with CRP levels as well (106). These observations suggest serum sRAGE was associated with BMD and markers of bone/cartilage metabolism in RA.

Yoshizaki *et al.* reported that serum HMGB1 and sRAGE levels in systemic sclerosis SSc were higher than those in controls (107). Since SSc patients with elevated HMGB1 and sRAGE levels had more frequent involvement of several organs and immunological abnormalities compared to those with normal levels, increased sRAGE level may be a biomarker that could reflect disease severity and immunological abnormalities in SSc. In contrast the case with SSc, sRAGE levels were decreased in patients with Kawasaki disease and primary Sjögren's syndrome (108,109).

We, along with others, have recently found that sRAGE levels are elevated in septic shock patients, and that nonsurvivors after 28 days have had higher plasma sRAGE concentrations than survivors (2302 +/- 189 versus 1326 +/- 112 pg/ml) (110,111). Receiver operating characteristic curve analysis of plasma sRAGE concentrations of septic patients showed a specificity of 75% and a sensitivity of 84.6% with 1596 pg/ml as cutoff.

Taken together, for different autoimmune diseases, sRAGE showed both a positive correlation and a negative correlation. The correlation between sRAGE levels and disease activity may be dependent on autoimmune disorder types and/or serum levels of RAGE ligands such as AGEs and HMGB1.

9. sRAGE AND OTHER DISORDERS

Plasma levels of sRAGE were significantly decreased in patients with nonalcoholic steatohepatitis, a hepatic manifestation of insulin resistance compared with controls (112).

Atherosclerotic mechanism may be involved in the pathogenesis of aortic valve stenosis (AVS) (113). sRAGE levels were significantly lower in AVS patients than in controls, and inversely correlated with coronary calcification in AVS patients (113).

sRAGE levels may be altered in patients with cancers. Despite higher serum levels of AGEs, sRAGE levels were significantly decreased in patients with breast cancer compared with healthy controls (114). Further, patients with better outcome (low grade histology and estrogen receptor-positive breast cancer) are reported to have higher sRAGE levels (114). Overall survival rate of lung cancer patients with low expression of cytoplasmic esRAGE was significantly lower than that of patients with normal expression (115).

It would be interesting to introduce some information on sRAGE in pregnancy. sRAGE levels in women with preterm labor are decreased and correlated negatively with the leukocyte count (116). Further, in women with preeclampsia, sRAGE is elevated and correlated with serum creatinine concentration and with uric acid concentration (116). In the first trimester, pregnant diabetic (DP) patients showed lower sRAGE and higher AGEs compared to healthy pregnants. In the DP group, significant negative correlations were seen between TNF-alpha and lipopolysaccharide-stimulated interleukin-6 in the first trimester and sRAGE in the third trimester (117).

10. CONCLUSION

We review here the kinetics, regulation and pathophysiological role of sRAGE and esRAGE in diabetes, CVD, HT, CKD, neurodegenerative disorders, inflammatory diseases and others. Further basic and clinical investigations are needed to clarify whether sRAGE and/or esRAGE levels are one of the most convenient biomarkers for evaluating disease activity and target organ damage in these devastating disorders.

11. REFERENCES

1. M. Takeuchi and S. Yamagishi: Involvement of toxic AGEs (TAGE) in the pathogenesis of diabetic vascular complications and Alzheimer's disease. *J Alzheimers Dis* 16, 845-858 (2009)

2. M.A. Glomb and V.M. Monnier: Mechanism of protein modification by glyoxal and glycoaldehyde, reactive intermediates of the Maillard reaction. *J Biol Chem* 70, 10017-26 (1995)

3. R. Bucala and A. Cerami: Advanced glycosylation:

chemistry, biology, and implications for diabetes and aging. *Adv Pharmacol* 23, 1-34 (1992)

4. H. Vlassara, R. Bucala and L. Striker: Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. *Lab Invest* 70, 138-151 (1994)

5. Brownlee M. Advanced protein glycosylation in diabetes and aging. Ann Rev Med 1995; 46: 223-34.

6. S. Yamagishi and T. Imaizumi: Diabetic vascular complications: pathophysiology, biochemical basis and potential therapeutic strategy. *Curr Pharm Des* 11, 2279-2299 (2005)

7. S. Rahbar and J.L. Figarola: Novel inhibitors of advanced glycation endproducts. *Arch Biochem Biophys* 419, 63-79 (2003)

8. A. Bierhaus, M.A. Hofmann, R. Ziegler and P.P. Nawroth: AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. *Cardiovasc Res* 37, 586-600 (1998)

9. A.M. Schmidt and D. Stern: Atherosclerosis and diabetes: the RAGE connection. *Curr Atheroscler Rep* 2, 430-436 (2000)

10. M. Takeuchi and S. Yamagishi: Possible involvement of advanced glycation end-products (AGEs) in the pathogenesis of Alzheimer's disease. *Curr Pharm Des* 14, 973-978 (2008)

11.R. Abe and S. Yamagishi: AGE-RAGE system and carcinogenesis. *Curr Pharm Des* 14, 940-945 (2008)

