

The Relationship between Circulating Levels of Osteopontin with Carotid Intima-Media Thickness in Children on Regular Hemodialysis

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How to cite this paper: Mohamed, R., Tawfeek, E., Abdel-Salam, M., Ghoraba, N.M. and Maghraby, H. (2021) The Relationship between Circulating Levels of Osteopontin with Carotid Intima-Media Thickness in Children on Regular Hemodialysis. *Open Journal of Nephrology*, **11**, 467-476. <https://doi.org/10.4236/ojneph.2021.114039>

Received: September 17, 2021

Accepted: November 8, 2021

Published: November 11, 2021

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Abstract

Background: Chronic kidney disease (CKD) is associated with cardiovascular morbidity and mortality. Osteopontin (OPN) is a critical factor in developing atherosclerosis and increases the risk for a major adverse cardiovascular event. **Aim:** To investigate osteopontin serum levels in hemodialysis children and detect the association between the main arteries' intimal medial thickness (IMT) and peak systolic velocity. **Material and Methods:** This case-control study included 30 children on regular hemodialysis and 30 children age and sex-matched as controls their age range from 4 to 18 years; we investigated osteopontin serum level in addition to the Doppler ultrasound assessment of intimal medial thickness and peak systolic velocity (PSV) of the main arteries in the same line with the traditional markers of the routine investigations of children on regular hemodialysis. **Results:** Significantly high osteopontin level in hemodialysis children than the controls was (0.85 ± 0.21 ng/ml) (0.69 ± 0.26 ng/ml), respectively ($p = 0.026$). A significant increase in the (IMT) of the main arteries, including the carotid and femoral arteries, in the patient's group than the controls, was (0.51 ± 0.01 mm) (0.69 ± 0.01 mm) (0.32 ± 0.036 mm) (0.55 ± 0.01), respectively ($p = 0.001$). There is a strong correlation between (OPN) with the (IMT) of carotid and femoral arteries, a significant positive correlation between (OPN) with urea, creatinine, triglyceride, PTH, ferritin, CRP, and ESR, and a negative correlation with RBCs count and carotid PSV. **Conclusion:** High osteopontin level is consistent with the increased IMT of the main arteries in hemodialysis children that seem to play a significant role in developing and propagating atherosclerosis in hemodialysis children, evidenced by significant association with inflammatory markers and uremic toxins.

Keywords

Children, Hemodialysis, Osteopontin

1. Introduction

CKD is associated with a substantially increased risk of cardiovascular morbidity and mortality, independent of traditional cardiovascular risk factors, such as diabetes and hypertension (Kakitapalli *et al.*, 2020) [1].

The risk of cardiovascular events is increased markedly in patients with severe CKD, with cardiovascular mortality being 10 - 30-fold higher than that of age-matched controls. Traditional and nontraditional or novel risk factors contribute to an elevated risk of cardiovascular events in patients with reduced estimated glomerular filtration rate (eGFR) (Webster *et al.*, 2017) [2].

Traditional risk factors of CVD such as hypertension and dyslipidemia cannot fully explain the increased rate of cardiovascular events reported in patients with CKD. Also, nontraditional risk factors, such as anemia, hyperhomocysteinemia, abnormal calcium and phosphate metabolism, oxidative stress, and inflammation, have been reported as potential risks (Alani *et al.*, 2014) [3].

Osteopontin (OPN) is a bone-specific sialoprotein with three splice variants with several post-translational modifications, acute and chronic inflammatory cells, smooth muscle, epithelial and endothelial cells, neurons, and several post-translational modifications fetal renal tissue. It is expressed in the thick ascending limb of the loop of Henle (Kaleta, 2019) [4].

OPN is a multifunctional protein that regulates bone remodeling, inhibits ectopic calcification, and is involved in inflammation, fibrosis, and cell survival. It has been demonstrated to play a pivotal role in atherosclerotic vasculopathy by inducing inflammation and inhibiting VC (Wolak, 2014) [5].

OPN is important in the regulation of vascular calcification and bone mineralization. Local increases in OPN in vessel walls have been linked to atherosclerotic plaque formation, inflammation within arteries, and smooth muscle mineralization (Scatena *et al.*, 2007; Abdalrhim *et al.*, 2016; Icer *et al.*, 2018) [6] [7] [8].

Clinical evidence has been provided that OP is associated with the extension and severity of coronary atherosclerosis and with adverse cardiac outcomes in patients with ischemic heart disease. Furthermore, OP plasma levels were positively correlated with VS in patients with coronary disease but not in young subjects without clinical symptoms or risk factors of atherosclerosis (Tousoulis *et al.*, 2013) [9]. OPN, besides proinflammatory functions, is physiologically a potent inhibitor of mineralization prevents ectopic calcium deposits and is a potent inducible inhibitor of vascular calcification (Wang and Denhardt, 2008) [10].

