Low Levels of sRAGE Are Associated With Increased Risk for Mortality in Renal Transplant Recipients

Sascha Gross,[1,2] Rutger M. van Ree,[1] Leendert H. Oterdoom,[1] Aiko P.J. de Vries,[1] Willem J. van Son,[1] Paul E. de Jong,[1] Gerjan J. Navis,[1] Mike W. Zuurman,[1] Angelika Bierhaus,[2] Rijk O.B. Gans,[1] and Stephan J.L. Bakker[1,3]

Objective. Infusion of the soluble form of the receptor for advanced glycation end-products (sRAGE) was protective against atherosclerosis and nephropathy in animal models. In this study we investigated determinants of endogenous sRAGE in renal transplant recipients and whether sRAGE was associated with mortality and graft loss.
Methods and Results. A total of 591 patients participated at a median time of 6 years after transplantation. Independent determinants of sRAGE were mycophenolate mofetil medication ($\beta=-0.21$, $P<0.001$), creatinine clearance ($\beta=-0.15$, $P<0.001$), BMI ($\beta=-0.12$, $P=0.003$) and fasting insulin concentration ($\beta=-0.14$, $P=0.001$). Low sRAGE levels were associated with a 2–3 times higher risk for mortality especially after correction for creatinine clearance ($P=0.006$).
Conclusion. A lack of sRAGE is a risk factor for mortality in renal transplant recipients. The putatively protective role of sRAGE and in particular its association with mycophenolate mofetil usage needs further investigation.

Keywords: Kidney, Risk factor, Advanced glycation end products, Receptor.

(*Transplantation* 2007;84: 659–663)

One-year graft survival after renal transplantation has steadily improved from approximately 40% in the 1970s, to almost 90% between 1998 and 2001 (*1*). Improvements in long-term graft survival, however, still strongly lag behind, especially if improvements in one-year survival are taken into account (*2*). Main reasons are graft failure due to chronic allograft nephropathy (CAN) and patient mortality due to accelerated atherosclerosis (*3*).

Toxic effects of advanced glycation end-products (AGEs) have been implicated in both accelerated atherosclerosis and CAN (*4*, *5*). Increased AGEs may be the consequence of accumulation during the dialysis period prior to transplantation, and a combination of increased production and decreased clearance due to CAN after transplantation (*6*, *7*). AGEs are supposed to exert their toxic effects in part through cross-linking of proteins and in part through eliciting a proinflammatory response upon binding to the receptor for advanced glycation end-products (RAGE) (*8*, *9*). RAGE activation has been shown to trigger the redox-sensitive transcription factor NFκB (*10*, *11*), while activation of NFκB is implicated in the pathophysiology of the inflammatory component of several chronic diseases, including atherosclerosis and posttransplant nephropathy (*12*, *13*).

Soluble isoforms of RAGE (sRAGE) have been shown to antagonize the development of diabetic complications, including nephropathy, disturbed wound-healing and accelerated atherosclerosis, in animal experimental models (*14–18*). High circulating sRAGE concentrations may therefore protect against the toxic effects of AGEs.

The present study aims to investigate cross-sectionally which factors determine circulating sRAGE concentrations in renal transplant recipients, and prospectively whether circulating sRAGE concentrations predict graft loss and mortality in this population.

The current study was part of a larger prospective study, which was incorporated in the Groningen Renal Transplant Outpatient Program, and details of which have been published previously (*19*, *20*). The Institutional Review Board approved the study protocol (METC 01/039), which was in adherence with the Declaration of Helsinki.

Blood was drawn after an 8- to 12-hour overnight fasting period. Plasma sRAGE levels were determined using the Quantikine human RAGE enzyme-linked immunosorbent assay kit (R&D Systems, Wiesbaden-Nordenstadt, Germany). This test employs a mouse monoclonal antibody to the ligand-binding domain of the RAGE protein, and thus recognizes all sRAGE isoforms. The samples had been stored frozen at −80°C in a refrigerator with continuous temperature registration and an automatic temperature alarm. Fasting insulin was determined on an AxSym auto-analyzer (Abbott Diagnostics, Hoofddorp, The Netherlands). Other parameters were determined as described before (*19*, *20*).