12. S. Yamagishi, S. Ueda and S. Okuda: Food-derived advanced glycation end products: a novel therapeutic target for various disorders. *Curr Pharm Des* 13, 2832-2836 (2007)

13. S. Yamagishi, K. Nakamura and T. Matsui: Regulation of advanced glycation end product (AGE)-receptor (RAGE) system by PPAR-gamma agonists and its implication in cardiovascular disease. *Pharm Res* 60, 174-178 (2009)

14. H.L. Nienhuis, J. Westra, A.J. Smit, P.C. Limburg, C.G. Kallenberg and M. Bijl: AGE and their receptor RAGE in systemic autoimmune disease: an inflammation propagating factor contributing to accelerated atherosclerosis. *Autoimmunity* 42, 302-304 (2009)

15. L. Park, K.G. Raman, K.J. Lee, Y. Lu, L.J.Jr. Ferran, W.S. Chow, D. Stern and A.M. Schmidt: Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. *Nat Med* 4, 1025-1031 (1998)

16. L.G. Bucciarelli, T. Wendt, W. Qu, Y. Lu, E. Lalla, L.L. Rong, M.T. Goova, B. Moser, T. Kislinger, D.C. Lee, Y. Kashyap, D.M. Stern and A.M. Schmidt: RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice. *Circulation* 106, 2827-2835 (2002)

17. G.R. Barile, S.I. Pachydaki, S.R. Tari, S.E. Lee, C.M. Donmoyer, W. Ma, L.L. Rong, L.G. Buciarelli, T. Wendt, H. Horig, B.I. Hudson, W. Qu, A.D. Weinberg. S.F. Yan and A.M. Schmidt: The RAGE axis in early diabetic retinopathy. *Invest Ophthalmol Vis Sci* 46, 2916-2924 (2005)

18. Y. Kaji, T. Usui, S. Ishida, K. Yamashiro, J. Moore, Y. Yamamoto, H. Yamamoto and A.P. Adamis: Inhibition of diabetic leukostasis and blood-retinal barrier breakdown with a soluble form of a receptor for advanced glycation end products. *Invest Ophthalmol Vis Sci* 48, 858-865 (2007)

19. S.F. Yan, V. D'Agati, A.M. Schmidt and R. Ramasamy R: Receptor for Advanced Glycation Endproducts (RAGE): a formidable force in the pathogenesis of the cardiovascular complications of diabetes & aging. *Curr Mol Med* 7, 699-710 (2007)

20. B. Moser, B.I. Hudson and A.M. Schmidt: Soluble RAGE: a hot new biomarker for the hot joint? *Arthritis Res Ther* 7, 142-144 (2005)

21. B.I. Hudson, E. Harja, B. Moser and A.M. Schmidt: Soluble levels of receptor for advanced glycation endproducts (sRAGE) and coronary artery disease: the next C-reactive protein? *Arterioscler Thromb Vasc Biol* 25, 879-882 (2005)

22. L.E. Hanford, J.J. Enghild, Z. Valnickova, S.V. Petersen, L.M. Schaefer, T.M. Schaefer, T.A. Reinhart and T.D. Oury: Purification and characterization of mouse soluble receptor for advanced glycation end products (sRAGE). *J Biol Chem* 279, 50019-50024 (2004)

23. H. Yonekura, Y. Yamamoto, S. Sakurai, R.G. Petrova, M.J. Abedin, H. Li, K. Yasui, M. Takeuchi, Z. Makita, S. Takasawa, H. Okamoto, T. Watanabe and H. Yamamoto: 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* 370, 1097-1109 (2003)

24. S. Yamagishi and T. Imaizumi: Serum levels of soluble form of receptor for advanced glycation end products (sRAGE) may reflect tissue RAGE expression in diabetes. *Arterioscler Thromb Vasc Biol* 27, e32 (2007)

25. K. Nakamura, S. Yamagishi, Y. Nakamura, K. Takenaka, T. Matsui, Y. Jinnouchi and T. Imaizumi: Telmisartan inhibits expression of a receptor for advanced glycation end products (RAGE) in angiotensin-II-exposed endothelial cells and decreases serum levels of soluble RAGE in patients with essential hypertension. *Microvasc Res* 70, 137-141 (2005)

26. A. Raucci, S. Cugusi, A. Antonelli, S.M. Barabino, L. Monti, A. Bierhaus, K. Reiss, P. Saftig and M.E. Bianchi:

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* 22, 3716-3727 (2008)

27. H. Maillard-Lefebvre, E. Boulanger, M. Daroux, C. Gaxatte, B.I. Hudson and M. Lambert: Soluble receptor for advanced glycation end products: a new biomarker in diagnosis and prognosis of chronic inflammatory diseases. *Rheumatology (Oxford)* 48, 1190-1196 (2009)

28. F. Santilli, N. Vazzana, L.G. Bucciarelli and G. Davì: Soluble forms of RAGE in human diseases: clinical and therapeutical implications. *Curr Med Chem* 16, 940-952 (2009)

