Elevated circulating S100A12 associates with vascular disease and worse clinical outcome in peritoneal dialysis patients

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Introduction and aim

Cardiovascular disease (CVD) in chronic kidney disease (CKD) is linked to inflammation, oxidative stress, and endothelial dysfunction, and to the advanced glycation end-products (AGE) - receptor of AGE (RAGE) system including RAGE-ligand S100A12 and soluble RAGE (sRAGE) .

S100A12 is expressed on cell surfaces of macrophages, lymphocytes and endothelial cells at sites of local inflammation where it participates in the AGE-RAGE inflammatory response by inducing production and release of pro-inflammatory cytokines.

Whereas in pro-inflammatory conditions, high plasma S100A12 and low plasma sRAGE associate with increased CVD risk, results in CKD are less consistent. In peritoneal dialysis (PD) patients, heat sterilization of glucose-based PD fluid could lead to accelerated AGE formation and over-expression of RAGE. In PD patients with 2 to 3-fold higher plasma concentrations of S100A12 as compared with healthy controls, S100A12 associated with carotid atherosclerosis and in another study with a high peritoneal solute transport rate. However, the mortality predictive role of S100A12 and sRAGE among PD patients is not known.

In the current study, we evaluated S100A12 and sRAGE in relation to inflammation, nutritional status, comorbidities including presence of vascular disease, and mortality risk in 82 prevalent PD patients. We included for comparative analysis also 190 prevalent HD patients who underwent similar protocol, and 50 community-dwelling controls.

Materials and Methods

We included **82 PD patients** with median age of 65 years, 70% men and median dialysis vintage time of 12 (IQR 6 to 29) months. The median urine volume of the PD patients was 950 (IQR 500-1300) ml, and mean glomerular filtration rate (GFR) calculated as the average of renal creatinine and urea clearance from 24 hours urine collection was 2.9±2.2 mL/min/1.73m^2, while median total (renal plus peritoneal) weekly Kt/V was 2.2 (IQR 1.8-2.5). A standard peritoneal equilibration test with assessment of dialysate-to-plasma ratio of creatinine was performed according to the method of Twardowski. Survival was recorded from the day of examination and for a follow-up time of up to five years. As the rate of renal transplantation was high, survival analysis was censored for transplantation.

In addition, for comparative analysis, S100A12 and sRAGE were measured also in **190 prevalent hemodialysis patients** (106 men, median age of 67 (IQR 51-74) years) and in **50 community-dwelling control subjects** (31 men, median age of 63 (IQR 58 to 70) years, median GFR of 82 (IQR 76 to 91) ml/min per 1.73 m^2) randomly selected by Statistics Sweden among individuals in the Stockholm region. The HD patients and control subjects underwent similar measurements as the PD patients.

Evaluation of peripheral or cerebrovascular disease

Peripheral vascular disease was defined by the presence of arterial insufficiency of the extremities, carotid or renal artery stenosis, or aortic aneurysm. Cerebrovascular disease was also defined by the presence of stroke, transient ischemic attack, subdural hematoma, and intracerebral or subarrachnoidal hemorrhage. In the current study, we combined the patients who had signs of peripheral vascular disease or cerebrovascular disease (PCVD) into one category.

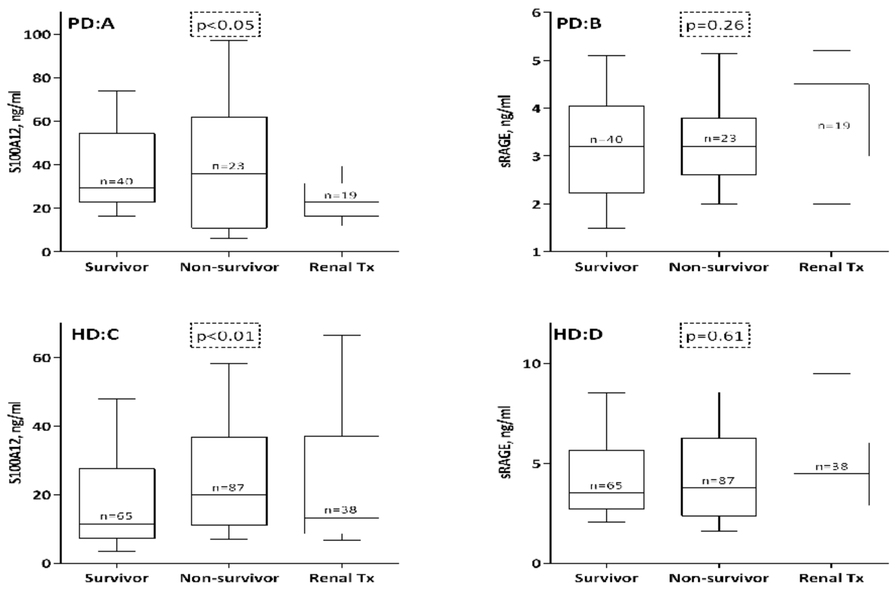
Results: Results are shown in **Figures 1 and 2** and in **Tables 1-4**.

