

Original article**Evaluation of Endocan Serum Level as a Marker of Cardiovascular Risk in Children on Maintenance Hemodialysis.****Manal Abdel-Salam¹, Aliaa Atef¹, Naglaa Fathy¹, Nadia Yousif², Hala Maghraby³****1-** Pediatric Department, Faculty of Medicine (for Girls), Al-Azhar University, Cairo, Egypt.**2-** Clinical Pathology Department, National Heart Institute, Cairo, Egypt.**3-** Radiology Department, Faculty of Medicine (for Girls), Al-Azhar University, Cairo, Egypt.**ABSTRACT**

Introduction: Chronic kidney disease (CKD) patients have a higher risk of premature death, mainly due to cardiovascular reasons. Endocan plays a crucial role in causing endothelial dysfunction and inflammation, which makes it a valuable biomarker for detecting cardiovascular disease prognosis.

Aim of the study: This study aims to investigate the correlation between Endocan levels in the serum of children undergoing hemodialysis and intimal-medial thickness (IMT) and peak systolic velocity of the main arteries.

Methods: A comprehensive analysis was conducted to evaluate serum levels of endocan, intimal medial thickness, and peak systolic velocity using Doppler ultrasound, in addition to routine laboratory investigations.

Result: Children who underwent hemodialysis had higher endocan levels than the control group; the median and (IQR) of endocan serum levels were 144.35 (122.2 – 247.55 pg/ml) and 61 (29.05 – 108.8 pg/ml), respectively (P<0.01). The hemodialysis group showed a significant increase in the intima-media thickness (IMT) of the carotid, ulnar, and femoral arteries. Moreover, there was a substantial decrease in the peak systolic velocity (PSV) of the carotid and ulnar arteries in the hemodialysis group. The study also found a positive correlation between the levels of endocan and C-reactive protein (CRP) and the IMT of the carotid, ulnar, and femoral arteries.

Conclusion: Children undergoing hemodialysis displayed elevated endocan levels, significantly associated with increased IMT in major arteries. Endocan plays a significant role in developing and propagating atherosclerosis, thereby increasing the risk of cardiovascular disease.

KEYWORDS

Endocan, Hemodialysis, Children, Cardiovascular Risk, IMT

Corresponding author: Manal Abd El-Salam

Affiliation: Prof of pediatrics and Pediatric Nephrology Al-Azhar University

Email: manal24969@gmail.com

Phone: 01006337676

Address: children's hospital at Al Zahraa Hospital AL Azhar -University, Egypt.

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INTRODUCTION

Unfortunately, individuals with end-stage renal disease (ESRD) often experience cardiovascular disease as a leading cause of mortality. Dialysis treatment for ESRD can exacerbate chronic electrolyte and hemodynamic imbalances, leading to abrupt and drastic fluctuations in fluid volume and electrolyte levels. These changes can result in subendocardial ischemia, increased left ventricular wall mass, diastolic dysfunction, and a complex pathophysiological cascade that may lead to severe arrhythmia [1].

A tool to predict cardiovascular risk in patients with ESRD would be beneficial. Endocan is a promising biomarker for cardiovascular disease, as serum levels are significantly increased in patients with cardiovascular disease, and it is considered a risk factor [2].

Endocan is a soluble dermatan sulfate proteoglycan primarily secreted by activated endothelium and expressed in lung and kidney endothelial cells. Pro-inflammatory cytokines influence the levels of its secretion. The production and secretion of endocan are stimulated by tumour necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), lipopolysaccharide, and angiogenic factors such as vascular endothelial growth factor (VEGF). In contrast, interferon- γ is known to have a down-regulatory effect on endocan. [3].

Endocan is crucial in endothelial dysfunction and inflammation and is associated with poor clinical outcomes in various diseases [4]. It is an independent risk factor that regulates many essential bodily functions, such as angiogenesis,

vascular remodelling, vascular tone, tissue-fluid homeostasis, host defence, and inflammation. In atherosclerosis and ischemic heart, impaired endothelial cell integrity and function are significant. Endothelial damage increases the production of reactive oxygen species (ROS), which decreases nitrous oxide (NO) production by increasing the concentration of calcium ions in the cytoplasm [5].