29. S. Yamagishi, T. Matsui T and K. Nakamura: Kinetics, role and therapeutic implications of endogenous soluble form of receptor for advanced glycation end products (sRAGE) in diabetes. *Curr Drug Targets* 8, 1138-1143 (2007)

30. D. Geroldi, C. Falcone and E. Emanuele: Soluble receptor for advanced glycation end products: from disease marker to potential therapeutic target. *Curr Med Chem* 13, 1971-1978 (2003)

31. M. Brownlee: Biochemistry and molecular cell biology of diabetic complications. *Nature* 414, 813-820 (2001)

32. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 342, 381-389 (2000)

33. Writing Team For The Diabetes Control And Complications Trial/Epidemiology Of Diabetes Interventions And Complications Research Group: Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 290, 2159-2167 (2003)

34. D.M. Nathan, P.A. Cleary, J.Y. Backlund, S.M. Genuth, J.M. Lachin, T.J. Orchard TJ, P. Raskin and B. Zinman; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353, 2643-2653 (2005)

35. R.R. Holman, S.K. Paul, M.A. Bethel, D.R. Matthews and H.A. Neil: 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359, 1577-1589 (2008)

36. N. Tanaka, H. Yonekura, S. Yamagishi, H. Fujimori, Y. Yamamoto and H. Yamamoto: The receptor for advanced glycation end products is induced by the glycation products themselves and tumor necrosis factor-alpha through nuclear factor-kappa B, and by 17beta-estradiol through Sp-1 in human vascular endothelial cells. *J Biol Chem* 275, 25781-25790 (2000)

37. S. Yamagishi, S. Amano, Y. Inagaki, T. Okamoto, M. Takeuchi and Z. Makita: Beraprost sodium, a prostaglandin I2 analogue, protects against advanced gycation end products-induced injury in cultured retinal pericytes. *Mol Med* 8, 546-550 (2002)

38. A. Bierhaus, S. Schiekofer, M. Schwaninger, M. Andrassy, P.M. Humpert, J. Chen, M. Hong, T. Luther, T. Henle, I. Klöting, M. Morcos, M. Hofmann, H. Tritschler, B. Weigle, M. Kasper, M. Smith, G. Perry, A.M. Schmidt, D.M. Stern, H.U. Häring, E. Schleicher and P.P. Nawroth: Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. *Diabetes* 50, 2792-2808 (2001)

39. M. Challier, S. Jacqueminet, O. Benabdesselam, A. Grimaldi and J.L. Beaudeux: Increased serum concentrations of soluble receptor for advanced glycation endproducts in patients with type 1 diabetes. *Clin Chem* 51, 1749-1750 (2005)

40. A. Dettoraki, A.P. Gil and B.E. Spiliotis: Association between serum levels of the soluble receptor (sRAGE) for advanced glycation endproducts (AGEs) and their receptor (RAGE) in peripheral blood mononuclear cells of children with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 22, 895-904 (2009)

41. K. Nakamura, S. Yamagishi, H. Adachi, Y. Kurita-Nakamura, T. Matsui, T. Yoshida, A. Sato and T. Imaizumi: Elevation of soluble form of receptor for advanced glycation end products (sRAGE) in diabetic subjects with coronary artery disease. *Diabetes Metab Res Rev* 23, 368-371 (2007)

42. K.C. Tan, S.W. Shiu, W.S. Chow, L. Leng, R. Bucala and D.J. Betteridge: Association between serum levels of soluble receptor for advanced glycation end products and circulating advanced glycation end products in type 2 diabetes. *Diabetologia* 49, 2756-2762 (2006)

43. K. Nakamura, S. Yamagishi, T. Matsui, H. Adachi, M. Takeuchi and T. Imaizumi: Serum levels of soluble form of receptor for advanced glycation end products (sRAGE) are correlated with AGEs in both diabetic and non-diabetic subjects. *Clin Exp Med* 7, 188-190 (2007)

44. S. Yamagishi, H. Adachi, K. Nakamura, T. Matsui, Y. Jinnouchi, K. Takenaka, M. Takeuchi, M. Enomoto, K. Furuki, A. Hino, Y. Shigeto and T. Imaizumi: Positive association between serum levels of advanced glycation end products and the soluble form of receptor for advanced glycation end products in nondiabetic subjects. *Metabolism* 55, 1227-1231 (2006)

45. M. Steiner, K.M. Reinhardt, B. Krammer, B. Ernst and

A.D. Blann: Increased levels of soluble adhesion molecules in type 2 (non-insulin dependent) diabetes mellitus are independent of glycaemic control. *Thromb Haemost* 72, 979-984 (1994)

46. F. Cipollone, A. Iezzi, M. Fazia, M. Zucchelli, B. Pini, C. Cuccurullo, D. de Cesare, G. de Blasis, R. Muraro, R. Bei, F. Chiarelli, A.M. Schmidt, F. Cuccurullo, and A. Mezzetti: The receptor RAGE as a progression factor amplifying arachidonate-dependent inflammatory and proteolytic response in human atherosclerotic plaques: role of glycemic control. *Circulation* 108, 1070-1077 (2003)