Table 1. Characteristics and laboratory variables in control subjects and PD patients.

	Controls (n=50)	PD (n=82)	HD (n=190)
Age, (years)[a]	63 (58-70)	65 (56-76)	67 (51-74)
Males (%)	31 (62%)	57 (70%)	106 (56%)
Vintage (months)[b]	-	12 (6 to 29)	29 (14 to 55)
DM, n (%)	0 (0%)	20 (24%)	46 (24%)
CVD, n (%)	**0 (0%)**	**24 (29%)**	121 (64%)
PVCD, n (%)	-	**23 (28%)**	56 (29%)
GFR (ml/min/1.73m^2)[a]	82 (76 to 91)	2.6 (1.2 to 3.9)	-
BMI (kg/m^2)	25.4 ±3.9	25.5 ±3.9	24.8 ±5.3
FBMI (kg/m^2)	-	8.4 ±2.9	8.2 ±3.3
LBMI (kg/m^2)	-	16.3 ±2.1	16.5 ±2.7
SGA>1 (%)	2 (4%)	30 (39%)	89 (47%)
S-albumin (g/l)	39.0 ±2.8	31.4 ±4.5	35.0 ±4.2
S-creatinine (µmol/l)	79 ±15	725 ±175	780 ±209
Total cholesterol (mmol/L)	5.2 ±0.8	5.1 ±1.3	4.3 ±0.9
IL-6 (pg/ml)[b]	-	6.4 (3.9 to 9.6)	8.5 (4.8 to 15.0)
CRP (mg/l) [b]	**1.2 (0.6 to 2.6)**	**4.1 (1.4 to 9.8)**	6.4 (2.5 to 19.5)
CML (µg/ml, n=59) [b]	-	0.75 (0.64 to 0.9)	-
S100A12 (ng/ml) [b]	**6.7(4.6 to 10.0)**	**28.6 (19.6 to 46.2)**	14.7 (8.8 to 33.9
sRAGE (ng/ml) [b]	1.3 (0.8 to 1.7)	3.3 (2.5 to 4.2)	3.8 (2.6 to 5.9)
S100A12/sRAGE ratio [b]	**5.2 (4.0 to 8.4)**	**9.9 (5.5 to 16.9)**	4.1 (1.8 to 9.9)

Data are expressed as [a]median (range), [b]median (25th to 75th percentile), or as mean ± SD or n (%).
DM, diabetes mellitus; CVD, cardiovascular disease; PCVD, peripheral or cerebrovascular disease; GFR, **glomerular filtration rate;** BMI, body mass index; FBMI, fat body mass index; LBMI, lean body mass index; SGA>1, subjective global assessment score (indicating protein-energy wasting); IL-6, Interleukin-6; CRP, C-reactive protein; CML, Nε-(Carboxymethyl)lysine. stage 3-4 patients, and 50 controls.

Figure 1 A-D. Baseline plasma concentration of S100A12 (A C) and sRAGE (B D) in survivors, non-survivors and patients who underwent renal transplantation (Renal Tx) in PD and HD patients. Differences were assessed by Kruskal Wallis rank test.



Summary and conclusions

Plasma S100A12 and sRAGE concentrations, and the ratio S100A12/sRAGE, are markedly elevated in PD patients as compared to community-dwelling subjects with similar age and sex distribution (Table 1 and Figure 1).

S100A12 associated with inflammation, presence of PCVD and clinical outcome(Table 2, 3 and 4.), and median S100A12 at baseline in non-survivors was higher than in survivors who remained on PD or underwent renal transplantation during the follow-up period (Figure 2.).

Plasma S100A12 and sRAGE concentrations, and the ratio S100A12/sRAGE, are markedly elevated in PD patients. Plasma sRAGE, which is thought to be anti-inflammatory and protective against atherosclerotic CVD was inversely related to body mass indices but did not associate with inflammation, presence of PCVD or clinical outcome. Plasma S100A12 associated with inflammation, presence of PCVD, and increased mortality suggesting that S100A12 may identify PD patients at risk for vascular disease and increased mortality.

Table 2. Clinical characteristics and laboratory variables in 82 PD patients without (n=59) and with (n=23) signs or history of peripheral or cerebrovascular disease (PCVD).