When endothelial function is impaired, NO release significantly decreases, and vascular ROS generation increases, leading to arterial vasoconstriction and hypertension. Clinical data found that endocan remained independent and positively correlated with hypertension. For every increase of 1 pg/mL of endocan, hypertension increased by 32.2%. [6].

In children with early-stage hypertension, the plasma concentration of endocan is significantly elevated. Endocan levels are positively associated with renal enzymes, norepinephrine, carotid intima-media thickness, and high-sensitivity C-reactive protein (hsCRP) [7]. In addition, patients with higher endocan levels showed higher arterial pulse wave velocity, a sign of arterial stiffness [8].

Endocan has been identified as a potentially helpful biomarker for monitoring the progression of coronary heart disease in hypertensive patients. According to clinical data, endocan levels in serum are positively associated with myocardial infarction thrombolysis risk score and major adverse cardiac events (MACE) and are independently correlated with MACE [9].

The current study aims to compare Endocan serum concentration levels

between children with chronic kidney disease on hemodialysis and healthy controls and identify the association between Endocan levels and medial intimal thickness and peak systolic velocity of the main vessels [10].

METHODS

The study was conducted between February 2022 and August 2022, including 80 participants. The participants were selected from the nephrology and hemodialysis unit and the outpatient paediatric clinic. The study population was divided into two groups: the dialysis group, which included 40 individuals undergoing regular haemodialysis⁽¹⁰⁾ for more than three months 27 (67.5%) males and (32.5%) females; the control group, which included 40 healthy children of the same age and sex. Children with chronic or acute infections and primary cardiovascular disease were excluded from the study.

All children who participated in the study underwent a careful medical history-taking process, which included a detailed preformed sheet of medical history, including the aetiology of chronic kidney disease, duration of kidney impairment, duration of haemodialysis, medications, and history of any other disease. They also underwent a thorough clinical examination, which included meticulous general examination with particular emphasis on general manifestations of renal disease (oedema, hypertension, and growth affection), complete general and local systemic examination, and laboratory and radiological investigations.

Before the study, the parents of the participating children were informed of the

study's purpose. They gave written consent to our hospital's ethical guidelines. All participants underwent identical procedures; the study was performed collaboratively with the paediatric nephrology, haemodialysis, clinical pathology, and radiology departments.

Investigations:

Sampling

Five milliliters' of venous blood was collected on the mid-week dialysis day after overnight fasting for analysis. 2 millilitres of blood was utilized for a complete blood count test using EDTA solution. The remaining 3 millilitres of blood were allowed to clot, and the serum was immediately separated to assess biochemical parameters such as Blood Urea Nitrogen (BUN), serum creatinine, calcium, phosphorus, ALP and PTH. The HITACHI auto analyser performed all tests. Additionally, 2 millilitres of the serum sample were carefully labelled and stored at -20°C until the Endocan assay was conducted using the ELISA technique.

Endocan concentration in serum was determined using sandwich enzyme-linked immunosorbent assay (ELISA). Antibody-coated wells were incubated with predetermined concentrations of standards and test samples. After washing, biotin-labelled and Horseradish peroxidase (HRP) conjugate antibodies were added. The TMB substrate solution was added to each well to visualise the enzymatic reaction. The optical density was read at 450 nm, and the concentration of Endocan was calculated from the standard curve. <http://www.fn-test.com>.

Radiological investigations:

Doppler U/S assessment of:

Intimal medial thickness (IMT) and peak systolic velocity (PSV) of the main

arteries, including the carotid, femoral and ulnar arteries. Both intimal medial thickness and peak systolic velocity are measured using the Doppler U/S “Esaote My lab50X vision” apparatus in Al-Zahra University Hospital.

Carotid, femoral and ulnar intimal medial thickness assessment:

The carotid, femoral, and ulnar intimal medial thicknesses were measured by greyscale ultrasound using a 7.5 MHZ probe. Patients were examined supine with heads slightly tilted to the side in (CIMT), and groin and abdominal areas were exposed in femoral and articular intima-media thickness. The IMT was calculated as the distance between the leading edge of the lumen–intima interface and the media–adventitia interface on the far wall of the artery.

