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Endogenous soluble receptor of advanced glycation end-products (esRAGE) is negatively associated with vascular calcification in non-diabetic hemodialysis patients

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Abstract
Background Advanced glycation end-products (AGE) accumulate in CKD and may predispose to cardiovascular disease by inducing inflammatory and oxidant stress in the vascular endothelium. Soluble forms of the receptor for AGE (RAGE) may be protective against these effects by binding AGE in the soluble phase. Accumulating evidence suggests a protective role of soluble RAGE against vascular calcification. This study investigates the association between endogenous soluble RAGE (esRAGE) and vascular calcification in hemodialysis patients.

Methods We studied 65 non-diabetic hemodialysis patients, on 3×4 h dialysis schedule, and 19 controls. Serum levels of esRAGE, hsCRP, parathormone, lipids, calcium, and phosphorus were measured. Aortic calcification index (ACI) was measured using non-contrast CT of the abdominal aorta.
Results Aortic calcification was detected in 64 out of 65 hemodialysis patients. Levels of esRAGE were lower in hemodialysis patients (278 pg/ml, SD 101.1) than in controls (443 ± 109 pg/ml; $P = 0.001$). ACI correlated negatively in stepwise multivariate analysis with esRAGE ($P = 0.002$) and positively with hsCRP (<0.0001), systolic blood pressure ($P < 0.0001$) and dialysis vintage ($P = 0.05$); $R^2 = 0.65$.
Conclusion Levels of esRAGE were low among hemodialysis patients and correlated negatively with ACI.

Keywords Vascular calcification · RAGE · Inflammation · CKD-MBD · hsCRP · Advanced glycation end-products

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Introduction

Vascular calcification in patients with chronic kidney disease (CKD) has drawn much attention as an index of cardiovascular disease and a predictor of mortality, particularly in hemodialysis (HD) patients. Several risk factors for vascular calcifications have been

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incriminated, such as age, systolic blood pressure, diabetes, hyperphosphatemia, and the use of high dialysate calcium concentrations. None of these factors, however, completely explains this phenomenon [1–5].

The process of vascular calcification in CKD is not a passive process of calcium and phosphate deposition, and several active mechanisms have been implicated, including elevated levels of fibroblast growth factor-23 [6] and low levels of matrix gla protein and fetuin [7, 8]. Oxidative stress and amplified inflammatory activity have also been associated with accelerated atherosclerosis and vascular calcification [9].

Advanced glycation end-products (AGE) accumulate in patients with CKD as a result of increased oxidative and carbonyl stress, hyperglycemia, dyslipidemia, as well as decreased renal clearance [10]. They are thought to play a role in tissue aging, as well as inflammatory and oxidative stress, by binding to their cell-bound receptor and by cross-linking tissue proteins. AGE have been linked to the progression of renal disease, atherosclerosis, ventricular hypertrophy and mortality in late stages of CKD [10–12]. Several forms of soluble receptors of AGE (RAGE) were identified and considered as possible decoys that bind AGE and prevent them from inducing tissue damage. Reduced levels of soluble RAGE have been associated with atherosclerosis and cardiovascular disease in diabetics and non-diabetics, as well as in CKD patients. Studies performed on animal models have reported success of therapeutic interventions using genetically engineered soluble RAGE against diabetic micro- and macrovascular disease, among other diseases [11, 13–18].

When it comes to vascular calcification, AGE can promote calcification in cultures of bovine microvascular pericytes [19]. Moreover, incubation of rodent aortic tissue with AGE provoked the calcification of vascular smooth muscles, and this effect was partially inhibited by the addition of soluble RAGE [20]. In a study on type 2 diabetic patients, esRAGE levels were negatively associated with both inflammatory markers and vascular stiffness [16], a surrogate marker of vascular calcification [3, 21]. More recently, it was shown that levels of soluble RAGE were significantly lowered in patients with calcific aortic valve stenosis [22]. However, so far, no clinical study has examined the presence of a possible link between soluble isoforms of RAGE and vascular calcification in CKD.

