

Research Article

Serum Endocan Levels and Subclinical Atherosclerosis in Patients with Chronic Kidney and End-Stage Renal Diseases

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Background and Aim. Chronic kidney disease (CKD) and its final stage: end-stage renal disease (ESRD), are common clinical conditions. Endocan is a human endothelial cell-specific molecule produced by endothelial cells. Its production is related to activation of endothelium and angiogenesis. In this study, we assessed the relation between serum endocan levels and subclinical atherosclerosis (SCA) in CKD and hemodialysis (HD) patients. **Subjects and Methods.** The present case control study enrolled 30 patients on regular HD for at least 6 months, 30 patients with CKD, and 30 age and sex-matched healthy controls. All participants were subjected to careful history taking and thorough clinical examination. Laboratory investigations included complete blood count, kidney functions, and serum cholesterol, triglycerides, calcium, phosphorus, albumin, PTH, hsCRP, and endocan levels. **Results.** HD and CKD groups had significantly higher endocan levels when compared with control group (median (IQR): 519.0 (202.3–742.0) versus 409.0 (245.3–505.3) and 273.0 (168.0–395.5) ng/L, respectively). Also, HD patients had significantly higher endocan levels when compared with CKD levels. HD patients had significantly higher carotid intima-media thickness (CIMT) when compared with CKD patients (median (IQR): 0.80 (0.80–0.90) versus 0.75 (0.73–0.75) mm, $p < 0.001$). HD patients had significantly higher frequency of SCA when compared with CKD patients (46.7% versus 13.3%, $p = 0.005$). Patients with SCA had significantly higher hsCRP (median (IQR): 36.5 (26.8–43.5) versus 24.0 (15.8–29.0) mg/dl) and endocan levels (697.0 (528.3–974.8) versus 222.5 (158.8–565.8) ng/L) when compared with patients without SCA. ROC curve analysis of endocan for identification of SCA in HD patients showed that at a cutoff of 380.5 ng/L, endocan has an AUC of 0.862 with a sensitivity and specificity of 92.9% and 68.7%, respectively. **Conclusions.** Serum endocan levels are related to SCA in HD patients. In addition, it is associated with the hyperinflammatory state in those patients.

1. Introduction

Chronic kidney disease (CKD) and its final stage: end-stage renal disease (ESRD), are common clinical conditions [1, 2]. CKD may be complicated by mineral and bone disorders,

cardiovascular disease (CVD), and other complications [3]. Cardiovascular complications include coronary heart disease (CHD), congestive cardiac failure, and sudden arrest [4]. Atherosclerosis is one of the known cardiovascular complications in these patients [5]. Identification of

subclinical atherosclerosis (SCA) in those patients is essential for prediction of forthcoming CVD [6].

Carotid intima-media thickness (CIMT) provides a non-invasive measurement of the intima and media thickening in carotid arteries as an early indicator of systemic atherosclerosis. It is correlated with CHD and stroke in the ESRD patients [7]. Early atherogenesis is associated with endothelial dysfunction [8]. Endocan is a human endothelial cell-specific molecule produced by endothelial cells. Its production is related to activation of endothelium and angiogenesis [9]. Elevation of serum endocan was previously linked to SCA in type 2 diabetic patients [10], systemic lupus erythematosus [11], and psoriasis [12].

In this study, we assessed the relation between serum endocan levels and SCA in CKD and HD patients.

2. Subjects and Methods

The present case control study was conducted at Al-Azhar University Hospitals, Al-Azhar University, Cairo, Egypt, from December 2020 to September 2021. The study protocol was approved by the ethical committee of Al-Azhar Faculty of Medicine, and all included subjects provided informed consent before enrollment in the study.

The study included 30 patients on regular HD for at least 6 months, 30 patients with chronic kidney disease (CKD) diagnosed according to National Kidney Foundation Disease Outcomes Quality Initiative (NKF-K/DOQI) clinical practice guidelines, and 30 age and sex-matched healthy controls. Patients were excluded if they had other causes of chronic inflammation, active malignancies, acute and chronic infection, kidney transplantation, or other cardiovascular diseases.