Peak systolic velocity (PSV)

PSV was measured using a 7.5MHZ probe in the supine position. Gel was applied to the examination area. Carotid, aortic, and femoral arteries were examined longitudinally using Doppler examination through B mode, colour mode, and pulse wave [11].

STATISTICAL ANALYSIS

The data was collected, revised, coded, and entered into IBM SPSS version 20 for statistical analysis. Qualitative data was presented as numbers and

percentages, while quantitative data was presented as mean, standard deviation, and range if the distribution was parametric. In the case of a non-parametric distribution, the data was presented as a median with interquartile ranges (IQR). The Receiver Operating Characteristic (ROC) curve was utilized to determine the best cutoff point with sensitivity and specificity. The significance level was considered as follows: $P > 0.05$ (significant), $P < 0.05$ (significant).

RESULTS

The findings of the current case-control study indicate that children on hemodialysis have significantly higher systolic blood pressure than the control group. Furthermore, the study revealed a significant decrease in haemoglobin and red blood cell count. At the same time, there was a significant increase in urea, creatinine, phosphate, parathyroid hormone, cholesterol, triglycerides, C-reactive protein and endocan serum levels

Table 1.

Doppler assessment revealed increased IMT of carotid, ulnar, and femoral arteries, with decreased PSV of carotid and ulnar arteries in children on hemodialysis than their controls **Table 2.**

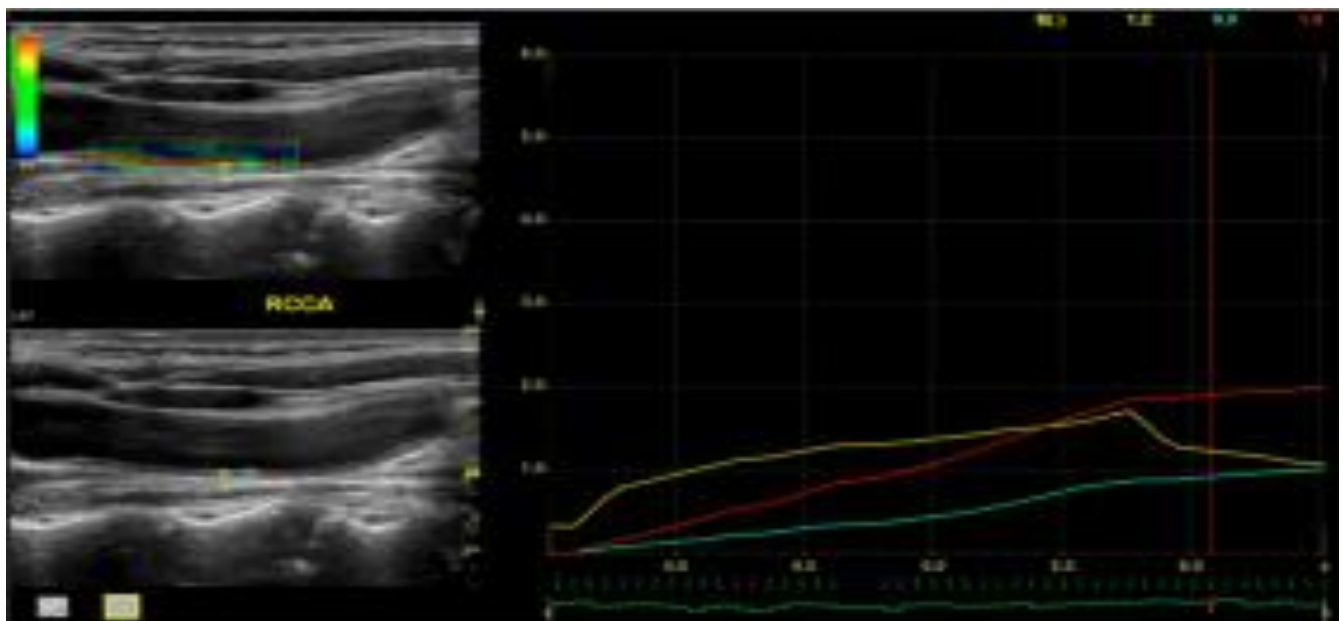
Table 1: Clinical and Laboratory data.