This study was performed to investigate the association between aortic vascular calcification, measured by non-contrast CT scans of the abdominal aorta, and levels of the spliced, C-terminal truncated isoform of soluble RAGE (esRAGE) in CKD stage 5 HD patients.

Subjects and methods

Patients and controls

The study population included 65 CKD stage 5 patients on regular HD as 3 sessions/week, 4 h/session, using polysulfone dialysers and calcium dialysate of 1.5 mEq/l. Nineteen age- and gender-matched controls were enrolled; they had no evidence of CKD as shown by an eGFR >60 ml/min, absence of proteinuria or active urinary sediment, as well as normal kidney size and shape on abdominal ultrasound scans. Controls had a blood pressure ≤130/80 mm Hg and had no evidence of ischemic heart disease, as proven by history and electrocardiography, and no clinical evidence of previous strokes or peripheral vascular disease. Subjects receiving oral anticoagulants and diabetics were excluded from the study. None of the study participants had evidence of active autoimmune disease or evident infection during the study.

Patient consents for participation in the study and approval by local ethics committee were obtained. It is noteworthy to state that the CKD patients were included and described in a previous study [6]; however, we selected a new control group because some of the previous controls had cardiovascular diseases that could affect esRAGE levels [13, 18].

Laboratory parameters

Fasting pre-dialysis blood samples were obtained and stored at −70°C. Serum levels of esRAGE were determined using an ELISA kit (provided by Daiichi Fine Chemical Co Ltd, Takaoka, Japan, and distributed by B-Bridge International Inc). High-sensitivity C-reactive protein (hsCRP) was measured by an ELISA-based kit (Oxis International Inc, CA; USA). Intact parathormone levels were determined by

enzyme-amplified sensitivity immunoassay (Roche diagnostics, In, USA). Pre-dialysis levels of serum calcium, phosphorus, creatinine, lipid profile, and albumin were also measured.

Aortic calcification index

Aortic calcification was evaluated only in the CKD patients, using the aortic calcification index (ACI). This is a semiquantitative technique involving non-contrast abdominal CT scans, validated in several previous studies [6, 23, 24]. ACI was determined as follows: ten consecutive slices of the abdominal aorta at 1-cm intervals were subdivided radially into 12 sectors. The number of sectors showing areas of calcification (≥100H.U.) were counted and divided by 120, then multiplied by 100 to be expressed as a percentage, with an intra-observer variability of 3.7% [6, 23, 24], Fig. 1.

Statistics

Statistical Package for Social Sciences (SPSS) version 7.5 was used for data analysis. Data were summarized as mean, standard deviation, and median. Comparison between groups was performed by Student's *t* test; Mann–Whitney U test was used for the analysis of non-symmetrically distributed data. Spearman's correlation was used for bivariate analysis. Multiple regression and stepwise multiple regression analysis were performed to study relationships between ACI and other factors.

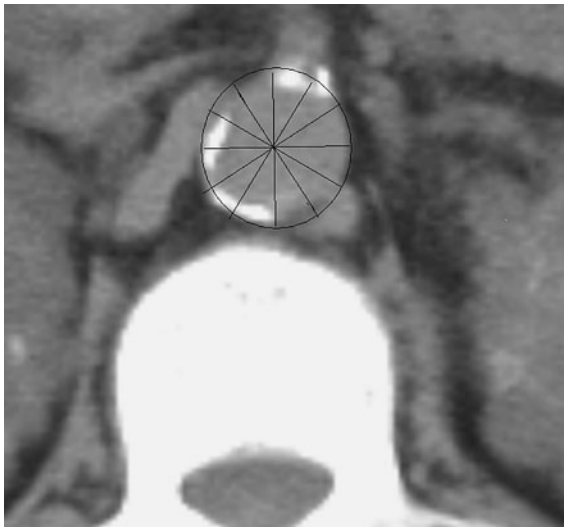

Fig. 1 Aortic calcification score 6/12 in this CT cut

Results

The characteristics of our study population are summarized in Table 1. Aortic calcification was present in 64 out of 65 HD patients. Approximately 70% of our patients were on calcium-based phosphate binders and 30% were on alphacalcidol during the 3 months preceding the study. No significant differences were noted in the ACI of those on calcium or alphacalcidol versus those not receiving the drugs.