All participants were subjected to careful history taking and thorough clinical examination.

For laboratory assessment, 4 ml of peripheral venous blood was withdrawn from each individual and divided into two aliquots; 2 ml was collected in an EDTA tube for CBC. The remaining part was collected in serum separator tube, centrifuged at 3500 rpm for 10 min and divided into two parts; the first part was used for biochemical tests and for measurement of parathyroid hormone (PTH) and the remaining part of the serum was frozen at -20°C for analysis of endocan. Laboratory investigations included complete blood count, kidney functions, and serum cholesterol, triglycerides, calcium, phosphorus, albumin, and PTH levels. Determination of high-sensitivity C-reactive protein (hsCRP) was performed by commercial solid-phase immunosorbent assay (ELISA) kits (DRG International Inc., Springfield, New Jersey, USA). Measurement of serum endocan was performed using quantitative double-antibody sandwich ELISA kit (Bioassay Technology Laboratory, China, Cat. No. E3160Hu). CIMT measurement was done using B-mode ultrasound with a high definition L12-5 linear wideband probe (Philips HDI 5000, Bothell, Washington, USA). Patients were categorized to have SCA if their CIMT measurement was ≥ 0.9 mm [13].

Data were computerized and analyzed using IBM SPSS software package version 20.0. (IBM Corp., Armonk, New

York, USA). Quantitative data were described using mean and standard deviation (SD) or median and interquartile range (IQR) and were compared using *t*-test, Mann-Whitney *U* test, or Kruskal-Wallis test as appropriate. Qualitative data were presented in numbers and percentages and were compared using Fisher's exact test or chi-square test as appropriate. Correlation analysis was achieved using Spearman's correlation coefficient. *p* value less than 0.05 was considered statistically significant. Receiver operator characteristic (ROC) curve analysis was used to identify diagnostic value of the investigated marker. *p* value less than 0.05 was considered statistically significant.

3. Results

The present study included 30 patients under HD, 30 CKD patients, and 30 age and sex-matched healthy controls. HD and CKD groups had significantly higher endocan levels when compared with control group (median (IQR): 519.0 (202.3–742.0) versus 409.0 (245.3–505.3) and 273.0 (168.0–395.5) ng/L, respectively). Also, HD patients had significantly higher endocan levels when compared with CKD levels (Table 1, Figure 1).

Comparison between HD and CKD patients revealed significantly higher hsCRP levels in HD patients (median (IQR): 28.5 (21.8–39.5) versus 15.0 (9.8–20.3) mg/dl, $p < 0.001$). In addition, it was found that HD patients had significantly higher CIMT when compared with CKD patients (median (IQR): 0.80 (0.80–0.90) versus 0.75 (0.73–0.75) mm, $p < 0.001$). HD patients had significantly higher frequency of SCA when compared with CKD patients (46.7% versus 13.3%, $p = 0.005$) (Table 1).

Comparison between HD patients with SCA and patients without showed that patients with SCA had significantly higher hsCRP (median (IQR): 36.5 (26.8–43.5) versus 24.0 (15.8–29.0) mg/dl) and endocan levels (697.0 (528.3–974.8) versus 222.5 (158.8–565.8) ng/L) when compared with patients without SCA (Table 2).

Correlation analysis identified significant correlation between endocan levels and PTH levels ($r = 0.5$, $p = 0.005$), hsCRP levels ($r = 0.55$, $p = 0.002$), and CIMT measurements ($r = 0.59$, $p = 0.001$) (Table 3). ROC curve analysis of endocan for identification of SCA in HD patients showed that at a cutoff of 380.5 ng/L, endocan has an AUC of 0.862 with a sensitivity and specificity of 92.9% and 68.7%, respectively (Figure 2).

4. Discussion

Serum endocan levels showed significant changes in many acute and chronic conditions [14, 15]. The present study found significantly higher endocan levels in patients' groups as compared to healthy controls. Moreover, HD patients were found to have significantly higher endocan levels when compared with their CKD counterparts. These findings are in line with other reports [16–18]. Lee et al. [16] noted that CKD patients have significantly higher serum endocan levels as compared to controls. They also noted a significant association between serum endocan levels and poor renal function.