Variable	Control group No. = 40 Mean± SD	Patients group No. = 40 Mean ±SD	Test value	P-value
SBP (mmHg)	101.75 ± 7.89	131.0 ± 13.92	-11.560•	0.001
DBP (mmHg)	61.38 ± 6.20	83.63 ± 9.13	-12.753•	0.001
TLCx10 ³ /UL	7.72 ± 1.30	6.61 ± 2.31	2.655•	0.010
RBCsX10 ⁶ /UL	4.74 ± 0.37	3.51 ± 0.63	10.669•	0.001
Hb(gm/dl)	12.00 ± 0.86	9.46 ± 1.85	7.911•	0.001
Hct%	36.46 ± 2.50	28.61 ± 5.75	7.922•	0.001
PlatetetsX10 ³ /UL	291.78 ± 54.88	224.65 ± 79.96	4.377•	0.001
Ph(mg/dl)	4.36 ± 0.30	5.44 ± 2.18	-3.100•	0.003
Ca(mg/dl)	9.08 ± 0.37	8.46 ± 2.55	1.543•	0.127
Cholesterol mg/dl	101.95±11.79	168.93±32.41	-12.281•	0.001
Triglyceride mg/dl	83.38±17.44	175.33±46.46	-11.718	0.001
Variable	Median (IQR)	(Median IQR)		
Creatinine(mg/dl)	0.4 (0.25 – 0.50)	2.1 (1.65 – 3.20)	-7.704#	0.001
ALP(IU/l)	174.5 (154 – 212)	316 (176.5 – 494.5)	-3.864#	0.001
PTH (pg/ml)	54.5 (44.5 – 63.0)	342.5 (173.5 – 714)	-7.430#	0.001
CRP (mg/l)	3 (2 - 4)	12.5 (8 - 24)	-6.664#	0.001
Endocan (pg/ml)	61 (29.05 – 108.8)	144.35 (122.2 – 247.55)	-5.543#	0.001

SBP (Systolic blood pressure), DBP (diastolic blood pressure), PTH (parathyroid hormone), ALP (Alkaline phosphatase), IQR (Interquartile range)

Table 2: Comparison between patients' group and control group regarding IMT of the main arteries

IMT (mm)	Control group No. = 40 Mean± SD	Patients group No. = 40 Mean± SD	t-test	P-value
Carotid	0.05±0.01	0.06±0.02	-2.992•	0.004
Ulnar	0.04±0.01	0.05±0.01	-3.800•	0.001
Femoral	0.05±0.01	0.07±0.01	-6.616•	0.001
PSV (cm/sec.)				
Carotid	52.8 ± 8.16	47.35 ± 4.81	3.641	0.0001
Ulnar	43.53 ± 6.26	38.8 ± 6.36	3.349	0.0003
Femoral	60 ± 8.54	57.43 ± 9.88	1.247	0.10806