47. N. Tanji, G.S. Markowitz, C. Fu, T. Kislinger, A. Taguchi, M. Pischetsrieder, D. Stern, A.M. Schmidt and V.D. D'Agati: Expression of advanced glycation end products and their cellular receptor RAGE in diabetic nephropathy and nondiabetic renal disease. *J Am Soc Nephrol* 11, 1656-1666 (2000)

48. S.I. Pachydaki, S.R. Tari, S.E. Lee, W. Ma, J.J. Tseng, A.A. Sosunov, G. Cataldergirmen, N. Scarmeas, C. Caspersen, S. Chang, W.M. Schiff, A.M. Schmidt and G.R. Barile: Upregulation of RAGE and its ligands in proliferative retinal disease. *Exp Eye Res* 82, 807-815 (2006)

49. P.M. Humpert, Z. Djuric, S. Kopf, G. Rudofsky, M. Morcos, P.P. Nawroth and A. Bierhaus: Soluble RAGE but not endogenous secretory RAGE is associated with albuminuria in patients with type 2 diabetes. *Cardiovasc Diabetol* 6:9 doi:10.1186/1475-2840-6-9 (2007)

50. M. Neeper, A.M. Schmidt, J. Brett, S.D. Yan, F. Wang, Y.C. Pan, K. Elliston, D. Stren and A. Shaw: Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. *J Biol Chem* 267, 14998-15004 (1992)

51. K. Nakamura, S. Yamagishi, H. Adachi, T. Matsui, Y. Kurita-Nakamura, M. Takeuchi, H. Inoue and T. Imaizumi: 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* 76, 52-56 (2008)

52. K. Nakamura, S. Yamagishi, H. Adachi, T. Matsui, Y. Kurita-Nakamura, M. Takeuchi, H. Inoue and T. Imaizumi: Circulating advanced glycation end products (AGEs) and soluble form of receptor for AGEs (sRAGE) are independent determinants of serum monocyte chemoattractant protein-1 (MCP-1) levels in patients with type 2 diabetes. *Diabetes Metab Res Rev* 24, 109-114 (2008)

53. K. Nakamura, S. Yamagishi, H. Adachi, Y. Kurita-Nakamura, T. Matsui, T. Yoshida and T. Imaizumi: Serum levels of sRAGE, the soluble form of receptor for advanced glycation end products, are associated with inflammatory markers in patients with type 2 diabetes. *Mol Med* 13, 185-189 (2007)

54. X.X. Yan, W.H. Peng, L.J. Wang, Q. Zhang, R.Y. Zhang, Q.J. Chen and W.F. Shen: Increased serum HMGB1 level is associated with coronary artery disease in nondiabetic and type 2 diabetic patients. *Atherosclerosis* 205, 544-548 (2009)

55. J.W. Nin, I. Ferreria, C.G. Schalkwiik, M.H. Prins, N. Chaturvedi, J.H. Fuller and C.D. Stehouwer; EURODIAB Prospective Complications Study Group. Levels of soluble receptor for AGE are cross-sectionally associated with cardiovascular disease in type 1 diabetes, and this association is partially mediated by endothelial and renal dysfunction and by low-grade inflammation: the EURODIAB Prospective Complications Study. *Diabetologia* 52, 705-714 (2009)

56. J.W. Nin, A. Jorsal, I. Ferreria, C.G. Schalkwiik, M.H. Prins, H.H. Parving, L. Tarnow, P. Rossing and C.D.A. Stehouwer;Higher plasma levels are associated with incident cardiovascular morbility and mortality as well as all-cause mortality in type 1 diabetes: a 12-yr follow-up study. *Diabetologia* 52 (Suppl1), S155 (2009)

57. L. Gu, S. Hagiwara, Q. Fan, M. Tanimoto, M. Kobata, M. Yamashita, T. Nishitani, T. Gohda, Z. Ni, J. Qian, S. Horikoshi and Y. Tomino: Role of receptor for advanced glycation end-products and signalling events in advanced glycation end-product-induced monocyte chemoattractant protein-1 expression in differentiated mouse podocytes. *Nephrol Dial Transplant* 21, 299-313 (2006)

58. G. Rashid, S. Benchetrit, D. Fishman and J. Bernheim: Effect of advanced glycation end-products on gene expression and synthesis of TNF-alpha and endothelial nitric oxide synthase by endothelial cells. *Kidney Int* 66, 1099-1106 (2004)

59. G. Cataldegirmen, S. Zehg, N. Feirt, N. Ippagunta, H. Dun, W. Qu, Y. Lu, L.L. Rong, M.A. Hofmann, T. Kislinger, S.I. Pachydaki, D.G. Jenkins, A. Weinberg, J. Lefkowitch, X. Rogiers, S.F. Yan, A.M. Schmidt and J.C. Emond: RAGE limits regeneration after massive liver injury by coordinated suppression of TNF-alpha and NF-kappaB. *J Exp Med*, 201, 473-484 (2005)

