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Plasma Pentraxin-3 as a Predictor for Peripheral Arterial Disease in Maintenance Hemodialysis Egyptian Patients: A Single-Center Study

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ABSTRACT

Background: Peripheral arterial disease (PAD) is a common risk factor for mortality in hemodialysis (HD) patients. Pentraxin-3 (PTX3), an inflammatory mediator, is widely expressed in peripheral tissues and may have a predictive value for PAD.

Objective: To evaluate the role of plasma PTX3 as a predictor for PAD in maintenance HD patients.

Patients and Methods: 84 subjects were included; Group 1: 42 End-stage renal disease (ESRD) patients on maintenance HD, and Group 2: 42 Healthy controls. After history taking, examination, and routine laboratory investigations, the following was done; Assessment of lower limb arteries by Color and Pulsed Doppler Ultrasound, ankle-brachial index (ABI), measurement of high-sensitivity C-reactive protein (HS-CRP), and plasma Pentraxin-3 (PTX3) by ELISA. **Results:** The ABI in HD patients (0.67 ± 0.13) was significantly lower than controls (1.1±0.16), (P<0.001). HS-CRP levels in ng/ml in HD patients (10.5 ± 2.3) were significantly higher than controls (1.48 ± 0.34), (P<0.001). Plasma PTX3 levels in ng/ml in HD patients (6.87 ± 1.36) were significantly higher than controls (1.47 ± 0.25), (P<0.001). Plasma PTX3 had a significant negative correlation with ABI, and Hb% (P<0.001), and a significant positive correlation with cholesterol and triglycerides (P<0.001), whereas HS-CRP did not have correlation with ABI. Plasma PTX3 at a cutoff of 2.35 ng/ml showed a higher predictive value for PAD than HS-CRP at a cutoff of 2.25 ng/ml regarding sensitivity (95.2% vs 88.1%), and specificity (92.0% vs 86.7%) respectively, (P<0.001).

Conclusion: Plasma PTX3 maybe used as a predictor for PAD in maintenance HD patients, with a high sensitivity and specificity.

Keywords: Plasma Pentraxin-3 (PTX3), High-sensitivity C-reactive protein (HS-CRP), hemodialysis (HD), peripheral arterial diseases (PAD), ankle-brachial index (ABI), Pulsed Color Doppler Ultrasound.

INTRODUCTION

Peripheral arterial disease (PAD) includes all arterial diseases; carotid, mesenteric, renal, and lower extremity artery disease, other than the aorta and coronaries [(1)]. End-stage renal disease (ESRD) patients on hemodialysis (HD) are more prone to PAD due to systemic inflammation, hypercoagulability, oxidative stress, hyperphosphatemia, secondary hyperparathyroidism, atherosclerosis, and vascular calcification [(2)]. The normal ankle-brachial index (ABI) varies from (1.0-1.4), and individuals with ESRD who need dialysis have much higher incidence of PAD (46% in the USA) [(3)]. Intermittent claudication and critical limb ischemia are two symptoms of PAD that are linked to greater mortality in HD patients [(4)]. Short pentraxins, like C-reactive protein (CRP) and serum amyloid P, are structurally related to long pentraxin, an inflammatory mediator. Pentraxin-3 (PTX3) is expressed in a variety of peripheral tissues, including endothelial cells and mononuclear phagocytes, and it is increased in atherosclerotic plaques [(5)].

Higher PTX3 levels independently predict chronic kidney disease (CKD) in elderly persons and are linked to reduced glomerular filtration rate (GFR) [(6)]. Plasma PTX3 levels are higher in people with vascular disorders and atherosclerotic plaques, and they are related with an increased risk of mortality in HD patients [(7, 8)]. Assessment of PAD is indicated in both symptomatic and asymptomatic CKD patients for possible need to start a secondary preventive therapy with statins or platelet inhibition [(9)].

This study was conducted to assess the validity of plasma pentraxin-3 (PTX3) as a predictor for peripheral arterial disease (PAD) in maintenance HD patients.

MATERIALS AND METHODS

This case-control study was carried out in collaboration between Internal Medicine, Clinical Pathology, and Radio-Diagnosis Departments, Faculty of Medicine, Zagazig University, Egypt, during the period from April 2018 to March 2019. It included 84 age and sex-matched subjects: 42 ESRD patients on maintenance HD, age mean±SD (38.24 ± 12.92) years, (20 females and 22 males), and 42 healthy controls (37.4.5±11.37) years, (23 females and 19 males).

Inclusion criteria: Patients included were HD patients (age >18 years). presenting with symptoms and/or signs suggestive of PAD (intermittent claudication and diminished walking ability) [(10)]; that were referred for diagnosis of PAD by Doppler ultrasound from different hemodialysis units in Sharkia Governorate (from our dialysis unit and other dialysis units).

Exclusion criteria:

Patients with diabetes mellitus, malignancy, auto-immune diseases, active infection, amputation, and age < 18 years.

