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Plasma endocan levels associate with inflammation, vascular abnormalities, cardiovascular events, and survival in chronic kidney disease

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Plasma endocan levels are elevated in a large number of diseases, and may reflect endothelial cell dysfunction. There are currently no data on endocan in patients with chronic kidney disease (CKD). Therefore, we measured plasma endocan in 251 patients with CKD (stage 1–5) and 60 control individuals. Plasma endocan concentrations correlated with estimated glomerular filtration rate (eGFR), different markers of inflammation (pentraxin 3 and high-sensitivity C-reactive protein), and vascular abnormalities (flow-mediated vasodilation (FMV) and carotid intima media thickness (CIMT)). All-cause mortality and cardiovascular events (CVE) were also analyzed with respect to plasma endocan. Patients with CKD showed significantly increased plasma endocan (4.7 [IQR 1.9–9.4] compared with controls [IQR 1.1–1.5] ng/ml), with values progressively higher across stages of CKD. On univariate analysis, plasma endocan concentrations correlated negatively with eGFR and FMV, but positively with both markers of inflammation and CIMT. However, on multivariate analysis only high-sensitivity C-reactive protein, FMV, and CIMT remained significantly associated with plasma endocan. On Cox survival analysis, endocan levels were associated with all-cause mortality and CVE in these patients. Thus, plasma endocan increases in the presence of decreasing eGFR and influences all-cause mortality and CVE in patients with CKD independent of traditional and nontraditional risk factors.

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The prevalence of chronic kidney disease (CKD) has reached epidemic proportions, with ~10–13% of the population worldwide showing signs of this disease.[1] Cardiovascular disease (CVD) is the main cause of morbidity and mortality in CKD patients.[2] The process of cardiovascular damage starts very early during progression in well-defined CKD, long before the dialysis stage is reached,[3] which is important because individuals with CKD are more likely to die than to develop end-stage renal disease.[4] The connections between CKD and CVD are probably numerous,[5] with inflammation and endothelial dysfunction being the most important. Better understanding of the relationship between CKD and CVD is essential for guiding future strategies for screening and treatment.

Endocan, previously called endothelial cell-specific molecule-1, is a soluble proteoglycan of 50 kDa expressed by the vascular endothelium. Increasing experimental evidence has reported that endocan is overexpressed in cancer, sepsis, obesity, or inflammatory conditions[6] and is related to patients' outcome in different conditions such as sepsis[7] and cancer.[8–10] endocan may have roles in the vascular contribution to organ-specific inflammation and in endothelium-dependent pathological disorders and may represent a novel endothelial cell dysfunction marker.[7,11]

The aim of this study was threefold: (a) to evaluate endocan levels in CKD (vs. non-CKD) patients and their relation with GFR; (b) to investigate the relationship between endocan and different markers of inflammation and endothelial dysfunction in the same CKD population; and (c) to test the ability of endocan as a novel predictor of all-cause mortality and cardiovascular events (CVE) in CKD patients.

RESULTS

Main demographic, clinical, and biochemical parameters of the patients included in the study

A total of 251 patients (51% male; mean age = 45.8 ± 13.5 years) with CKD and 60 nondiabetic, non-CKD controls

(45% male) were evaluated in this study. The most frequent causes of CKD were diabetes mellitus (23.1%), hypertension (18.7%), and chronic glomerulonephritis (15.9%), but in a large proportion of patients (27.1%) the etiology was unknown. The mean arterial pressure was 135.5 ± 10.6/84.2 ± 4.4 mm Hg (Table 1). The demographic and clinical characteristics of the population across the different CKD stages are shown in Supplementary Table S1 online.

Patients in the control group were older and had lower diastolic and systolic blood pressure. Patients with CKD showed increased endocan (4.7 ng/ml [interquartile range (IR) 1.9–9.4 ng/ml] vs. 1.2 ng/ml [IR 1.1–1.5 ng/ml], $P<0.001$), hsCRP (11.0 mg/l [IR 7.0–22.0 mg/l] vs. 2.0 mg/l [IR 1.2–2.4 mg/l], $P<0.001$), and pentraxin 3 (PTX3) (4.9 ng/ml [IR 2.8–8.6 ng/ml] vs. 2.2 ng/ml [1.5–3.1 ng/ml], $P<0.001$) levels. The CKD patients had also higher carotid intima media thickness (CIMT) (0.7 mm [IR 0.6–0.8 mm] vs. 0.6 mm [0.6–0.6 mm], $P<0.001$) and reduced flow-mediated vasodilation (FMD) (7.0% [IR 6.1–7.5%] vs. 8.7% [8.1–9.2%], $P<0.001$) values compared with controls. Because of the nonmatched selection of the controls, we performed an additional analysis to compare endocan values between controls and the nondiabetic nonhypertensive CKD subpopulation ($N=165$ out of the total cohort). Even in this subgroup of CKD patients, we found significantly higher endocan values (3.5 ng/ml [IR 1.2–7.2 ng/ml], $P<0.001$) compared with non-CKD controls.