60. F. Galli, S. Benedetti, A. Floridi, F. Canestrari, M. Piroddi, E. Buoncristiani and U. Buoncristiani: Glycoxidation and inflammatory markers in patients on treatment with PMMA-based protein-leaking dialyzers. *Kidney Int* 67, 750-759 (2005)

61. G.E. Hein, M. Kohler, P. Oelzner, G. Stein and S. Franke: The advanced glycation end product pentosidine correlates to IL-6 and other relevant inflammatory markers in rheumatoid arthritis. *Rheumatol Int* 26, 137-141 (2005)

62. G. Basta, A.M. Sironi, G. Lazzerini, S. del Turco, E. Buzzigoli, A. Casolaro, A. Natali, E. Ferrannini and A. Gastaldelli: Circulating soluble receptor for advanced glycation end products is inversely associated with glycemic control and S100A12 protein. *J Clin Endocrinol Metab* 91, 4628-4634 (2006)

63. T. Chavakis, A. Bierhaus, N. Al-Fakhri, D. Schneider, S. Witte, T. Linn, M. Nagashima, J. Morser, B. Arnold, K.T. Preissner and P.P. Nawroth: The pattern recognition receptor (RAGE) is a counterreceptor for leukocyte integrins: a novel pathway for inflammatory cell recruitment. *J Exp Med* 198, 1507-1515 (2003)

64. E. Devangelio, F. Santilli, G. Formoso, P. Ferroni, L. Bucciarelli, N. Michetti, C. Clissa, G. Ciabattoni, A. Consoli and G. Davì: Soluble RAGE in type 2 diabetes: association with oxidative stress. *Free Radic Biol Med* 15, 511-518 (2007)

65. N. Grossin, M.P. Wautier, T. Meas, P.J. Guillausseau, P. Massin and J.L. Wautier: Severity of diabetic microvascular complications is associated with a low soluble RAGE level. *Diabetes Metab* 34, 392-395 (2008)

66. J.M. Forbes, M.E. Cooper, V. Thallas, W.C. Burns, M.C. Thomas, G.C. Brammar, F. Lee, S.L. Grant, L.A. Burrel, G. Jerums and T.M. Osicka: Reduction of the accumulation of advanced glycation end products by ACE inhibition in experimental diabetic nephropathy. *Diabetes* 51, 3274-3282 (2002)

67. H.L. Tam, S.W. Shiu, Y. Wong, W.S. Chow, D.J. Betteridge and K.C. Tan: Effects of atorvastatin on serum soluble receptors for advanced glycation end-products in type 2 diabetes. *Atherosclerosis* (2009)

68. K.C. Tan, W.S. Chow, A.W. Tso, A. Xu, H.F. Tse, R.L. Hoo, D.J. Betteridge and K.S. Lam: Thiazolidinedione increases serum soluble receptor for advanced glycation end-products in type 2 diabetes. *Diabetologia* 50, 1819-1825 (2007)

69. J. Miura, Y. Yamamoto, M. Osawa, T. Watanabe, H. Yonekura, Y. Uchigata, H. Yamamoto and Y. Iwamoto: Endogenous secretory receptor for advanced glycation endproducts levels are correlated with serum pentosidine and CML in patients with type 1 diabetes. *Arterioscler Thromb Vasc Biol* 27, 253-254 (2007)

70. T. Gohda, M. Tanimoto, J.Y. Moon, H. Gotoh, T. Aoki, M. Matsumoto, T. Shibata, I. Ohsawa, K. Funabiki and Y. Tomino: Increased serum endogenous secretory receptor for advanced glycation end-product (esRAGE) levels in type 2 diabetic patients with decreased renal function. *Diabetes Res Clin Pract* 81, 196-201, (2008)

71. M.L. Macrovecchio, C. Giannit, R.N. Dalton, B. Widmer, F. Chiarelit and D.B. Dunger: Reduced endpgenous secretory receptor for advanced glycation end products (esRAGE) in young people with type 1 diabetes developing microalbuminuria. *Diabetic Med* 26, 815-819 (2009)

72. N. Katakami, M. Matsuhisa, H. Kaneto, T.A. Matsuoka, K. Sakamoto, Y. Nakatani, K. Ohtoshi, R. Hayaishi-Okano, K, Kosugi, M. Hori and Y. Yamazaki: Decreased endogenous secretory advanced glycation end product receptor in type 1 diabetic patients. *Diabetes Care* 28, 2716-2721 (2005)

73. S. Sakurai, Y. Yamamoto, H. Tamei, H. Matsuki, K. Obata, L. Hui, J. Miura, M. Osawa, Y. Uchigata, Y. Iwamoto, T. Watanabe, H. Yonekura and H. Yamamoto: Development of an ELISA for esRAGE and its application to type 1 diabetic patients. *Diabetes Res Clin Pract* 73, 158-165 (2006)

74. N. Katakami, M. Matsuhisa, H. Kaneto, T.A. Matsuoka, K. Sakamoto, Y. T. Yasuda, Y. Umayahara, K. Kosugi and Y. Yamazaki: Serum endogenous secretory RAGE level is an independent risk factor for the progression of carotid atherosclerosis in type 1 diabetes. *Atherosclerosis* 204, 288-292 (2009)