Follow-up was complete for all participating patients until June 27, 2006. Duration of follow-up was calculated as the difference between this date and the date of the baseline visit. Follow-up for patients who died with a functioning graft was calculated until the date of death. Graft loss was censored for death and defined as return to dialysis or retransplantation. Follow-up for patients with graft loss was calculated until the date of return to dialysis or retransplantation.

Statistical analyses were performed with SPSS version 12 (SPSS Inc., Chicago, IL). Parametric variables are expressed as mean ± standard deviation, whereas nonparametric variables are given as median (interquartile range), and dichotomous vari-

This work is supported by the German Scientific Organization (DFG) and the Netherlands Organization for Scientific Research (NWO) as part of a collaboration program between the University of Mannheim/Heidelberg, Germany and the University of Groningen, the Netherlands.
[1] Kidney Center, Department of Internal Medicine, University Medical Center Groningen, Groningen, the Netherlands.
[2] Department of Internal Medicine I, University Medical Hospital, Heidelberg, Germany.
[3] Address correspondence to: S.J.L. Bakker, M.D., Ph.D., Department of Internal Medicine, University Medical Center Groningen, P.O. Box 30001, NL-9700 RB Groningen, the Netherlands.
E-mail: s.j.l.bakker@int.umcg.nl
Received 13 March 2007. Revision requested 29 May 2007.
Accepted 6 June 2007.

ISSN 0041-1337/07/8405-659
DOI: 10.1097/01.tp.0000280556.16275.2a

ables are given as percentage. Plasma sRAGE concentration data were categorized into quartiles for univariate and survival analyses. For linear regression analyses, their distribution was normalized by logarithmic transformation. For all analyses, a P value <0.05 was considered to indicate significance.

In the cross-sectional part of our study, groups of putative determinants of sRAGE were analyzed over quartiles of sRAGE using analysis of variance (ANOVA) for parametric variables, the Jonkheere-Terpstra test for non-parametric variables, and the χ^2-test for dichotomous variables. All variables which showed an association with sRAGE with a P value <0.10 were considered for inclusion in further multivariate regression analyses. However, if members of groups were highly correlated to each other ($r \geq 0.50$), only the variables with the strongest relation to sRAGE were included in order to prevent co-linearity and overadjustment in these analyses. Included variables were analyzed in a backward multivariate linear regression analysis in order to allow for assessment of the effect of adjustments. In the prospective part of our analyses, we applied Cox-regression models separately for mortality and death-censored graft loss with quartiles of sRAGE. Potential existence of a curvilinear relationship between sRAGE and end-points was tested in Cox-regression models in which sRAGE and a quadratic term of sRAGE were included as continuous variables.

A total of 591 outpatients (age 51±12 years, 45% females, creatinine clearance 62±22 ml/min) participated at a median (interquartile range) of 6.0 (2.6–11.4) years after transplantation in the baseline measurements of our study. Median (interquartile range) of plasma concentrations of sRAGE were 1,676 (1,231–2,240) pg/ml. Recipient and transplant characteristics for quartiles of sRAGE are shown in Table 1. Concentrations of sRAGE increased significantly with increasing time since transplantation, total cholesterol, low-density lipoprotein (LDL) cholesterol, cold ischemia time, serum creatinine, urinary protein excretion, and use of azathioprine.

Body mass index (standardized beta [β_{st}]$=-0.12$, $P=0.003$), fasting insulin concentration ($\beta_{st}=-0.14$, $P=0.001$), creatinine clearance ($\beta_{st}=-0.15$, $P<0.001$), and mycophenolate mofetil usage ($\beta_{st}=-0.21$, $P<0.001$) were significant independent determinants in the stepwise backward multivariate linear regression analysis of factors associated with sRAGE. Of the potential determinants in Table 1, body mass index (BMI) and waist circumference were strongly correlated ($r=0.81$, $P<0.001$), with BMI having a stronger relation with sRAGE than waist circumference. Total cholesterol was strongly correlated with LDL-cholesterol ($r=0.84$, $P<0.001$), creatinine clearance with serum creatinine ($r=-0.61$, $P<0.001$), and use of mycophenolate mofetil with use of azathioprine ($r=-0.58$, $P<0.001$), with the respective first parameters in these three correlations having the strongest relations with sRAGE.