TABLE 1: Clinical and laboratory data in the studied groups.

	HD N=30	CKD N=30	<i>p</i> value
Age (years) mean ± SD	55.5 ± 11.6	56.9 ± 10.5	0.62
Male/female n	20/10	16/14	0.43
<i>Cause of renal impairment n (%)</i>			
HTN	22 (90.0)	19 (63.3)	0.41
DM	13 (43.3)	15 (50.0)	0.61
PKD	1 (3.3)	—	0.31
Unknown	1 (3.3)	—	0.31
BMI (kg/m ²) mean ± SD	28.4 ± 2.6	27.9 ± 3.7	0.52
<i>Laboratory findings mean ± SD/median (IQR)</i>			
Urea (mg/dl)	163.5 (136.3–193.5)	118.5 (85.3–160.8)	0.005
Creatinine (mg/dl)	9.8 (7.9–10.8)	3.2 (2.2–4.8)	<0.001
Ca (mg/dl)	8.9 ± 1.0	8.5 ± 1.3	0.19
Po ₄ (mg/dl)	4.9 ± 1.8	5.5 ± 1.6	0.19
Albumin (mg/dl)	3.4 ± 0.7	4.1 ± 0.3	<0.001
PTH (pg/ml)	538.0 (342.3–654.8)	110.0 (50.0–170.0)	0.052
Cholesterol (mg/dl)	193.3 ± 43.6	174.1 ± 52.4	0.13
Triglycerides (mg/dl)	175.2 ± 75.1	157.3 ± 73.4	0.36
WBCs (×10 ³ /ml)	6.5 ± 2.4	7.6 ± 2.5	0.1
Hb (gm/dl)	10.8 ± 1.5	10.4 ± 1.5	0.38
Platelets (×10 ³ /ml)	205.2 ± 76.0	272.7 ± 86.5	0.002
Uric acid (mg/dl)	7.8 ± 1.5	6.2 ± 1.8	0.001
hsCRP (mg/dl)	28.5 (21.8–39.5)	15.0 (9.8–20.3)	<0.001
CIMT mm	0.80 (0.80–0.90)	0.75 (0.73–0.75)	<0.001
SCA n (%)	14 (46.7)	4 (13.3)	0.005
Endocan (ng/L)	519.0 (202.3–742.0)	409.0 (245.3–505.3)	0.014

BMI: body mass index, CIMT: carotid intima-media thickness, DM: diabetes mellitus, Hb: hemoglobin, hsCRP: high-sensitivity C-reactive protein, HTN: hypertension, PTH: parathyroid hormone, SCA: subclinical atherosclerosis, and WBCs: white blood cells. The values in italics are significant results.

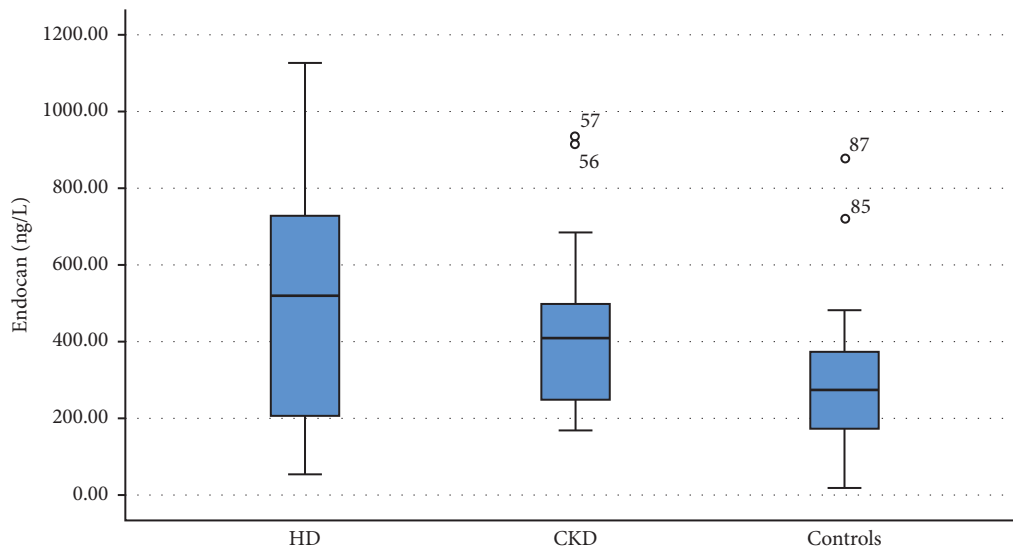


FIGURE 1: Serum endocan levels in the studied groups.