By definition, all patients in the CKD group were confirmed to be end-stage renal disease patients undergoing regular HD therapy. Out of these, 19 patients had been on dialysis for less than 2 weeks. These incident patients had higher levels of esRAGE than the prevalent dialysis patients who were on dialysis for more than 6 months (mean, 384; SD 78.5 vs. mean, 234; SD 73 pg/ml, $P = 0.002$). Further details and comparisons of the two subgroups have been presented elsewhere [6].

Association between esRAGE and ACI

The association between esRAGE and ACI was tested in various models, including an initial bivariate analysis and three multivariate regression models.

In bivariate analysis, levels of esRAGE correlated negatively with ACI ($R = -0.6, P < 0.0001$) (Fig. 2). ACI also correlated with dialysis vintage, $P < 0.0001$, $R = 0.44$; systolic blood pressure, $P = 0.001$, $R = 0.4$; and serum cholesterol $P = 0.027$, $R = 0.27$.

Multiple regression analysis was performed to detect the independence of this relationship after adjustment for factors that showed a correlation with ACI in bivariate analysis and other classical confounding factors associated with vascular calcification, i.e. age, dialysis vintage, cholesterol, triglycerides, calcium, phosphate, and systolic blood pressure (Table 2). ACI was still significantly associated with esRAGE ($\beta = -0.49$, $P < 0.0001$).

Appreciating the fact that esRAGE is a marker of inflammation [14, 16, 18], we further analyzed its association with ACI in a separate multivariate model after correction for another sensitive marker of

Table 1 Characteristics of the studied chronic kidney disease patients (CKD) and controls

	CKD	Controls	*P*-value
Number	65	19	
Age	50 ± 11.5 (50; 19–73)	48.5 ± 6.5 (45; 24–70)	0.7
Sex (males)	28 (43%)	13 (68%)	0.5
Smokers (number)	15 (23%)	5 (26%)	0.6
Dialysis vintage (months)	31.7 ± 39.8 (18; 0.1–204)	–	
Systolic BP (mmHg)	150 ± 20.2 (150; 90–190)	124 ± 8.9 (130; 110–130)	0.002
Diastolic BP (mmHg)	91 ± 11.3 (90; 60–110)	76 ± 5.4 (80; 65–80)	0.0001
Cholesterol (mg/dl)	154.9 ± 52 (146; 36–323)	164.3 ± 41.7 (170; 100–223)	0.19
Triglycerides (mg/dl)	127 ± 63.9 (102; 50–349)	110.5 ± 38.3 (102; 41–174)	0.5
Alphacalcidol*	19 (29.2%)	0	
Sevelamer, cinacalcet*	0	0	
Erythtopoeitin*	35 (53.8%)	0	
CaCO3*	46 (70.7%)	0	
Calcium (mg/dl)	8.9 ± 1 (8.9; 6.2-10.8)	N/A**	
Phosphate (mg/dl)	6.8 ± 2.7 (6.2; 3.1–16.7)	N/A**	
Hemoglobin (g/dl)	10.1 ± 1.3 (10.6; 8.5–12.3)	N/A**	
Albumin (g/dl)	3.4 ± 0.6 (3.4; 1.9–4.6)	N/A**	
Parathormone	314.7 ± 368.2 (169.4; 13.2–1,900)	N/A**	
ACI (%)	14.1 ± 12 (11.7; 0–67.5)	N/A**	
esRAGE (pg/ml)	278 ± 101.1 (278; 145–489)	443 ± 109 (460; 200–670)	0.001
hsCRP (ug/ml)	6.8 ± 4.7 (5.3; 0.45–21)	1.3 ± 0.8 (1.3; 0.5–3.2)	<0.0001
CVD***	20 (29.4%)	0	