Prospective follow-up was for 4.2 (3.7–4.6) years, with 72 (12%) deaths and 37 (6.1%) death censored graft losses at 2.5 (1.4–3.6) and 2.3 (0.9–3.2) years of follow-up respectively. Incidences and hazard ratios of crude and multivariate Cox-regression analyses for quartiles of sRAGE are shown in Table 2. Mortality was significantly predicted by baseline sRAGE concentrations in renal transplant recipients, with low concentrations being a risk factor, and higher concentrations being protective. There was a significant curvilinear relationship between sRAGE and mortality ($P=0.04$ for a quadratic term of sRAGE in a Cox regression analyses with sRAGE as a continuous variable), with the lowest hazard ratio for the second quartile of sRAGE (0.39 [0.19–0.79]), and higher hazard ratios for the third and fourth quartiles (0.54 [0.29–1.03] and 0.74 [0.41–1.31], respectively). Figure 1 shows a Kaplan-Meier curve for subjects in the lowest quartile of sRAGE concentrations versus subjects in the three higher quartiles of sRAGE concentrations.

Finally, we performed a multivariate analysis with continuous variables as covariates from which it can be judged which factors were independent predictors of mortality in addition to sRAGE. In this model, sRAGE ($\beta_{st}=-1.05$ per ng/ml, $P=0.004$), sRAGE^2 ($\beta_{st}=0.17$ per ng^2/ml^2, $P=0.006$), creatinine clearance ($\beta_{st}=-0.38$ per 10 ml/min, $P<0.001$), age of the recipient ($\beta_{st}=0.65$ per 10 years, $P<0.001$), C-reactive protein (CRP; $\beta_{st}=0.42$ per $\log_{10}$-transformed mg/l, $P=0.04$), and diabetes mellitus ($\beta_{st}=0.75$ per yes vs. no, $P=0.004$) appeared to be independent predictors of mortality.

Baseline concentrations of sRAGE appeared not predictive of future death-censored graft loss, in neither the crude model nor in the adjusted models.

To the best of our knowledge, this is the first study on sRAGE in renal transplant recipients, and the second prospective study at large. We found use of mycophenolate mofetil, creatinine clearance, fasting insulin concentrations, and body mass index as significant independent determinants of plasma sRAGE concentrations in this population. We furthermore found that low levels of plasma sRAGE are independently associated with an increased risk of mortality in this population. Subjects with intermediate concentrations appeared to have the lowest risk.

Recent studies have shown that augmentation of atherosclerosis and development of nephropathy in diabetic mice can be inhibited by infusion of recombinant sRAGE, a c-terminal truncated soluble isoform of the cell membrane receptor RAGE, which lacks the transmembrane and cytoplasmic domains (*17*, *18*). Consistent with a protective effect of sRAGE in humans, it has been demonstrated in a cross-sectional study that non-diabetic men with established coronary artery disease have significantly lower plasma sRAGE levels than men without coronary artery disease (*21*). Creatinine clearance has been identified as a more important determinant than such factors as prevalent coronary heart disease, hypertension or diabetes mellitus (*22*, *23*). We also found an inverse relation with creatinine clearance. The mechanism underlying the inverse association with creatinine clearance has been implicated glomerular filtration and subsequent tubular processing (*22*, *23*).

We also found mycophenolate mofetil usage, BMI and fasting insulin concentrations as independent determinants of sRAGE. The association with use of mycophenolate mofetil as an immunosuppressive drug has not been reported before. Determination of plasma sRAGE concentration before and after treatment with mycophenolate mofetil in plasma samples taken in intervention studies could resolve whether use of mycophenolate mofetil truly results in a decrease in sRAGE concentrations. The association with BMI and fasting insulin concentrations has not been reported before for sRAGE. However, consistent inverse associations have been reported for endogenous secretory RAGE (esRAGE) (*24–26*). esRAGE is one specific isoform of several different isoforms of pro-