	No PCVD (n=59)	PCVD (n=23)	p-value
Age (year)[a]	64 (53-76)	67 (57 to 80)	0.17
Males (%)	45 (76%)	12 (52%)	0.03
Vintage (months)[a]	12 (6 to 29)	11 (5 to 31)	0.62
DM (%)	12 (20%)	8 (35%)	0.28
CVD (%)	13 (22%)	11 (48%)	0.02
GFR[a]	2.9 (1.4 to 5.2)	1.7 (0.8 to 2.7)	0.01
Kt/V[a]	2.5 (1.8 to 2.5)	2.2 (1.9 to 2.4)	0.99
BMI (kg/m^2)	25.8 ±4.0	24.6 ±3.5	0.22
FBMI (kg/m^2)	8.6 ±2.7	8.1 ±3.2	0.43
LBMI (kg/m^2)	16.4 ±2.1	16.1 ±2.2	0.62
SGA>1 (%)	20 (34%)	10 (43%)	0.37
S-albumin (g/l)	32.5 ±4.0	28.4 ±4.5	0.001
Total cholesterol (mmol/L)	5.1 ±1.3	5.1 ±1.2	0.75
IL-6 (pg/ml)[b]	5.8 (3.4 to 9.1)	8.4 (4.9 to 13.6)	0.03
CRP (mg/l) [b]	3.7 (1.4 to 7.8)	5.7 (1.3 to 21.8)	0.06
mAOPP (µmol/L)[b]	138 (119-154)	127 (107-147)	0.24
CML (µg/ml, n=59) [b]	0.74 (0.62 to 0.90)	0.80 (0.70 to 0.93)	0.36
S100A12 (ng/ml) [b]	25.3 (16.9 to 39.4)	37.0 (24.9 to 57.1)	0.03
sRAGE (ng/ml) [b]	3.3 (2.4 to 4.3)	3.3 (2.8 to 3.9)	0.70
S100A12/sRAGE ratio [b]	**8.7 (4.7 to 16.6)**	**11.9 (8.2 to 22.2)**	0.05

Table 3. Odds ratios and 95% confidence intervals (CI) for the presence of peripheral and cerebrovascular disease in 82 PD patients.

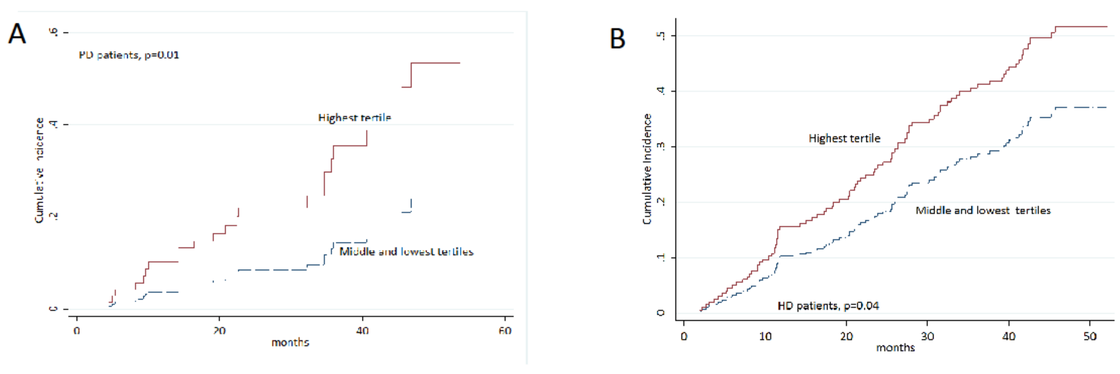
Peripheral or cerebrovascular vascular disease (PCVD)	Odds Ratio (95% confidence interval)	z	Std. Err.	P value
Sex, female	0.35 (0.11 to 1.16)	0.21	1.72	0.09
Albumin, >35 g/L	1.36 (0.22 to 8.23)	1.25	0.33	0.74
SGA, well-nourished	1.53 (0.49 to 4.79)	0.89	0.73	0.47
sRAGE, >3.3 ng/ml	2.23 (0.70 to 7.05)	1.31	1.36	0.17
S100A12, >28.6 ng/ml	3.52 (1.09 to 11.41)	2.11	2.10	0.04

Pseudo r^2=0.11

Table 4. Sub hazard ratio (SHR) and 95% confidence intervals (CI) for all-cause mortality risk in 82 PD and 190 HD patients.

	PD SHR (95% CI)	P	HD SHR (95% CI)	P
S100A12, highest tertile vs other	2.91 (1.01 to 1.16)	0.01	1.57 (1.20 to 7.02)	0.04
Sex, female	0.99 (0.38 to 2.55)	0.99	1.36 (0.87 to 2.10)	0.17
Age,<45 yrs vs 45-65yrs	1.22 (0.12 to 12.22)	0.86	2.51 (0.59 to 10.64)	0.47
Age,<45 yrs vs >65yrs	2.61 (0.25 to 26.46)	0.41	9.02 (2.24 to 36.32)	0.002
CVD, presence	3.11 (1.27 to 7.61)	0.01	1.51 (0.93 to 2.46)	0.09
DM, presence	1.17 (0.65 to 2.10)	0.59	1.46(0.89 to 2.36)	0.12

Figure 2A-B. Relation between S100A12 Cumulative incidence rates for the competing end-points of renal transplantation or death in patients with highest tertile of S100A12 versus the lower tertiles of S100A12 in PD (Fig. 2A) and HD (Fig. 2B) patients.



These incidence rates are adjusted for age, gender and presence of co-morbid conditions diabetes and cardio-vascular disease.

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