Acute increases in OPN have protective roles, including wound healing, neo-vascularization, and amelioration of vascular calcification. By contrast, chronic increases in OPN predict poor prognosis of a major adverse cardiovascular event independent of conventional cardiovascular risk factors. Thus, OPN can be a

therapeutic target for CVDs but is not clinically available (Shirakawa and Sano, 2021) [11].

Experimental and clinical evidence indicates that vascular calcification (VC) plays an essential role in developing cardiovascular diseases in CKD patients (Jain *et al.*, 2014) [12]. Increased intima-media thickness (IMT) of the common carotid artery represents a feature of atherosclerosis manifested as diffuse arterial wall thickening, whereas increased IMT of the proximal internal carotid artery is a surrogate for focal atherosclerotic plaque (Coll *et al.*, 2011) [13].

The mean IMT of the common carotid artery is a more reproducible measure than the IMT of the internal carotid artery and is believed to be better suited for cardiovascular risk assessment (Dalager *et al.*, 2007) [14].

We aimed to investigate OPN serum levels in hemodialysis children and detect the association with the IMT of the main arteries.

2. Material and Methods

This case-control study included 40 pediatric patients who fulfilled the criteria for the definition and classification of patients with chronic kidney diseases (Gordon *et al.*, 2008) [15], (they were on regular hemodialysis for 4 hours/setting, three times weekly, with low flux polysulphone dialyzer by 4008 Fresenius machine. The most common cause of CKD in patients group was acquired etiology 14 (35.0%), unknown 9 (22.5%) hereditary 9 (22.5%) followed by congenital causes 8 (20%); their ages ranged from 4 to 18. A group of 40 healthy children, matched age and sex with patients group served as controls. We exclude children with acute kidney injury, acute& chronic diseases, primary vascular or myocardial diseases that affect blood vessel status, such as (familial hypercholesterolemia). They were subjected to entire history taking, including etiology, the onset of CKD, duration of hemodialysis, laboratory investigations, Doppler ultrasound of IMT, and peak systolic velocity of the (carotid, femoral, brachial, and radial) arteries. Informed consent from the participating parents in adherence to the ethical committee guidelines of Alzhraa Hospital, AL-Azhar University, Cairo, Egypt. This study collaborated with pediatric (nephrology and hemodialysis), clinical pathology, and radiology departments.

2.1. Sampling and Methodology

Sample collection and laboratory investigations of children pre-HD: Under a complete aseptic condition, after fasting for 12 hrs.

5 ml venous blood samples were withdrawn.

2 ml for complete blood picture on EDTA solution. 3 ml of the samples left to clot, and sera were separated without delay for the biochemical parameters to be done on the same day, including and serum (urea, creatinine, calcium, phosphorus, ALP, and PTH), by HITACHI auto analyzer. 2 ml of the serum sample stored at -20°C after careful labeling till the time of osteopontin (quantitative determination using ELISA technique. These kits are supplied from Bioassay

Technology Laboratory, with Cat. No E1525Hu, sensitivity: 0.15 ng/ml, and Standard Curve Range from 0.3 ng/ml to 90 ng/ml (Sivakumar and Devaraj, 2011; Christensen *et al.*, 2005) [16] [17].

2.2. Radiology

Intimal medial thickness (IMT) and Peak systolic velocity (PSV) were measured using the doppler U/S “Esaote My lab50Xvisioin” apparatus in Al-Zhraa university hospital. The IMT is the distance between the leading edge of the lumen-intima interface and the media-adventitia interface (Jayanthi *et al.*, 2017) [18].

2.3. Statistical Analysis

Data were collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23. Spearman correlation coefficients to assess the correlation between two studied parameters in the same group. Interpretation of probability values was as follows: $p > 0.05$: non-significant < 0.05 : significant.

3. Results

Table 1 revealed a significant increase in systolic, diastolic blood pressure, CRP, K, cholesterol, triglyceride and PTH and osteopontin serum levels in hemodialysis children than the control group; meanwhile, there is a significant decrease in Wbcs, RBCs, platelets in hemodialysis than the control group.

Table 2 revealed a significant increase in IMT of the main arteries, including (carotid, brachial, ulnar, radial, and femoral arteries. Meanwhile, there is a significant decrease in the peak systolic velocity brachial and ulnar arteries.