**Figure 1: IMT of the carotid artery in one of the study cases**

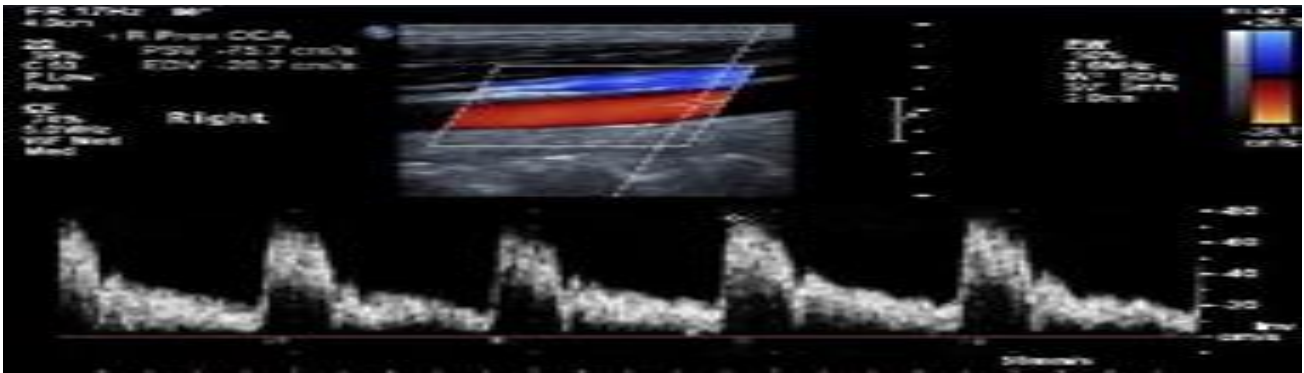


Figure 2: PSV of the carotid artery in one of the study cases

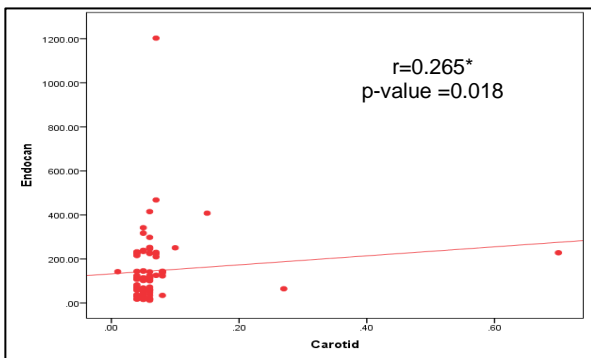


Figure 3: Correlation between Endocan level and Carotid IMT.

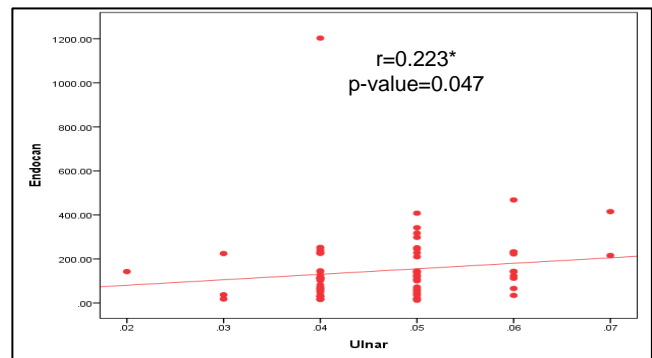


Figure 4: Correlation between Endocan level and ulnar IMT.

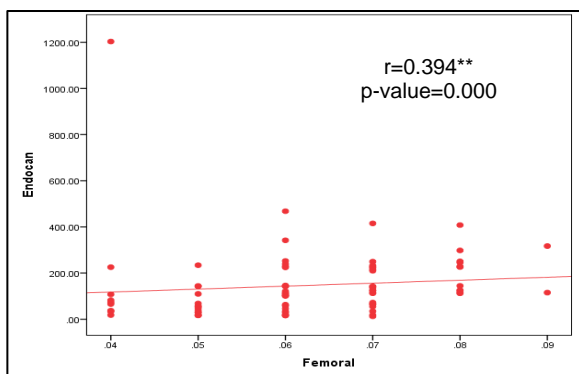


Figure 5: Correlation between Endocan level and femoral IMT.

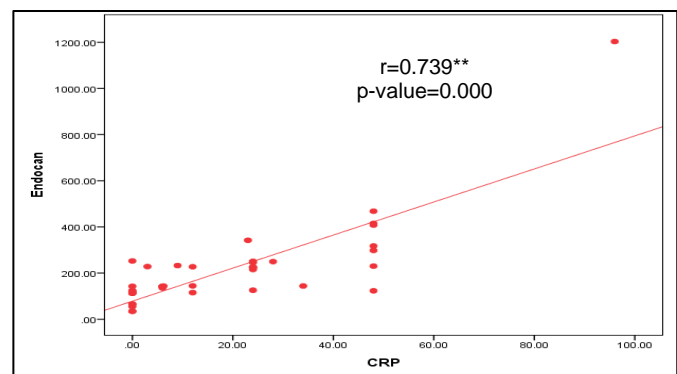


Figure 6: Correlation between Endocan level and CRP level

Based on the current study, we observed that there is a notable positive correlation between the intima-media thickness (IMT) of the main arteries and systolic and diastolic blood pressure, urea, creatinine, parathyroid hormone (PTH), cholesterol, phosphate, and triglycerides. On the other hand, there is a significant negative correlation between IMT and red blood cells (RBCs), haemoglobin (Hb), and hematocrit (Hct%). **Table 3**