Ethical Approvals:

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Informed consent was taken from all participants, and the protocol was approved by the Ethical Committee and the Institutional Review Board (IRB), at the Faculty of Medicine, Zagazig University, Egypt, (ZU-IRB#:10079), according to the Declaration of Helsinki for human studies.

All participants were subjected to: History taking, clinical examination, routine laboratory investigations including fasting blood glucose, HbA1c, complete blood count, serum urea, serum creatinine, calcium, phosphorous, total cholesterol, and triglycerides.

Assessment of lower limb arteries by Color and Pulsed Doppler Ultrasound:

The common femoral artery was identified using the Color Doppler, then the scanner was switched to the Duplex Mode (3.5 MHz). The peak systolic velocity (PSV) was obtained (normal range from 90-140 cm/s) and the shape of waveform was noted. Then a full lower limb scan was done, and any occlusion or reduction was reported. PAD was diagnosed if there was a reduction of ≥50% in the luminal diameter and graded as: Mild: diameter reduced by 50%–75% or PSV of 200–300 cm/s. Moderate: diameter reduced by 76%–99%, or PSV >300 cm/s. Severe stenosis: artery completely occluded **(11).**

Ankle-brachial index (ABI):

ABI represents the ratio of measured systolic blood pressure (SBP) at both ankle and brachial arteries. Patient was placed in supine position, with legs, arms, and heart at the same level, for 10 minutes before measurement, with using an appropriate size blood pressure cuff for the ankle and the arm. Doppler device detected the brachial, dorsalis pedis, and posterior tibial pulses. Ankle pressure is divided by the brachial artery pressure to get ABI: **(**ABI 0.7–0.89) (mild PAD), (ABI 0.4–0.69) (moderate), (ABI<0.4) (severe PAD), and **(**ABI > 1.3) (artery calcified or noncompressible) (in CKD or diabetes) **(12)**. PAD was defined by suggestive symptoms or signs, ABI of <0.9 in either leg, or previous history of lower limbs revascularization procedure or angiography findings**(13)**.

Measurement of plasma high-sensitivity CRP (HS-CRP): Using Human high sensitivity C-Reactive protein (hs-CRP) ELISA Kit Catalog No. CSB-E08617h, as per manufacturer's instructions **(14)**.

Measurement of plasma pentraxin-3 (PTX3) by ELISA: Using Human Pentraxin 3/TSG-14 Quantikine ELISA Kit Catalog No. DPTX30B, as per manufacturer's instructions **(15)**.

Statistical Analysis:

The data were analyzed by the "Statistical Package for the Social Sciences" (SPSS 25) for Windows (SPSS Inc., Chicago, IL, USA). Quantitative data were presented as mean, and standard deviation (± SD), and were compared by independent t-test and one-way ANOVA test. Qualitative data were presented as frequency and percentage and were compared by chi^2 test. Correlation analysis (using Pearson's correlation coefficient) was performed for the association between two quantitative variables. Using the receiver operating characteristic (ROC) curve; area under the curve (AUC), and standard errors (SE) were determined, and the optimal cutoff point was recognized at the point of maximum accuracy. All statistical comparisons were two-tailed with a P-value<0.05 indicated a significant difference and P-value<0.001 indicated highly significant difference.

RESULTS

As regards age and sex, both groups were matched. Among the studied 42 HD with clinical symptoms suggestive for PAD, 37 HD patients (88.1%) had PAD as proved by ABI and Color Doppler Ultrasound, while 5 HD patients who had normal ABI were found to have PAD by Color Doppler **(Table 1).**

Table (1): Comparison between HD patients and healthy controls as regards age and sex distribution, and grading of PAD severity as regards the ankle/brachial index (ABI)

Variable	**Cases (n=42)**		**Control (n=42)**		**p**
Age: (year) **Mean ± SD** **Range**	 38.24 ± 12.92 27 – 52		 37.4.5±13.37 26 – 51		 >0.05
Variable	N	%	N	%	P
Sex: **Female** **Male**	 17 25	 42 58	 20 22	 47.5 52.5	 0.51
Normal ABI (ABI 1.0-1.4) (PAD confirmed only by Color Doppler US) **Mild** (**ABI 0.7-0.89)** **Moderate** (**ABI 0.4-0.69)** **Severe** (**ABI <0.4)**	5 15 9 13	11.9 35.7 21.4 31	 --	 --	 --

There was a high statistically significant difference between the studied HD patients and the normal healthy controls as regards hemoglobin%, serum total cholesterol, triglycerides, calcium,

phosphorous, blood urea, and serum creatinine. The mean±SD ankle brachial index (ABI) was significantly lower in the studied HD patients than in healthy controls. The mean±SD plasma levels of high-sensitivity C-reactive protein (HS-CRP) were significantly higher in the studied HD patients, than healthy controls (**Table 2**). The ANOVA test showed no statistically significant difference as regards its levels in mild, moderate, and severe cases of Doppler-confirmed PAD (**Table 3**).