Table 3 revealed a significant positive correlation between osteopontin with urea, creatinine, K, ferritin, PTH, CRP ESR, and triglyceride, but a significant negative correlation with RBCs count and carotid PSV.

4. Discussion

Cardiovascular disease remains a leading cause of death globally (Dhindsa *et al.*, 2020) [19], especially those involving a systemic inflammatory process such as atherosclerosis, remain the leading cause of morbidity and mortality in patients with CKD (Carracedo *et al.*, 2020) [20]. Despite recent advances in preventive medicine, CVD remains the cause of death in CKD patients. This suggests that the risks of CVDs are underestimated (Shirakawa and Sano, 2021) [11]; therefore, the utility in identifying new biomarkers is so essential and one of the urgent matters.

Our study sought to evaluate the plasma levels of OPN in hemodialysis children and describe its relationship to the medial intimal thickening of the main arteries. OPN is of particular interest as a biomarker because of its detectability in body fluids that thus, OPN is measurable by minimally invasive means, which

Table 1. Comparison between the control group and patients group regarding age, sex, blood pressure, routine laboratory data and osteopontin serum levels.

Variable	Control group (No. = 40) Mean ± SD	Patients group (No. = 40) Mean ± SD	Independent t-test	
			t	P-value
Age (yrs)	12.22 ± 3.18	11.23 ± 2.97	1.238•	0.221
Male	17 (56.7%)	10 (33.3%)	3.300*	0.069
Female	13 (43.3%)	20 (66.7%)		
Systolic (mmHg)	105.38 ± 3.40	122.33 ± 7.74	3.496	0.001
Diastolic (mmHg)	68.4 ± 1.69	86.35 ± 7.62	3.117	0.003
WBCs/m ³	6.40 ± 0.78	9.32 ± 2.25	4.15	0.004
RBCs × 10 ³	4.97 ± 0.39	3.09 ± 0.59	16.871	0.001*
Hb (mg/dL)	12.05 ± 0.78	9.26 ± 1.17	11.2	0.01
PLT/m ³	281.13 ± 38.13	233.43 ± 36.32	6.899	0.01
ESR/hour	15.63 ± 4.36	37.4 ± 12.33	-8.92	0.01
CRP (mg/l)	4.40 ± 1.37	16.43 ± 5.07	-14.47	0.01
K (meq/L)	4.03 ± 0.5	6.24 ± 0.7	-18.23	0.001
Ca (mg/dL)	10.88 ± 0.44	8.77 ± 0.82	7.513	0.01
Ph mg/dl	3.62 ± 0.43	6.6 ± 2.16	6.762	0.001
Chole (mg/dL)	107.72 ± 1.98	168.64 ± 19.14	-21.81	0.01
TG (mg/dL)	84.67 ± 7.24	171.9 ± 24.67	-21.46	0.001
Ferrrine (µg/l)	110 (90 - 130)	300 (83 - 579)	-2.146 [†]	0.032
PTH pg/ml	91.5 (76 - 110)	1583 (894 - 2000)	-4.850 [†]	0.001
OPN ng/ml	0.69 ± 0.26	0.85 ± 0.21	2.507	0.015

Table 2. Comparison between patients group and the controls regarding intima-media thickness (IMT) and peak systolic velocity (PSV) of the main arteries.

IMT (mm)	Control group (No. = 40) Mean ± SD	Patients group (No. = 40) Mean ± SD	Independent t-test	
			t	P-value
Carotid	0.32 ± 0.036	0.51 ± 0.01	-1.87	0.001
Brachial	0.46 ± 0.01	0.57 ± 0.01	-4.73	0.001
Ulnar	0.43 ± 0.01	0.5 ± 0.01	-3.78	0.001
Radial	0.42 ± 0.01	0.5 ± 0.01	-3.72	0.001
Femoral	0.55 ± 0.01	0.69 ± 0.01	-6.36	0.001
PSV (cm/s) Carotid	52.8 ± 8.16	47.35 ± 4.81	3.641	0.002
Brachial	55.65 ± 8.14	46.53 ± 5.56	5.858	0.001
Ulnar	43.53 ± 6.26	38.8 ± 6.36	3.349	0.001
Radial	40.75 ± 7.42	39.68 ± 6.59	0.685	0.24758
Femoral	60 ± 8.54	57.43 ± 9.88	1.247	0.10806

Table 3. Correlation between osteopontin with laboratory and radiological data.