75. N. Katakami, M. Matsuhisa, H. Kaneto and Y. Yamazaki: Serum endogenous secretory RAGE levels are inversely associated with carotid IMT in type 1 diabetic patients. *Atherosclerosis* 190, 22-23 (2007)

76. H. Koyama, T. Shoji, H. Yokoyama, K. Motoyama, K. Mori, S. Fukumoto, M. Emoto, T. Shoji, H. Tamei, H. Matsuki, S. Sakurai, Y. Yamamoto, H. Yonekura, T. Watanabe, H. Yamamoto and Y. Nishizawa: Plasma level of endogenous secretory RAGE is associated with components of the metabolic syndrome and atherosclerosis. *Arterioscler Thromb Vasc Biol,* 25, 2587-2593 (2005)

77. L. Lu, L.J. Pu, Q. Zhang, L.J. Wang, S. Kang, R.Y. Zhang, Q.J. Chen, J.G. Wang, R. de Caterina and W.F. Shen: 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* 206, 540-545 (2009)

78. K.M. Choi, H.J. Yoo, H.Y. Kim, K.W. Lee, J.A. Seo, S.G. Kim, N.H. Kim, D.S. Choi and S.H. Basik: Association between endogenous secretory RAGE, inflammatory markers and arterial stiffness. *Int J Cardiology* 132, 96-101 (2009)

79. P.M. Humpert, G. Papadopoulos, K. Schaefer, Z. Djuric, I. Konrade, M. Morcos, P.P. Nawroth and A. Biehaus: sRAGE and esRAGE are not associated with peripheral or autonomic neuropathy in type 2 diabetes. *Horm Metab Res* 39, 899-902 (2007)

80. G. Basta, S. Berti, F. Cocci, G. Lazzerini, S. Parri, A. Papa, D. Battaglia, V. Lubrano, S. Del Turco, M. Ravani, A. Rizza, R. De Caterina, P. Marraccini and A. Mazzone: Plasma N-epsilon- (carboxymethyl)lysine levels are associated with the extent of vessel injury after coronary arterial stenting. *Coron Artery Dis* 19, 299-305 (2008)

81. G. Basta, M. Castagnini, S. Del Turco, M.C. Epistolato, P. Righini, G.M. Sangiorgi, R. De Caterina and P. Tanganelli: High plasma levels of the soluble receptor for advanced glycation endproducts in patients with symptomatic carotid atherosclerosis. *Eur J Clin Invest* 39, 1065-1072 (2009)

82. Y. Kotyama, Y. Takeishi, T. Niizeki, S. Suzuki, T. Kitahara, T. Sasaki and I. Kubota: Soluble receptor for

advanced glycation end products (sRAGE) is a prognostic factor for heart failure. *J Card Fail* 14, 133-129 (2008)

83. J.D. Christie, C.V. Shah, S.M. Kawut, N. Mangalmurti, D.J. Lederer, J.R. Sonett, V.N. Ahya, S.M. Palmer, K. Wollie, V. Lama, P.D. Shah, A. Shah, A. Weinacker, C.S. Deutschman, B.A. Kohl, E. Demissie, S. Bellamy and L.B. Ware for the Lung Transplant Outcomes Group: Plasma levels of receptor for advanced glycation end products, blood transfusion, and risk of primary graft dysfunction. *Am J Respir Cri Care Med* 180, 1010-1015 (2009)

84. N. Mahajan, N. Malik, A. Bahl and V. Dhawan: Receptor for advanced glycation end products (RAGE) and its inflammatory ligand EN-RAGE in non-diabetic subjects with pre-mature coronary artery disease. *Atherosclerosis* 207, 597-602 (2009)

85. C. Falcone, E. Emanuele, A. D'Angelo, M.P. Buzzi, C. Belvito, M. Cuccia and D. Geroldi: Plasma levels of soluble receptor for advanced glycation end products and coronary artery disease in nondiabetic men. *Arterioscler Thromb Vasc Biol* 25, 1032-1037 (2005)

86. K.H. Chiang, P.H. Huang, S.S. Huang, T.C. Wu, J.W. Chen and S.J. Lin: Plasma levels of soluble receptor for advanced glycation end products are associated with endothelial function and predict cardiovascular events in nondiabetic patients. *Coronary Artery Dis* 20, 267-273 (2009)

87. A. Fukami, H. Adachi, S. Yamagishi, T. Matsui, S. Ueda, K. Nakamura, M. Enomoto, M. Otsuka, S. Kumagae, Y. Nanjo, E. Kumagai, E. Esaki, K. Murayama, Y. Hirai and T. Imaizumi: Factors associated with serum high mobility group box 1 (HMGB1) levels in a general population. *Metabolism* 58, 1688-1693 (2009)

88. A.M. Schmidt, S.D. Yan, S.F. Yan and D.M. Stern: The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. *J Clin Invest* 108, 949-955 (2001)