The study of Pawlak et al. [17] found similar results. They also noted significant correlations between endocan levels and other markers including soluble intercellular (sICAM-1) and vascular cellular (sVCAM-1) adhesion molecules and tumor necrosis factor alpha (TNF- α), highlighting the contribution of endocan to vascular pathology and inflammation. Likewise, the study of Samouilidou et al. [18] found significantly higher endocan levels in CKD patients. Furthermore, they reported

inverse correlation between endocan levels and paraoxonase 1 (PON), a marker known for its antiatherogenic properties. Their conclusions again confirm the detrimental influence of enhanced endocan expression on vascular health. Yilmaz et al. [19], in addition, found a positive correlation between endocan and CKD stage and negative correlation between it and eGFR. They also found a highly significant positive correlation between endocan and proteinuria. Similarly, Su

TABLE 2: Comparison between HD patients with and without SCA regarding clinical and laboratory data.

	SCA + ve n = 14	SCA -ve n = 16	p value
Age (years) mean \pm SD	60.8 \pm 6.6	50.9 \pm 13.2	<i>0.017</i>
Male/female n	11/3	9/7	0.2
<i>Cause of renal impairment n (%)</i>			
HTN	12 (85.7)	10 (62.5)	0.15
DM	7 (50.0)	6 (37.5)	0.49
PKD	—	1 (6.3)	0.34
Unknown	1 (7.1)	—	0.28
BMI (kg/m ²) mean \pm SD	28.1 \pm 2.3	28.7 \pm 2.8	0.57
<i>Laboratory findings mean \pm SD/median (IQR)</i>			
Urea (mg/dl)	165.0 (102.5–184.8)	162.0 (141.0–202.5)	0.58
Creatinine (mg/dl)	10.2 (7.3–11.0)	9.8 (8.2–10.7)	0.73
Ca (mg/dl)	9.4 \pm 0.9	8.6 \pm 1.0	<i>0.022</i>
Po4 (mg/dl)	4.1 \pm 2.0	5.6 \pm 1.5	<i>0.029</i>
Albumin (mg/dl)	3.6 \pm 0.6	3.3 \pm 0.7	0.24
PTH (pg/ml)	614.5 (571.5–752.5)	384.5 (206.5–507.3)	<i>0.01</i>
Cholesterol (mg/dl)	202.9 \pm 52.1	184.9 \pm 34.1	0.27
Triglycerides (mg/dl)	187.1 \pm 77.7	164.8 \pm 73.7	0.43
WBCs ($\times 10^3$ /ml)	6.1 \pm 1.8	6.9 \pm 2.8	0.35
Hb (gm/dl)	10.6 \pm 1.5	10.9 \pm 1.5	0.5
Platelets ($\times 10^3$ /ml)	219.3 \pm 95.2	193.0 \pm 54.6	0.35
Uric acid (mg/dl)	8.2 \pm 1.3	7.4 \pm 1.5	0.14
hsCRP (mg/dl)	36.5 (26.8–43.5)	24.0 (15.8–29.0)	<i>0.003</i>
Endocan (ng/L)	697.0 (528.3–974.8)	222.5 (158.8–565.8)	<i><0.001</i>

The values in italics are significant results.

TABLE 3: Correlations between serum endocan levels and clinical and laboratory data in the studied patients.