TABLE 1. Baseline characteristics over quartiles of sRAGE plasma concentration

	Quartiles of sRAGE				
	I	II	III	IV	*P* value
N	147	148	148	148	
Range of sRAGE concentration (pg/ml)	386–1230	1231–1675	1676–2240	2241–6750	
Demographics					
Age recipient (years)	51.9±11.8	51.8±11.3	51.1±12.9	51.3±12.4	0.94
Age donor (years)	37±16	36±14	37±15	38±16	0.72
Male sex recipient (%)	55.8	60.8	54.7	47.3	0.13
Male sex donor (%)	47.6	59.5	53.7	58.2	0.16
Time since transplantation (years)	3.9 (1.6–7.9)	6.1 (2.6–12.5)	6.4 (3.1–12.2)	7.5 (4.2–12.2)	<0.001
Body composition recipient					
BMI (kg/m^2)	27.3±4.2	26.2±4.3	25.6±4.4	25.2±4.0	<0.0001
Waist circumference (cm)	101±13	98±14	96±14	94±13	<0.001
Smoking recipient (%)					
Current	19.0	20.3	21.6	27.0	0.36
Never	36.7	34.5	34.5	35.1	0.97
Blood pressure (mm Hg)					
Systolic	153.7±23.3	150.8±23.3	152.6±23.2	154.9±24.8	0.91
Diastolic	90.4±9.1	89.8±9.8	89.9±10.3	89.6±10.5	0.47
Antihypertensive medication (%)	92.5	89.9	82.4	83.1	0.07
Number of antihypertensives	2.07±1.01	1.96±1.16	1.78±1.17	1.80±1.22	0.09
ACE inhibitor (%)	32.7	29.1	25.7	23.0	0.27
β-blocker (%)	65.3	63.5	60.8	57.4	0.53
Hyperglycemia parameters					
Glucose (mmol/l)	4.6 (4.2–5.1)	4.5 (4.0–5.0)	4.5 (4.1–5.0)	4.5 (4.1–5.0)	0.60
Insulin (μU/ml)	13.0 (9.5–18.9)	11.3 (7.8–15.7)	10.5 (8.0–14.5)	10.3 (7.2–14.1)	<0.001
Diabetes mellitus (%)	23.1	16.9	14.2	17.6	0.24
HbA_{1c} (%)	6.7±1.1	6.5±1.1	6.4±1.0	6.5±1.1	0.09
Use of antidiabetic (%)	16.3	12.8	9.5	14.9	0.34
History of cardiovascular disease					
Prior myocardial infarction (%)	7.6	9.5	8.1	7.5	0.92
Use of antiplatelet drugs (%)	21.8	21.6	17.6	17.6	0.66
Lipid parameters (mmol/l)					
Total cholesterol	5.4 (4.8–6.1)	5.6 (4.8–6.1)	5.6 (5.0–6.2)	5.8 (5.2–6.6)	0.001
HDL cholesterol	1.0 (0.9–1.2)	1.0 (0.8–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	0.18
LDL cholesterol	3.5 (2.8–4.0)	3.5 (2.9–4.0)	3.5 (3.0–4.2)	3.6 (3.0–4.3)	0.03
Triglycerides	1.9 (1.3–2.6)	1.9 (1.4–2.6)	2.0 (1.4–2.7)	1.9 (1.6–2.7)	0.14
Use of statins (%)	49.0	51.4	45.9	52.0	0.72
History of kidney failure					
Previous transplantation (%)	6.8	8.8	10.1	14.9	0.13
Prior dialysis duration (months)	33 (17–51)	28 (13–47)	26 (11–47)	25 (12–56)	0.24
Allograft viability					
No dead donor (%)	19.0	11.5	12.8	10.1	0.12
Warm ischemia (min)	35 (30–43)	36 (30–45)	35 (30–45)	36 (30–46)	0.21
Cold ischemia (hours)	20 (13–24)	23 (16–28)	20 (14–27)	24 (18–28)	0.004
Allograft function					
Serum creatinine (μmol/l)	130 (109–150)	132 (110–165)	132 (111–159)	146 (120–187)	0.001
Creatinine clearance (ml/min)	66±21	64±22	62±21	55±23	<0.001
Urinary protein excretion (g/24 hr)	0.2 (0.0–0.4)	0.2 (0.0–0.5)	0.2 (0.0–0.5)	0.3 (0.1–0.7)	0.02
Acute rejection treatment (%)					
High-dose corticosteroids	35.6	43.9	38.2	41.2	0.50
Antilymphocyte antibodies	18.5	15.5	12.2	10.8	0.23