Figures are reported as mean ± SD and (*median; range)* in brackets

* Number of patients using the drug within preceding 3 months

** N/A data not available

*** Number of patients with cardiovascular disease (defined as documented clinical events related to ischemic stroke, ischemic heart disease, and/or peripheral vascular disease)

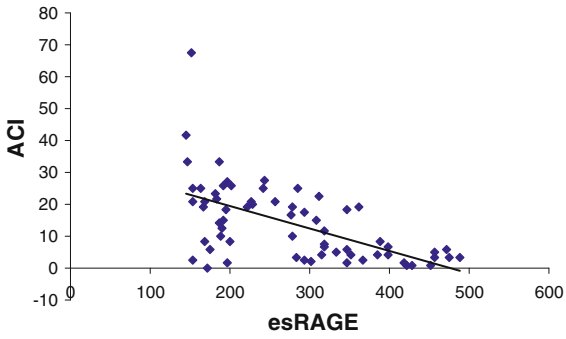

Fig. 2 Linear regression of esRAGE and aortic calcification index, $R = -0.6$, $P < 0.0001$

inflammation, hsCRP, in addition to the previous risk factors. The correlation coefficient for the association of esRAGE with ACI was reduced ($\beta = -0.24$) but remained significant, $P = 0.02$ (Table 3). This was reassessed by stepwise multiple regression analysis, which confirmed the significant independent association of ACI with both esRAGE ($P = 0.002$) and hsCRP ($P < 0.0001$) (Table 4).

Factors associated with esRAGE

Bivariate analysis of data from HD patients showed that, in addition to ACI, the following factors correlated negatively with esRAGE: hsCRP $R = -0.47$, $P < 0.0001$; dialysis vintage $R = -0.43$, $P < 0.0001$; and parathyroid hormone $R = -0.27$, $P = 0.03$.

Discussion

This study was performed on non-diabetic HD patients and showed that levels of esRAGE

Table 2 Multiple regression analysis of factors associated with aortic calcification index (model excluding hsCRP), R^2 0.55

	β	P	95% CI
esRAGE	−0.49	<0.0001	−0.086–0.034
Systolic BP	0.43	<0.0001	0.1–0.4
Age	0.29	0.014	0.07–0.52
Vintage	0.23	0.04	0.002–0.14
Phosphate	0.18	0.13	−0.24–2
Parathormone	−0.06	0.6	−0.01–0.005
Triglycerides	−0.07	0.5	−0.05–0.03
Cholesterol	−0.02	0.8	−0.06–0.05
Calcium	0.036	0.72	−1.9–2.8

Table 3 Multiple regression analysis of factors associated with aortic calcification index (model including hsCRP), R^2 0.69

	β	P	95% CI
hsCRP	0.48	<0.0001	0.7–1.7
Systolic BP	0.39	<0.0001	0.13–0.34
esRAGE	−0.24	0.02	−.05–0.005
Vintage	0.3	0.02	0.01–0.13
Phosphate	0.15	0.14	−0.2–1.7
Age	0.13	0.17	−0.8–3.5
Parathormone	−0.113	0.22	−0.01–0.003
Triglycerides	−0.1	0.24	−0.05–0.04
Cholesterol	−0.04	0.7	−0.06–0.04
Calcium	0.1	0.2	−0.8–3.3

are low and negatively associated with aortic calcification.

AGE are products of glycation and oxidation of lipids and proteins that act as ligands of RAGE, an endothelial multi-ligand receptor that also binds amphoterin, S100/crangranulins, and amyloid β-peptides. The interaction of cell surface RAGE with its ligands triggers reactive oxygen species, promotes the release of growth factors, activates NF-κB pathway, and increases the expression of inflammatory molecules like monocyte chemoattractant protein-1 and adhesion molecules [14, 18, 25–27]. The consequences of this interaction are all involved in the pathogenesis of diabetic micro- and macrovascular complications and are associated with atherosclerosis in diabetics and non-diabetics [11, 14, 26–28].

