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Circulating soluble receptor for advanced glycation end product (sRAGE) and left ventricular hypertrophy in patients with chronic kidney disease (CKD)

D. Leonardis [a], G. Basta [b], F. Mallamaci [a], S. Cutrupi [a], P. Pizzini [a], R. Tripepi [a], G. Tripepi [a], R. De Caterina [b], C. Zoccali [a,*]

[a] *Renal and Transplantation Unit OO.RR. and CNR-IBIM, Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension of Reggio Calabria, Italy*
[b] *CNR, Institute of Clinical Physiology, Pisa, Italy*

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Abstract *Background and Aim:* A decoy receptor for advanced glycation end product (soluble RAGE or sRAGE) is involved in left ventricular hypertrophy (LVH), and cardiomyopathy myocardial damage in experimental models and observational studies in patients with heart failure support the hypothesis that sRAGE attenuates the progression of heart disease and prevents death. Since sRAGE accumulates in patients with chronic kidney disease (CKD) we studied the relationship between plasma sRAGE with LVH in CKD patients.

Methods and results: We enrolled 142 patients with an average estimated glomerular filtration rate (eGFR) of 32 ml/min/1.73 m^2 and 49 healthy control individuals matched for age and gender.

Plasma sRAGE was significantly higher in CKD patients than in healthy controls. Significant inverse relationships were found between sRAGE with left ventricular mass index (LVMI) and mean wall thickness (MWT) but no such associations were found in controls. A bootstrap resampling validation study confirmed the estimates of the link between sRAGE and these variables. On covariance analysis, the slopes of LVMI and MWT to sRAGE were significantly steeper in CKD patients than in the controls. On logistic regression analysis 1 log unit increase in sRAGE was associated with a 82% decrease in the odds for LVH in CKD patients.

Conclusions: sRAGE is an inverse marker of LVH in CKD patients. This association generates the hypothesis that the RAGE pathway could be a causal risk factor for LVH in this population and that blockade of this pathway by the endogenous decoy receptor sRAGE could attenuate LVH in the same population.

* Corresponding author. Renal and Transplantation Unit OO.RR. and CNR-IBIM, c/o EUROLINE di Ascrizzi Vincenzo, Via Vallone Petrara 55-57, 89124 Reggio Calabria, Italy. Tel.: +39 0965 397010; fax: +39 0965 26879.
E-mail address: carmine.zoccali@tin.it (C. Zoccali).

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Introduction

The Receptor for Advanced Glycation End Products (RAGE) is a member of the immunoglobulin super family which is located at the cell surface of several cell species including endothelial cell, vascular smooth cells and the myocardiocyte [1]. Besides mediating the effects of advanced glycation end products (AGEs), RAGE has a broad repertoire of ligands that share the propensity to accumulate in tissues during aging, chronic degenerative diseases, inflammation and the host immune response [2]. AGE and other RAGE ligands accumulate in renal failure [3,4] and these compounds are currently considered as likely players in atherosclerosis in these patients (CKD) [5]. RAGE exists in several variants. A C-truncated variant, the soluble RAGE (sRAGE), could be a naturally occurring inhibitor of the ligand–RAGE interaction [6]. sRAGE attenuates atherosclerosis in experimental models in animals [7] and a vasculoprotective effect of sRAGE has been inferred also in studies in diabetic [8] and non-diabetic individuals [9]. The relevance of RAGE in human diseases goes beyond diabetes and we have recently reported a robust, inverse link between sRAGE and the plaque burden in patients with chronic kidney disease (CKD) [10] implicating the RAGE pathway in vascular damage in this population.