The study determined that an endocan level greater than 111 pg/ml had a sensitivity of 87.5% and specificity of 80.0% for predicting CKD-CVD in hemodialysis children. **Table 4 and Figure 7.**

During the assessment of carotid and ulnar arteries, IMT showed that carotid IMT is highly specific but not sensitive in predicting cardiovascular risk in children undergoing hemodialysis **Table 5 and Figure 8.**

Table 3: Correlation between IMT of main arteries (carotid, ulnar and femoral) with clinical and laboratory data

Variable	IMT mm	Carotid		Ulnar		Femoral	
		r	p-value	r	p-value	r	p-value
Duration		0.157	0.334	0.063	0.699	-0.182	0.261
SBP (mmHg)		0.340**	0.002	0.289**	0.009	0.455**	0.001
DBP (mmHg)		0.279*	0.012	0.286*	0.010	0.452**	0.001
WBC (cmm) ³		-0.032	0.779	-0.120	0.289	-0.163	0.149
RBC (cmm) ³		-0.492**	0.001	-0.458**	0.000	-0.540**	0.001
Hb (gm/dl)		-0.464**	0.001	-0.445**	0.000	-0.394**	0.001
Hct%		-0.485**	0.001	-0.458**	0.000	-0.433**	0.001
PLT (cmm) ³		-0.055	0.628	-0.042	0.709	-0.269*	0.016
Urea (mg/dl)		0.237*	0.034	0.310**	0.005	0.385**	0.001
Creatinine (mg/dl)		0.246*	0.028	0.269*	0.016	0.435**	0.001
Ca (mg/dl)		-0.115	0.311	0.078	0.494	-0.072	0.526
Ph (mg/dl)		0.312**	0.005	0.350**	0.001	0.181	0.107
ALP (IU/L)		0.148	0.190	0.058	0.612	0.204	0.069
PTH (pg/ml)		0.273*	0.014	0.277*	0.013	0.475**	0.001
Cholesterol (mg/dl)		0.293**	0.008	0.333**	0.003	0.537**	0.001
Triglyceride mg /dl		0.348**	0.002	0.451**	0.000	0.576**	0.001

Table 4: Receiver operating characteristic curve (ROC) for endocan level in predicting CKD-CVD) in hemodialysis children.

Parameters	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
Endocan (pg/ml)	>111	0.860	87.50	80.00	81.4	86.5