TABLE 1. Continued

	Quartiles of sRAGE				
	I	II	III	IV	*P* value
HLA mismatches (%)					
HLA-AB	70.7	70.9	74.3	74.3	0.49
HLA-DR	40.3	40.0	36.8	30.3	0.35
Immunosuppression therapy					
Prednisolone dose (mg/d)	10 (10–10)	10 (7.5–10)	10 (7.5–10)	10 (7.5–10)	0.007
Ciclosporine (%)	69.4	60.8	64.9	62.2	0.43
Tacrolimus (%)	17.0	14.2	14.9	10.1	0.39
Mycophenolate mofetil use (%)	51.7	46.6	39.2	25.0	<0.001
Azathioprine (%)	25.2	32.4	31.8	41.9	0.02
Inflammation					
C-reactive protein (mg/l)	2.6 (1.1–5.7)	1.9 (0.9–4.2)	1.7 (0.6–4.7)	2.1 (1.0–5.0)	0.05

Data are presented as range for sRAGE quartiles and as means ± SD, median (interquartile range), or percentage for the other parameters.

TABLE 2. Analyses of mortality and death-censored graft loss for sRAGE quartiles

	Quartiles of sRAGE				
	I	II	III	IV	*P* value
Mortality					
Incidence, n (%)	26 (17.7)	11 (7.4)	15 (10.1)	21 (14.2)	
Cox regression models					
Crude	1.00	0.39 (0.19–0.79)	0.54 (0.29–1.03)	0.74 (0.41–1.31)	0.04
Model A	1.00	0.35 (0.17–0.71)	0.51 (0.27–0.97)	0.68 (0.38–1.23)	0.02
Model B	1.00	0.34 (0.17–0.70)	0.44 (0.23–0.84)	0.46 (0.25–0.85)	0.006
Model C	1.00	0.33 (0.16–0.68)	0.43 (0.22–0.83)	0.50 (0.26–0.95)	0.008
Model D	1.00	0.36 (0.18–0.75)	0.43 (0.22–0.85)	0.51 (0.26–0.97)	0.015
Death-censored graft loss					
Incidence, n (%)	7 (4.8)	9 (6.1)	7 (4.7)	13 (8.8)	
Cox regression models					
Crude	1.00	1.20 (0.45–3.21)	0.95 (0.33–2.71)	1.78 (0.71–4.46)	0.48
Model A	1.00	1.32 (0.49–3.56)	0.96 (0.34–2.73)	1.84 (0.73–4.66)	0.45
Model B	1.00	0.60 (0.21–1.71)	0.85 (0.30–2.45)	0.83 (0.32–2.15)	0.80
Model C	1.00	0.64 (0.22–1.91)	1.00 (0.33–3.03)	1.05 (0.39–2.85)	0.76
Model D	1.00	0.50 (0.16–1.56)	0.89 (0.29–2.68)	1.02 (0.38–2.72)	0.53

Model A: adjusted for sex donor, sex recipient, age donor, age recipient. Model B: additionally adjusted for creatinine clearance. Model C: additionally adjusted for BMI, fasting insulin, and mycophenolate mofetil usage. Model D: additionally adjusted for diabetes mellitus, history of MI, CRP, and total cholesterol. For Cox-regression models hazard ratios with 95% confidence intervals are displayed.

teins that are collectively referred to as sRAGE. Although sRAGE isoforms have slightly different protein sequences, they have in common that they contain the ligand-binding domain of the full-length RAGE protein, but not its transmembrane and signaling domains.