Atherosclerosis apart, evidence is accruing that the RAGE pathway may be implicated in a direct manner in heart disease. AGE concentration and RAGE expression is increased in the heart of Sprague–Dawley rats with streptozocin-induced diabetes while treatment with drugs that break the AGEs-connective tissue cross-links attenuate left ventricular hypertrophy (LVH) and cardiomyopathy in this model [11]. In a previous study in patients with end stage renal disease (ESRD) we observed that high levels of a major AGE, pentosidine, are associated with LVH [12]. LVH occurs early in CKD and its prevalence increases as renal function deteriorates [13,14]. LVH is a strong risk factor for cardiovascular sequelae in CKD, particularly in ESRD where this alteration is considered as the strongest predictor of death [15]. Since sRAGE is an inverse marker of the severity of atherosclerosis in CKD and since AGEs and the RAGE pathway are involved in a causal manner in LVH in experimental models, an analysis of the link between sRAGE and LV mass and function in CKD may provide useful information for exploring the hypothesis that the RAGE pathway is implicated in LVH in patients with CKD. With this background in mind we investigated the relationship between circulating sRAGE and LV mass in the same series of patients with CKD where we had studied the association between sRAGE and atherosclerosis.

Methods

The study protocol was in conformity with the ethical guidelines of our institution, and informed consent was obtained from each participant.

Patients

We studied 142 patients with CKD. All patients were in steady state condition and without inter-current inflammatory diseases. Their mean age was 56 ± 13 years (80 M and 62 F) and their estimated glomerular filtration rate (eGFR) ranged from 5 to 83 ml/min/1.73 m^2 [eGFR (mean ± SD): 32 ± 15 ml/min/1.73 m^2]. Thirty-six patients out of 142 were diabetic (type-1 diabetes: 64%; type-2 diabetes: 36%). The main demographic, somatometric, clinical and biochemical characteristics of patients included in the study are detailed in Table 1.

Control group

As control group we selected 49 healthy subjects (HS) accurately matched to CKD patients as for age (CKD patients: 56 ± 13 years versus Controls: 55 ± 11 years) and gender (CKD patients, Males: 56% versus Controls, Males: 57%). To be selected, HS had to have no alteration at an extensive clinical and biochemical work-up (including absence of albuminuria), and had to have normal urine analysis and eGFR equal or greater than 60 ml/min/1.73 m^2, which is the recommended threshold for the diagnosis of CKD [16].

Laboratory measurements

Blood sampling was performed after 20–30 min of quiet resting in a semi-recumbent position. After an overnight fasting, blood samples for serum lipids, creatinine, albumin, calcium and phosphate, and haemoglobin were obtained from all patients. GFR was estimated by using the simplified modification diet of renal disease study (MDRD) formula [eGFR (mL/min/1.73 m^2) = 186 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American) (conventional units)] derived by Levey et al. [17]. Plasma samples were stored at −80 °C until the analysis. Plasma sRAGE levels were determined by an ELISA kit (DuoSet ELISA Development kit, R&D systems, Minneapolis, Minnesota, USA) containing the basic components required for the development of a double sandwich ELISA. Intra-assay and inter-assay coefficients of variation values were 5.9% and 8.2%, respectively. The lower limit of detection of sRAGE was 21.5 pg/mL. Serum C-Reactive Protein (CRP) was measured by a high-sensitivity immuno-turbidimetric method (hsCRP-Dade Behring, Marburg, Germany).

Echocardiography

All echocardiographic measurements were carried out according to the recommendations of the American Society of Echocardiography by an observer unaware of biochemical results. Left ventricular mass (LVM) was calculated according to the Devereux formula and indexed to $heigh^{2.7}$ (LVMI) [18]. LVH was defined as a LVMI of over 47 $g/m^{2.7}$ in women or over 50 $g/m^{2.7}$ in men. Mean wall thickness (MWT) was calculated by the standard formula [MWT = (posterior wall thickness + inter-ventricular septum thickness)/2]. The relative wall thickness (RWT: 2*posterior wall thickness/left ventricular end diastolic diameter) was also calculated, as an index of the left ventricular geometric pattern.

Eco-colour doppler of carotid arteries

Both in patients and controls, ultrasonographic studies on common carotid arteries were performed bilaterally by