89. A. Soro-Paavonen, A.M. Watson, J. Li, K. Paavonen, A. Koitka, A.C. Calkin, D. Bari, M.T. Coughlan, B.G. Drew, G.I. Lancaster, M. Thomas, J.M. Forbes, P.P. Nawroth, A. Bierhaus, M.E. Cooper and K.A. Jandeleit-Dahm: Receptor for advanced glycation end products (RAGE) deficiency attenuates the development of atherosclerosis in diabetes. *Diabetes* 57, 2461-2469 (2008)

90. O. Hori, J. Brett, T. Slattery, R. Cao, J. Zhang, J.X. Chen, M. Nagashima, E.R. Lundh, S. Vijay, D. Nitechi, J. Morser, D. Stern and A.M. Schmidt: The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin. Mediation of neurite outgrowth and co-expression of rage and amphoterin in the developing nervous system. *J Biol Chem* 270, 25752-25761 (2005)

91. M. Takeuchi, Z. Makita, R. Bucala, T. Suzuki, T. Koiek and Y. Kameda: Immunological evidence that non-carboxymethyllysine advanced glycation end-products are produced from short chain sugars and dicarbonyl compounds *in vivo*. *Mol Med* 6, 114-125 (2000)

92. D. Geroldi, C. Falcone, E. Emanuele, A. D'Angelo, M. Calcagnino, M.P. Buzzi, G.A. Scioli and R. Fogari: Decreased plasma levels of soluble receptor for advanced glycation end-products in patients with essetial hypertension. *J Hypertension* 23, 1725-1729 (2005)

93. K. Nakamura, H. Adachi, T. Matsui, Y. Kurita, M. Takeuchi and S. Yamagishi: Independent determinants of soluble form of receptor for advanced glycation end products in elderly hypertensive patients. *Metabolism* 58, 421-425 (2009)

94. T. Nakamura, E. Sato, N. Fujiwara, Y. Kawagoe, Y. Ueda, T. Suzuki, S. Yamada, M. Takeuchi, K. Fukami, S. Ueda, H. Adachi, T. Matsui, S. Okuda and S. Yamagishi: Positive association of serum levels of advanced glycation end products and high mobility group box-1 with asymmetric dimethylarginine in nondiabetic chronic kidney disease patients. *Metabolism* 58, 1624-1628 (2009)

95. M. Kalousová, M. Hodková, M. Kazderová, J. Fialová, V. Tesar, S. Dusilová-Sulková and T. Zima: Soluble receptor for advanced glycation end products in patients with decreased renal function. Am J Kidney Dis 47, 406-411 (2006)

96. G. Basta, D. Leonardis, F. Mallamaci, S. Cutrupi, P. Pizzini, L. Gaetano, R. Tripepi, G. Tripepi, R. De Caterina and C. Zoccali: Circulating soluble receptor of advanced glycation end product inversely correlates with atherosclerosis in patients with chronic kidney disease. *Kidney Int* (2009 in press)

97. S. Gross, R.M. van Ree, L.H. Oterdoom, A.P. de Vries, W.J. van Son, P.E. de Jong, G.J. Navis, M.W. Zuurman, A. Bierhaus, R.O. Gans and S.J. Bakker: Low levels of sRAGE are associated with increased risk for mortality in renal transplant recipients. *Transplantation* 84, 659-663 (2007)

98. H. Koyama, T. Shoji, S. Fukumoto, K. Shinohara, T. Shoji, M. Emoto, K. Mori, H. Tahara, E. Ishimura, R. Kakiya, T. Tabata, H. Yamamoto and Y. Nishizawa: Low circulating endogenous secretory receptor for AGEs predicts cardiovascular mortality in patients with end-stage renal disease. *Arterioscler Thromb Vasc Biol* 27,147-153 (2007)

99. E. Emanuele, A. D'Angelo, C. Tomaino, G. Binetti, R. Ghidoni, P. Politi, L. Bernardi, R. Maletta, A.C. Bruni and D. Geroldi: Circulating levels of soluble receptor for advanced glycation end products in Alzheimer disease and vascular dementia. *Arch Neurol* 62, 1734-1736 (2005)

100. R. Ghidoni, L. Benussi, M. Glionna, M. Franzoni, D. Geroldi, E. Emanuele and G. Binetti: Decreased plasma levels of soluble receptor for advanced glycation end products in mild cognitive impairment. *J Neural Transm* 115, 1047-1050 (2008)

101. D. Geroldi, C. Falcone, P. Minoretti, E. Emanuele, M. Arra and A. D'Angelo: High levels of soluble receptor for advanced glycation end products may be a marker of extreme longevity in humans. *J Am Geriatr Soc* 54, 1149-1150 (2006)

102. J. Iłzecka: Serum-soluble receptor for advanced glycation end product levels in patients with amyotrophic lateral sclerosis. *Acta Neurol Scand* 120, 119-122 (2009)