One of the studies reporting on esRAGE also contained a prospective part on the prediction of cardiovascular mortality in patients with end-stage renal disease (*25*). In this study, highest risk for cardiovascular mortality was present in patients with low esRAGE concentrations, and lowest risk in patients with intermediate concentrations. This is the same pattern which we find for the association of sRAGE with total mortality in renal transplant recipients. We also performed a multivariate analysis from which it can be judged which variables predict mortality independently in addition to sRAGE. Creatinine clearance appeared one of these factors, in addition to age, CRP, and diabetes.

Our study has some limitations. One of them concerns sRAGE clearance, which was not measured in this study. Second, this study measured sRAGE from plasma, which reflects a systemic picture rather than a local picture. We did not find an association between plasma sRAGE concentrations and subsequent graft loss. To see the effect of sRAGE on kidney function it might have been useful to measure sRAGE from kidney tissue directly. Third, there were only a relatively small number of death-censored graft losses, which lowers the power of detecting an association between death-censored graft loss and sRAGE. With a higher number it might have been possible to also detect

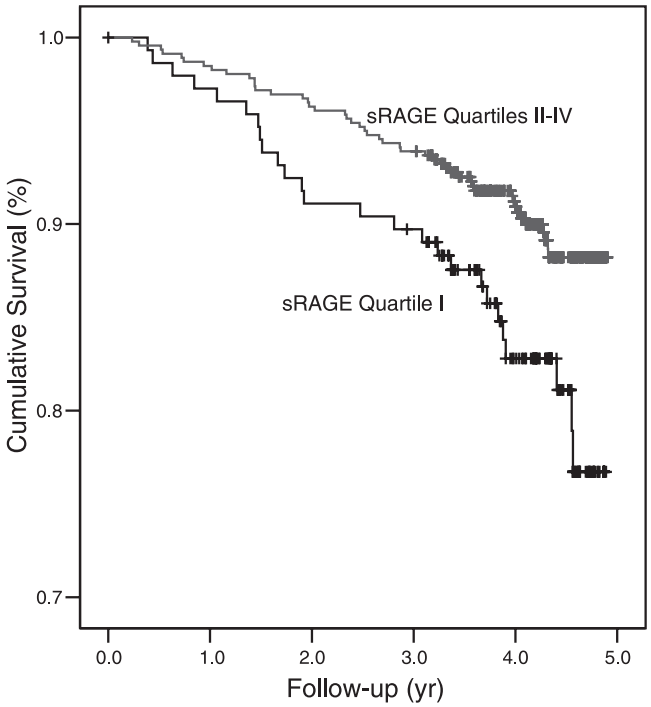

FIGURE 1. Kaplan-Meier curve of patient survival for the lowest quartile of sRAGE concentration compared to the higher quartiles.

this association. Last not least, it was not possible to split up mortality in cardiovascular mortality and other causes. Given the similarity between our results of the prospective analyses with sRAGE and those of the prior prospective study of esRAGE in patients with end-stage renal disease (*25*), analyses restricted to cardiovascular mortality might have given an even stronger relationship between sRAGE and increase in risk.

In conclusion, we provide evidence that low sRAGE levels are associated with increased risk for all-cause mortality. Our cross-sectional findings of an inverse association of sRAGE with use of mycophenolate mofetil, BMI, and fasting insulin concentrations merits further investigation in the mechanisms underlying these associations.

ACKNOWLEDGMENTS

This study was performed as part of the Graduiertenkolleg 880, a study exchange project of the University of Mannheim and the University of Groningen. The authors of this study thank all collaborators, but especially the Deutsche Forschungsgesellschaft, who provided funding of this project. This work was further funded by a grant from the Dutch Kidney Foundation (Nierstichting Nederland C00.1877). Aiko de Vries is supported by a Clinical Research Fellowship from the Netherlands Organization for Scientific Research (NWO-AGIKO 920-03-181).