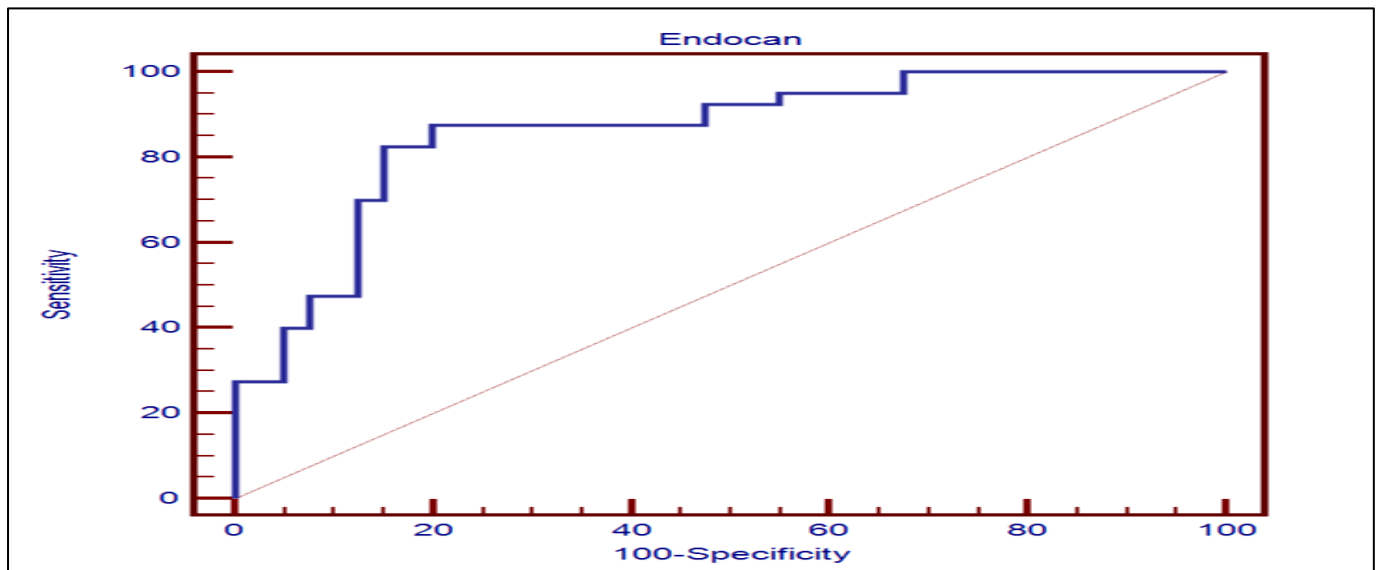


Figure 7: Receiver operating characteristic curve (ROC) for endocan level predicting CVD) in hemodialysis children.

Table 1: Receiver operating characteristic curve (ROC) for IMT parameters in predicting CKD-CVD) in hemodialysis children

IMT (mm)	Cut off point	AUC	Sensitivity%	Specificity%	+PV	-PV
Carotid	>0.06	0.710	37.50	97.50	93.7	60.9
Ulnar	>0.04	0.726	70.00	67.50	68.3	69.2

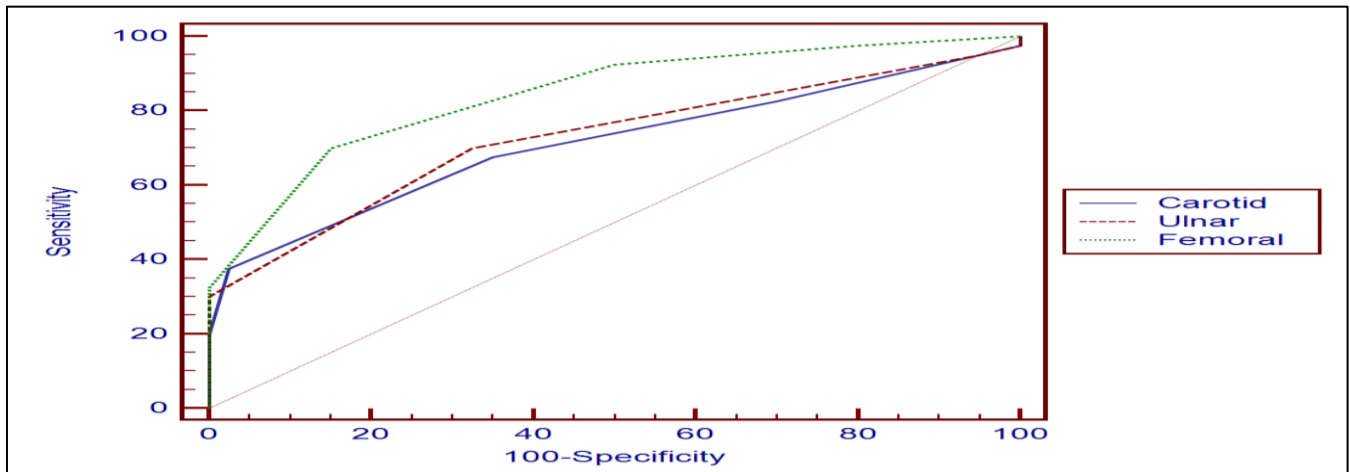


Figure 8: ROC for carotid and Ulnar IMT in predicting CKD-CVD in hemodialysis children.

DISCUSSION

Despite the medical community's recent advances in preventive medicine, cardiovascular disease (CVD) remains the leading cause of death among chronic kidney disease (CKD) patients [12]. This indicates that the risks associated with CVDs are potentially underestimated [13]. Therefore, it is crucial to identify new biomarkers that can aid in the early detection and prevention of CVDs, making it one of the most pressing matters in medicine.

Our study aimed to evaluate the relationship between Endocan plasma levels and intimal medial thickening in children on regular hemodialysis as a marker of cardiovascular risk in these patients.