103. Z. Sternberg, B. Weinstock-Guttman, D. Hojnacki, P. Zamboni, R. Zivadinov, K. Chadha, A. Lieberman, L. Kazim, A. Drake, P. Rocco, E. Grazioli and F. Munschauer: Soluble receptor for advanced glycation end products in multiple sclerosis: a potential marker of disease severity. *Mult Scler* 14, 759-763 (2008)

104. R. Pullerits, H.F. d'Elia, A. Tarkowski and H. Carlsten: The decrease of soluble RAGE levels in rheumatoid arthritis patients following hormone replacement therapy is associated with increased bone mineral density and diminished bone/cartilage turnover: a randomized controlled trial. *Rhematology (Oxford)* 48, 785-790 (2008)

105. R. Pullerits, M. Bokarewa, L. Dahlberg and A. Tarkowski: Decreased levels of soluble receptor for advanced glycation end products in patients with rheumatoid arthritis indicating deficient inflammatory control. *Arthritis Res Ther* 7, R817-824 (2005)

106. Y.S. Chen, W. Yan, C.L. Geczy, M.A. Brown and R. Thomas: Serum levels of soluble receptor for advanced glycation end products and of S100 proteins are associated with inflammatory, autoantibody and classical risk markers of joint and vascular damage in rheumatoid arthritis. *Arthritis Res Ther* 11, R39 (2009)

107. A. Yoshizaki, K. Komura, Y. Iwata, F. Ogawa, T. Hara, E. Muroi, M. Takenaka, K. Shimizu, M. Hasegawa, M. Fujimoto and S. Sato: Clinical significance of serum HMGB-1 and sRAGE levels in systemic sclerosis: association with disease severity. *J Clin Immunol* 29, 180-189 (2009)

108. H. Wittkowski, K. Hirono, F. Ichida, T. Vogl, F. Ye, X. Yanlin, K. Saito, K. Uese, T. Miyawaki, D. Viemann, J. Roth and D. Foell: Acute Kawasaki disease is associated with reverse regulation of soluble receptor for advance glycation end products and its proinflammatory ligand S100A12. *Arthritis Rheum* 56, 4174-4181 (2007)

109. C. Stewart, S. Cha, R.M. Caudle, K. Berg and J. Katz: Decreased levels of soluble receptor for advanced glycation end products in patients with primary Sjögren's syndrome. *Rheumatol Int* 28, 771-776 (2008)

110. T. Nakamura, E. Sato, N. Fujiwara, Y. Kawagoe, T. Suzuki, Y. Ueda, S. Yamada, S. Shoji, M. Takeuchi, S. Ueda, T. Matsui, H. Adachi, T. Matsui, S. Okuda and S. Yamagishi: Circulating levels of advanced glycation end products (AGE) and interleukin-6 (IL-6) are independent determinants of serum asymmetric dimethylarginine (ADMA) levels in patients with septic shock. *Pharm Res* 60, 515-518 (2009)

111. C. Bopp, S. Hofer, J. Weitz, A. Bierhaus, P.P. Nawroth, E. Martin, M.W. Büchler and M.A. Weigand: sRAGE is elevated in septic patients and associated with patients outcome. *J Surg Res* 47, 79-83 (2008)

112. Y. Yilmaz, E. Ulukaya, O.O. Gul, M. Arabul, C.B. Gul, O. Atug, A.Y. Oral, S. Aker, E. Dolar: Decreased plasma levels of soluble receptor for advanced glycation endproducts (sRAGE) in patients with nonalcoholic fatty liver disease. *Clin Biochem* 42, 802-807, (2009)

113. G, Basta, A.I. Corciu, A. Vianello, S. Del Turco, I. Foffa, T. Navarra, D. Chiappino, S. Berti, A. Mazzone: Circulating soluble receptor for advanced glycation end-product levels are decreased in patients with calcific aortic valve stenosis. *Atherosclerosis* doi:10.1016/j.atherosclerosis.2009.12.029 (2010)

114. P, Tesarová, M. Kalousová, M. Jáchymová, O. Mestek, L. Petruzelka, T. Zima: Receptor for advanced glycation end products (RAGE)--soluble form (sRAGE) and gene polymorphisms in patients with breast cancer. *Cancer Invest* 25, 720-725 (2007)

115. S, Kobayashi, H. Kubo, T. Suzuki, K. Ishizawa, M. Yamada, M. He, Y. Yamamoto, H. Yamamoto, H. Sasano, H. Sasaki, S. Suzuki: Endogenous secretory receptor for advanced glycation end products in non-small cell lung carcinoma. *Am J Respir Crit Care Med* 175, 184-189, (2007)

116. A, Germanová, M. Koucký, Z. Hájek, A. Pařízek, T. Zima, Kalousová M: Soluble receptor for advanced glycation end products in physiological and pathological pregnancy. *Clin Biochem* in press (2010)

117. M. Pertyńska-Marczewska, E. Głowacka, M. Sobczak, K. Cypryk, J. Wilczyński: Glycation endproducts, soluble receptor for advanced glycation endproducts and cytokines in diabetic and non-diabetic pregnancies. *Am J Reprod Immunol* 61, 175-182, (2009)

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