Variable	r	p
RBCs ($\times 10^6/\text{mm}^3$)	-0.307*	0.017
Hb (g/dl)	-0.245	0.059
Urea (mg/dl)	0.466**	0.010
Creat (mg/dl)	0.568**	0.001
K (meq/L)	0.255*	0.049
PTH pg/ml	0.446**	0.000
Ferritin ug/l	0.290*	0.024
Chole (mg/dL)	0.182	0.164
TG (mg/dL)	0.291*	0.024
ESR	0.678**	0001
CRP	0.599**	0001
Carotid (mm)	0.473**	0.008
Radial (mm)	-0.085	0.520
Femoral (mm)	0.268*	0.039
Carotid PSV (cm/s)	-0.436*	0.016

allows for rapidly repeated measures.

Currently, not many studies have previously shown the circulating levels of OPN in end-stage renal disease in hemodialysis children.

The present study demonstrates a significantly high level of OPN in hemodialysis children than in their controls. OPN expression levels remain elevated in several disease pathologies with a chronic inflammatory component (Lock and Alicia, 2019) [21] and is a multicellular protein that mediates diverse biological functions (Mohamed *et al.*, 2019; Waller *et al.*, 2010) [22] [23]. Indeed, matricellular proteins like OPN are often induced during tissue remodeling and repair, as well as in disease states (Murphy-Ullrich and Sage, 2014) [24].

The current study findings are consistent with previous studies in CKD showing elevated OPN serum levels mainly in the adult population with CKD (Druck *et al.*, 2019; Barreto *et al.*, 2011) [25] [26] some studies have related high circulating levels of OPN to adverse cardiovascular events in the general population (Waller *et al.*, 2010) [23] and in CKD patients (Lamort *et al.*, 2019) [27].

In the current study, we found a significant association between OPN with ESR, CRP, ferritin, and creatinine; our findings indicate that OPN is associated with inflammation and uremic toxins, OPN as T-helper 1 cytokine is believed to exacerbate inflammation in several chronic inflammatory diseases, including atherosclerosis (Wang *et al.*, 2008; Scatena *et al.*, 2007) [6] [10]. Inflammation is now considered one of the main mechanisms of atherosclerosis, and CKD is characterized by systemic inflammation (Swaminathan and Shah, 2011; Zoccali

et al., 2017) [28] [29]. Moreover, it is reported that the upregulation of OPN expression in immune systems leads to the worsening of chronic inflammatory conditions, including atherosclerosis and vascular dysfunction (Podzinkova *et al.*, 2019) [30].

In the current study, lipid parameters cholesterol and triglyceride are significantly elevated in the study patients group with the significant association of serum triglyceride with osteopontin. Dyslipidemia is common in patients with chronic kidney disease on regular hemodialysis; indeed, the accumulation of triglycerides in hemodialysis patients is due to increased production and impaired catabolism Batista *et al.*, 2004 [31]. In addition, in the current study, we found a strong correlation between osteopontin and PTH. This is consistent with a recent study by (Druck *et al.*, 2019) [25]. Indeed osteopontin may play an essential role in vascular calcification OPN knockout mice have been shown to have higher bone formation secondary to PTH-induced increase in osteoblast activity, and PTH infusion has been shown to increase OPN levels. These studies exemplify how OPN expression can be significantly altered by changes in several variables in the Ca²⁺-P-vitamin D-PTH axis (Yuan *et al.*, 2012; Ono *et al.*, 2008) [32] [33].

We studied the association between osteopontin and the intimal medial thickness and the peak systolic velocity of the main vessels.

In this study, carotid, femoral intimal medial thickness is higher in children with end-stage renal disease than in healthy control and consequently decreased in the peak systolic velocity of carotid and femoral arteries. Carotid 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 (Gepner *et al.*, 2006; Stein *et al.*, 2008) [34] [35]. CIMT is a surrogate measure of atherosclerosis and an independent predictor of cardiovascular events (Chaitanya *et al.*, 2018; Dalager *et al.*, 2007) [14] [36].

In the current study, systemic osteopontin is strongly correlated with the intimal medial thickness of the carotid and femoral arteries and negatively correlated with PSV of the carotid artery, which is a marker of cardiovascular risk.

The systemic osteopontin level, a pro-inflammatory mediator, related to vascular remodeling and intimal hyperplasia, increases in AFV stenosis and may be used in clinical surveillance (Content *et al.*, 2021) [37]. The current study results are inconsistent with (Chaitanya *et al.*, 2018 and Lorenzen *et al.*, 2010) [36] [38], but with the age difference.

5. Conclusion

In conclusion, OPN is upregulated in children with CKD and may share early atherosclerosis initiation and propagation, evidenced by significant association with inflammatory markers and uremic toxins. Furthermore, additional work on many CKD patients is also necessary to determine the role of OPN in CKD patients, and new therapeutic strategies for those patients are essential.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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