REFERENCES

1. Merville P. Combating chronic renal allograft dysfunction: Optimal immunosuppressive regimens. *Drugs* 2005; 65: 615.
2. Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 2000; 342: 605.
3. Kreis HA, Ponticelli C. Causes of late renal allograft loss: Chronic allograft dysfunction, death, and other factors. *Transplantation* 2001; 71: SS5.
4. Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: Molecular mechanisms. *Cardiovasc Diabetol* 2002; 1: 1.
5. Hartog JW, Smit AJ, van Son WJ, et al. Advanced glycation end products in kidney transplant patients: A putative role in the development of chronic renal transplant dysfunction. *Am J Kidney Dis* 2004; 43: 966.
6. Hartog JW, de Vries AP, Bakker SJ, et al. Risk factors for chronic transplant dysfunction and cardiovascular disease are related to accumulation of advanced glycation end-products in renal transplant recipients. *Nephrol Dial Transplant* 2006; 21: 2263.
7. Raj DS, Lim G, Levi M, et al. Advanced glycation end products and oxidative stress are increased in chronic allograft nephropathy. *Am J Kidney Dis* 2004; 43: 154.
8. Ahmed N. Advanced glycation endproducts–role in pathology of diabetic complications. *Diabetes Res Clin Pract* 2005; 67: 3.
9. Schleicher ED, Bierhaus A, Haring HU, et al. Chemistry and pathobiology of advanced glycation end products. *Contrib Nephrol* 2001; 1.
10. Sousa MM, Yan SD, Stern D, Saraiva MJ. Interaction of the receptor for advanced glycation end products (RAGE) with transthyretin triggers nuclear transcription factor kB (NF-kB) activation. *Lab Invest* 2000; 80: 1101.
11. Bierhaus A, Schiekofer S, Schwaninger M, et al. Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. *Diabetes* 2001; 50: 2792.
12. Monaco C, Andreakos E, Kiriakidis S, et al. Canonical pathway of nuclear factor kappa B activation selectively regulates proinflammatory and prothrombotic responses in human atherosclerosis. *Proc Natl Acad Sci U S A* 2004; 101: 5634.
13. Hong SW, Jeong HJ, Kim YS, et al. Nuclear factor kappa B activation in glomeruli of posttransplant IgA nephropathy using southwestern histochemistry. *Transplant Proc* 2003; 35: 179.
14. Wautier JL, Zoukourian C, Chappey O, et al. Receptor-mediated endothelial cell dysfunction in diabetic vasculopathy. Soluble receptor for advanced glycation end products blocks hyperpermeability in diabetic rats. *J Clin Invest* 1996; 97: 238.
15. Wear-Maggitti K, Lee J, Conejero A, et al. Use of topical sRAGE in diabetic wounds increases neovascularization and granulation tissue formation. *Ann Plast Surg* 2004; 52: 519.
16. Goova MT, Li J, Kislinger T, et al. Blockade of receptor for advanced glycation end-products restores effective wound healing in diabetic mice. *Am J Pathol* 2001; 159: 513.
17. Bucciarelli LG, Wendt T, Qu W, et al. RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice. *Circulation* 2002; 106: 2827.
18. 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.
19. de Vries AP, Bakker SJL, van Son WJ, et al. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. *Am J Transplant* 2005; 4: 1675.
20. van Ree RM, Oterdoom LH, de Vries AP, et al. Elevated levels of C-reactive protein independently predict accelerated deterioration of graft function in renal transplant recipients. *Nephrol Dial Transplant* 2007; 22: 246.
21. 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.
22. Kalousova M, Hodkova M, Kazderova M, et al. Soluble receptor for advanced glycation end products in patients with decreased renal function. *Am J Kidney Dis* 2006; 47: 406.
23. Kalousova M, Bartosova K, Zima T, et al. Pregnancy-associated plasma protein a and soluble receptor for advanced glycation end products after kidney transplantation. *Kidney Blood Press Res* 2007; 30: 31.
24. Koyama H, Shoji T, Yokoyama H, et al. Plasma level of endogenous secretory RAGE is associated with components of the metabolic syndrome and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2005; 25: 2587.
25. Koyama H, Shoji T, Fukumoto S, et al. Low circulating endogenous secretory receptor for AGEs predicts cardiovascular mortality in patients with end-stage renal disease. *Arterioscler Thromb Vasc Biol* 2007; 27: 147.
26. Yonekura H, Yamamoto Y, Sakurai S, et al. Novel splice variants of the receptor for advanced glycation end-products expressed in human vascular endothelial cells and pericytes, and their putative roles in diabetes-induced vascular injury. *Biochem J* 2003; 370: 1097.