	HD		CKD	
	r	p value	r	p value
Age	0.33	0.07	0.49	<i>0.006</i>
BMI	0.05	0.81	-0.26	0.17
Urea	-0.02	0.9	0.13	0.5
Creatinine	0.09	0.65	0.32	0.08
Ca	0.29	0.12	-0.13	0.49
Po4	-0.3	0.1	0.05	0.78
Albumin	-0.2	0.3	-0.16	0.39
PTH	0.5	<i>0.005</i>	-0.004	0.98
Cholesterol	0.28	0.14	-0.04	0.82
Triglycerides	0.31	0.1	0.09	0.64
WBCs	0.12	0.53	-0.06	0.74
Hb	-0.29	0.12	0.19	0.31
Platelets	0.3	0.11	-0.19	0.33
Uric acid	-0.03	0.88	0.07	0.71
hsCRP	0.55	<i>0.002</i>	0.1	0.6
CIMT	0.59	<i>0.001</i>	0.36	<i>0.049</i>

The values in italics are significant results.

et al. [20] found that endocan showed a drift of elevation in late-stage CKD.

In our work, HD patients with SCA had significantly higher endocan level. This novel finding is supported by similar findings reported in other patient groups. In SLE patients, Icli et al. [11] showed an association between serum endocan levels and SCA. Likewise, Lv et al. [10] found that elevated endocan levels are significant risk factors for SCA associated with diabetes mellitus. Similarly, SCA was related to serum endocan levels in psoriatic patients [12].

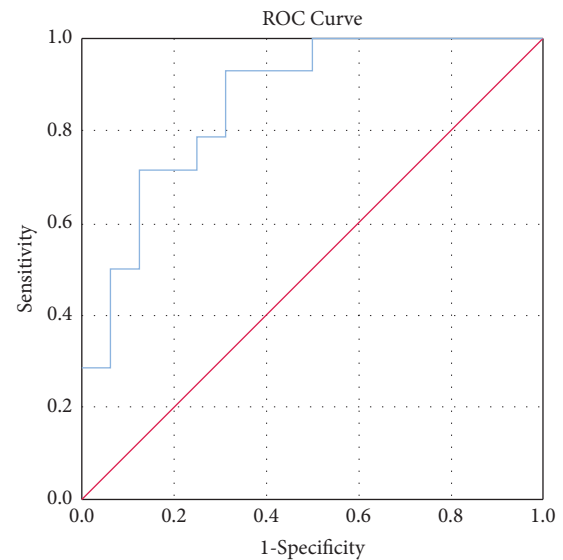


FIGURE 2: ROC curve for endocan levels in HD patients.

In our work, HD patients with SCA had significantly higher hsCRP when compared with patients without. The relation between SCA and elevated CRP levels in HD patients is well documented. Yilmaz et al. [19], Buyukhatipoglu et al. [21], and Tirmenstajn-Jankovic and Dimkovic [20] identified a relation between CRP levels and CIMT.

Interestingly, the present study identified a significant direct correlation between serum endocan and PTH levels in HD patients. The association between endocan and PTH levels was previously reported in renal transplant patients

[22]. The association between endocan and PTH is probably related to the contribution of both biomarkers to the augmented inflammatory condition during HD. In our study, endocan was well correlated with the inflammatory biomarker CRP while previous reports documented the relation between PTH and CRP [23, 24].

There are multiple mechanisms that can explain the contribution of endocan to SCA in HD patients. Endocan was reportedly involved in endothelial dysfunction in many pathological conditions including sarcoidosis [25], pre-eclampsia [26], and silent brain infarction [27]. Endocan probably exerts its effects on the vascular endothelium through alteration of nitric oxide secretion by activation of AKT/eNOS and NF- κ B/iNOS pathways [28].

Moreover, endocan expression was pronounced in association with exaggerated inflammatory conditions in multiple diseases including prediabetes and type 2 diabetes [29], systemic sclerosis [30], and chronic kidney disease [31]. Gaudet et al. [32] suggested that the inflammatory actions of endocan may be mediated through control of human leukocyte trans-endothelial migration.

In conclusion, the present study suggests that serum endocan levels are related to SCA in HD patients. In addition, it is associated with the hyperinflammatory state and secondary hyperparathyroidism in those patients. Findings of this study may have therapeutic implications. Targeting endocan can be proposed as a novel approach for management of cardiovascular pathology in HD patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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