Table 4 Stepwise multiple regression analysis of factors associated with aortic calcification index

	β	Significance; P	95% CI
$R^2 = 0.65$			
*hs*CRP	0.48	<0.0001	0.76–1.7
Systolic *BP*	0.4	<0.0001	0.1–0.3
esRAGE	−0.28	0.002	−0.056–0.013
Vintage	0.16	0.05	0.001–0.098

Circulating soluble forms of RAGE span various isoforms including the spliced C-terminal truncated form (esRAGE). These soluble isoforms are thought to act as decoy ligands in plasma, exerting protective roles by competing with the cell-bound receptor for its ligands. Patients with carotid and coronary atherosclerosis have low levels of esRAGE that inversely correlate with disease severity [13–18, 29]. In pre-dialysis CKD patients, carotid intima media thickness was negatively correlated with soluble RAGE with steep covariance slopes [12]. Moreover, levels of soluble RAGE are low in several chronic inflammatory diseases and are negatively associated with markers of inflammation, including hsCRP [14, 16, 29, 30]. We found levels of esRAGE to be lower in CKD patients, in contrast with several preceding studies [12, 17, 31]. This may be explained by the florid inflammatory status of our patients, as exhibited by the levels of hsCRP that were more than 5 times higher than in controls. Nonetheless, our study population demonstrated unusually intense vascular disease, which may have contributed to this finding; all but one patient, i.e., 98%, had evidence of aortic calcification. Polymorphisms of the RAGE gene could also play a role in the disparity of levels of esRAGE among subjects from different populations [32]. Indeed, the fact that levels of AGE are elevated in CKD [10, 27], which could presumably consume soluble RAGE, makes our finding of low levels of esRAGE in CKD patients an intuitively anticipated finding.

Interestingly, the process of vascular calcification, involves inflammatory and oxidant stresses [9, 33, 34]. We found robust relationships between hsCRP, vascular calcification, and esRAGE. Thus, esRAGE may merely be another marker of inflammation that correlates with vascular calcification. However, the association of esRAGE with ACI was still significant after

correction for the classic, sensitive inflammatory marker hsCRP, which permits an alternative interpretation. It is possible that the consequences of the interaction between endothelial RAGE and its ligands may have a pathogenic role in vascular calcification; an effect that could be neutralized by soluble RAGE. Experimental and clinical evidence, as mentioned earlier, is rapidly accumulating and pointing to the pro-calcific effect of AGE on blood vessels and to the protective role of soluble RAGE, with a promise of a potential therapeutic option [16, 19, 20, 22].

Last but not least, we wish to comment on two points. First, we did not find a correlation between ACI levels and phosphate, as this relationship could be missed with single phosphate measurements in relatively small numbers of patients [6, 9, 35]. Second, we found a negative correlation between parathormone and esRAGE, but we cannot speculate on its significance as we only performed a bivariate analysis, since studying the factors associated with esRAGE was not controlled for and was not the aim of this study. The significance of this finding probably needs further investigation.

To our knowledge, this is the first clinical study to investigate the link between soluble RAGE and calcification of the blood vessels in general and particularly in CKD patients. We excluded diabetic patients, as diabetes is a confounding risk factor for vascular calcification [23, 24] and may alter the levels of esRAGE [13, 18]. The spliced isoform of RAGE, esRAGE, was specifically measured, rather than the commonly measured total soluble RAGE, as it seems to be more strongly correlated with atherosclerosis and has produced less conflicting results in various studies under different settings [15, 18, 36].

Limitations of this study are its cross-sectional nature, the relatively small number of patients and controls involved, and the absence of an interventional approach to assess the clinical value of the associations that we found. These limitations were partially overcome by the use of CT scans to monitor vascular calcification, which is semiquantitative and more accurate than conventional radiography [37], thus giving a better chance to demonstrate positive research findings in a relatively small number of patients.

Conclusions

We demonstrated that vascular calcification is a common finding in HD patients, as shown by CT scans of the abdominal aorta. We also showed that levels of esRAGE are low among these patients and are negatively correlated with the aortic calcification index, independently of the severity of systemic inflammation (as estimated by hsCRP).

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Conflict of interest The authors have no conflict of interests to declare regarding the results of this study.

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