The current research has found that children undergoing hemodialysis have higher Endocan levels than healthy children. Elevated Endocan levels indicate inflammation and endothelial injury, as stated in a report by Gunay and Mertoglu [14]. We have also observed a significant correlation between Endocan and CRP. Another study conducted by Pawlak et al. [15] reported that patients with chronic

kidney disease (CKD) had increased plasma Endocan levels, which was linked to a higher prevalence of cardiovascular disease in such patients.

Numerous studies have shown that endocan plays a role in endothelial dysfunction and inflammation. It could also be an independent risk factor for unfavourable clinical outcomes in different disease conditions [16-18].

A meta-analysis found that higher serum endocan levels increase patients' risk of cardiovascular disease [19-21]. A research study by Lee et al. [22] reported a correlation between plasma endocan levels and cardiovascular events.

According to the current study, children undergoing hemodialysis had significantly higher intima-media thickness (IMT) in their carotid, ulnar, and femoral arteries compared to the control group. These results were like those of Lopes et al. [23]. Furthermore, Lawal et al. [24], Kajitani et al. [25], and Lahoti et al. [26] also reported higher mean carotid IMT in CKD patients compared to the control group. Intima-media thickness is a measure of atherosclerotic vascular disease, and it is considered a comprehensive picture of all alterations

caused by multiple cardiovascular risk factors over time on the arterial walls. [27-28].

The results of the current study reveal a significant correlation between endocan and the thickness of the carotid, ulnar, and femoral arteries (IMT). Furthermore, there was a significant correlation between endocan and CRP levels. According to [29], there is a positive correlation between endocan levels, CRP levels, and arterial stiffness markers.

In a study conducted by Oktar et al. [7], it was found that endocan was significantly correlated with cIMT. Likewise, [30] reported that serum endocan levels were positively correlated with cIMT and hsCRP. The endocan level in the blood is positively correlated with renal enzymes, norepinephrine [31], and CKD-related inflammation. This inflammation can lead to endothelial dysfunction and increase the risk of atherosclerosis [32]. Patients with subclinical atherosclerosis (SCA) undergoing HD had significantly higher CRP levels than those without. The relationship between SCA and elevated CRP levels in HD patients has been well documented. Studies conducted by Yilmaz et al. [33], Buyukhatipoglu et al. [34], and Tirmenstajn-Jankovic and Dimkovic [35] identified a correlation between CRP levels and carotid intimal thickness (cIMT).

The study revealed that children with chronic kidney disease who were on hemodialysis had increased cholesterol, triglycerides, urea, creatinine, CRP, phosphate, and PTH levels. The study also

showed increased systolic and diastolic blood pressure; these children were anemic. These traditional markers for cardiovascular risk were significantly correlated with increased thickness of the main arteries studied (IMT).

Various factors have been considered for the increasing incidence of cardiovascular morbidity and mortality in ESRD patients, including dyslipidemia, hypertension, low-grade inflammation, high homocysteine, and disturbances in calcium and phosphorus homeostasis [36]. Uremia can worsen atherosclerosis by disrupting lipid metabolism and causing inflammation due to renal or systemic inflammatory disease, heart failure, and dialysis-dependent procedures in patients with chronic kidney disease (CKD) [37-38].

Roc curve analysis demonstrated that Endocan is highly sensitive as a predictor of cardiovascular risk compared to cIMT, which is highly specific but not sensitive for early detection of CVS risk in hemodialysis children.

CONCLUSION

This research is the first to discuss the endocan levels in children who undergo hemodialysis, along with its relation to the main arteries' intima-media thickness (IMT). The study revealed a significant increase in serum endocan levels in these children, which is associated with the development and progression of cardiovascular risk.

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AUTHORS’ CONTRIBUTIONS.

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Conception and design of study: MS
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STATEMENTS

Ethics approval and consent to participate.

This study protocol and the consent were approved and deemed sufficient by the Ethical Committee of AL-Zahraa Hospital, Al-Azhar University, and informed written consent was obtained from their legal guardians in every case.

Consent for publication

The contents and material of the manuscript have yet to be previously reported at any length or are being considered for publishing elsewhere.

Availability of data and material

“Not applicable”

Conflict of interest

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