The median value of endocan was 4.71 ng/ml (IR 1.9–9.4 ng/ml), with values progressively higher across the CKD stages (see Supplementary Table S2 online and Figure 1). Higher endocan values were recorded in diabetic vs. nondiabetic patients (7.2 ng/ml [IR 3.2–12.5 ng/ml] vs. 3.7 ng/ml [IR 1.3–8.2 ng/ml], $P<0.001$), but there were no significant differences between genders or other CKD etiologies.

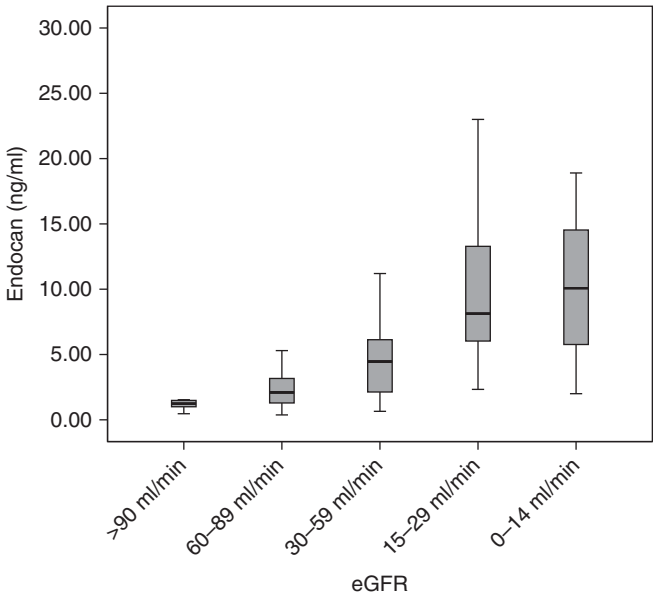

Figure 1 | Endocan values (ng/ml) in the control group and across the CKD population.

Table 1 | Demographic and clinical characteristics of the study population

	All ($n=251$)	1st quartile ($n=63$)	2nd quartile ($n=64$)	3rd quartile ($n=62$)	4th quartile ($n=62$)	P^a
Endocan, ng/ml	4.7 (1.9–9.4)	1.2 (0.9–1.3)	2.8 (2.1–3.7)	6.6 (5.5–7.8)	13.3 (10.9–15.8)	
Age, years	45.8 ± 13.5	47.1 ± 13.3	47.1 ± 13.7	44.6 ± 12.8	44.1 ± 14.3	0.45
Male, *n* (%)	128 (51.0)	31 (49.2)	30 (46.9)	34 (54.8)	33 (53.2)	0.80
BMI, kg/m^2	25.9 ± 2.7	26.6 ± 2.5	26.0 ± 2.7	25.6 ± 3.1	25.4 ± 2.4	0.06
Hypertension, *n* (%)	47 (18.7)	4 (6.3)	13 (20.3)	11 (17.7)	19 (30.6)	**0.01**
Systolic pressure, mm Hg	135.5 ± 10.6	133.9 ± 7.9	137.0 ± 9.6	133.3 ± 11.5	137.5 ± 12.6	0.10
Diastolic pressure, mm Hg	84.2 ± 4.4	83.4 ± 3.9	84.4 ± 4.1	83.2 ± 4.9	85.6 ± 4.1	**0.01**
Diabetes, %	58 (23.1)	3 (4.8)	15 (23.4)	17 (27.4)	23 (37.1)	**<0.001**
History of CVD, %	46 (18.3)	11 (17.5)	7 (10.9)	11 (17.7)	17 (27.4)	0.12
Cardiovascular episode	33 (13.1)	6 (9.5)	4 (6.3)	11 (17.7)	12 (19.4)	0.09
Stroke	6 (2.4)	2 (3.2)	1 (1.6)	0 (0)	3 (4.8)	0.34
PVD	6 (2.4)	3 (4.8)	1 (1.6)	0 (0)	2 (3.2)	0.40
Aortic aneurysm	1 (0.4)	0 (0)	1 (1.6)	0 (0)	0 (0)	1.00
Etiology of CKD, n (%)						
Diabetes	58 (23.1)	3 (4.8)	15 (23.4)	17 (27.4)	23 (37.1)	**<0.001**
Glomerulonephritis	40 (15.9)	15 (23.8)	7 (10.9)	11 (17.7)	7 (11.3)	0.15
Hypertension	47 (18.7)	4 (6.3)	13 (20.3)	11 (17.7)	19 (30.6)	**0.01**
ADPKD	10 (4.0)	3 (4.8)	1 (1.6)	3 (4.8)	3 (4.8)	0.73
Reflux nephropathy	12 (4.8)	5 (7.9)	2 (3.1)	4 (6.5)	1 (1.6)	0.32
Amyloidosis	16 (6.4)	8 (12.7)	2 (3.1)	4 (6.5)	2 (3.2)	0.09
Unknown	68 (27.1)	25 (39.7)	24 (37.5)	12 (19.4)	7 (11.3)	**<0.001**
Smoking, *n* (%)	112 (44.6)	24 (38.1)	24 (37.5)	28 (45.2)	36 (58.1)	0.07

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; IR, interquartile range; PVD, peripheral vascular disease; SD, standard deviation.
Data are expressed as mean ± SD, median with IR, or percent frequency, as appropriate. Bold values are statistically significant.
[a]Comparison between groups.