The mean±SD plasma levels of Pentraxin-3 (PTX3) were significantly higher in the studied HD patients, than healthy controls (**Table 2**). There was a high statistically significant difference as regards PTX3 levels in mild, moderate, and severe cases. Plasma PTX3 was significantly higher in HD patients with severe Doppler-confirmed PAD than in those with moderate or mild PAD **(Table 3).**

Table (2): Comparison between HD patients and healthy controls as regards laboratory tests, HS-CRP, plasma Pentraxin-3 (PTX3), and ankle-brachial index

Variable	HD Cases (n=42)	Healthy Controls (n=42)	p
Hemoglobin (Hb)% (g/dl) Mean ± SD	9.17 ± 1.31	13.34 ± 1.18	<0.001**
Serum total cholesterol (mg/dl) Mean ± SD	183.81 ± 14.68	163.98 ± 13.43	<0.001**
Serum triglyceride (mg/dl) Mean ± SD	134.52 ± 30.41	96.88 ± 3.6	<0.001**
Serum calcium (mg/dl) Mean ± SD	7.65 ± 1.41	9.2 ± 0.81	<0.001**
Serum phosphorus(mg/dl) Mean ± SD	5.12 ± 1.23	4.21 ± 0.67	<0.001**
Blood urea (mg/dl) Mean ± SD	113.88 ± 23.64	26.83 ± 4.42	<0.001**
Serum creatinine (mg/dl) Mean ± SD	9.83 ± 2.31	0.94 ± 0.2	<0.001**
(HS-CRP) (ng/ml) Mean ± SD	10.5 ± 2.3	1.48 ± 0.34	<0.001**
PTX3 (ng/ml) Mean ± SD	6.87 ± 1.36	1.47 ± 0.25	<0.001**
Ankle brachial index (ABI) Mean ± SD	0.67 ± 0.13	1.1± 0.16	<0.001**

** High statistically significant difference.

Table (3): Correlation between HS-CRP and Pentraxin3 levels in the HD group and the severity of Doppler-confirmed PAD

Variable	HS-CRP		P
	N	**mean±SD**	
Doppler-confirmed PAD:			
Mild	15	8.65± 1.84	0.06
Moderate	9	13.83± 2.05	
Severe	13	10.76±1.51	
Variable	Pentraxin3		P
	N	mean± SD	
Doppler-confirmed PAD:			
Mild	15	4.93± 1.15	
Moderate	9	6.8±0.89	<0.001**
Severe	13	10.93±2.29	

** High statistically significant difference. PAD (peripheral arterial disease).

Plasma levels of pentraxin-3 had a significant positive correlation with serum total cholesterol, and triglycerides, and a significant negative correlation with hemoglobin%, and the ABI, but no correlation was found with age, serum calcium, phosphorous, blood urea and serum creatinine. Plasma levels of HS-CRP had no correlations with the ABI, or other laboratory tests **(Table 4).**

Table (4): Correlation between HS-CRP and Pentraxin-3 with other laboratory investigations and ankle-brachial index in HD patients (n=42)

Variable	HS-CRP		Pentraxin.3	
	r	P	r	P
Age in years	0.22	0.16	0.27	0.08
Hemoglobin g/dl	0.22	0.15	-0.36	0.02*
Serum total Cholesterol mg/dl	0.19	0.23	0.6	<0.001**
Serum triglycerides mg/dl	0.12	0.44	0.51	<0.001**
Serum calcium mg/dl	0.06	0.73	0.09	0.6
Serum Phosphorous mg/dl	0.03	0.84	0.12	0.45
Ankle-brachial index	0.22	0.15	-0.87	<0.001**
Blood urea mg/dl	0.06	0.72	0.28	0.07
Serum creatinine mg/dl	0.14	0.4	0.14	0.37

* Statistically significant difference. ** High statistically significant difference.

The receiver operator characteristic (ROC) curve for the validity of plasma pentraxin-3 level as a predictor for PAD disease in the HD patients showed that at a cutoff 2.35 ng/ml, sensitivity was 95.2% and specificity was 92.9%. While, for the validity of plasma HS-CRP level, as a predictor for PAD disease in the HD patients, it showed that at a cutoff 2.25 ng/ml, sensitivity was 88.1% and specificity was 86.7% **(Figure 1 and Table 5).**

Table (5): The validity of CRP and plasma Pentraxin 3 (PTX3) levels in the prediction of peripheral arterial disease (PAD) in HD patients

	Cutoff	Sens.	Spec.	+PV	-PV	Accuracy	AUC	CI	p-value
HS-CRP	**2.25**	**88.1**	**86.7**	**85.4**	**83.7**	**84.5**	**0.96**	**0.92-0.99**	**<0.001****
PTX 3	**2.35**	**95.2**	**92.9**	**93**	**95.1**	**94**	**0.98**	**0.96-1.1**	**<0.001****

** High statistically significant difference. Sens. (sensitivity). Spec. (specificity). +PV (positive predictive value). -PV (negative predictive value). AUC (area under the curve). CI (confidence interval).

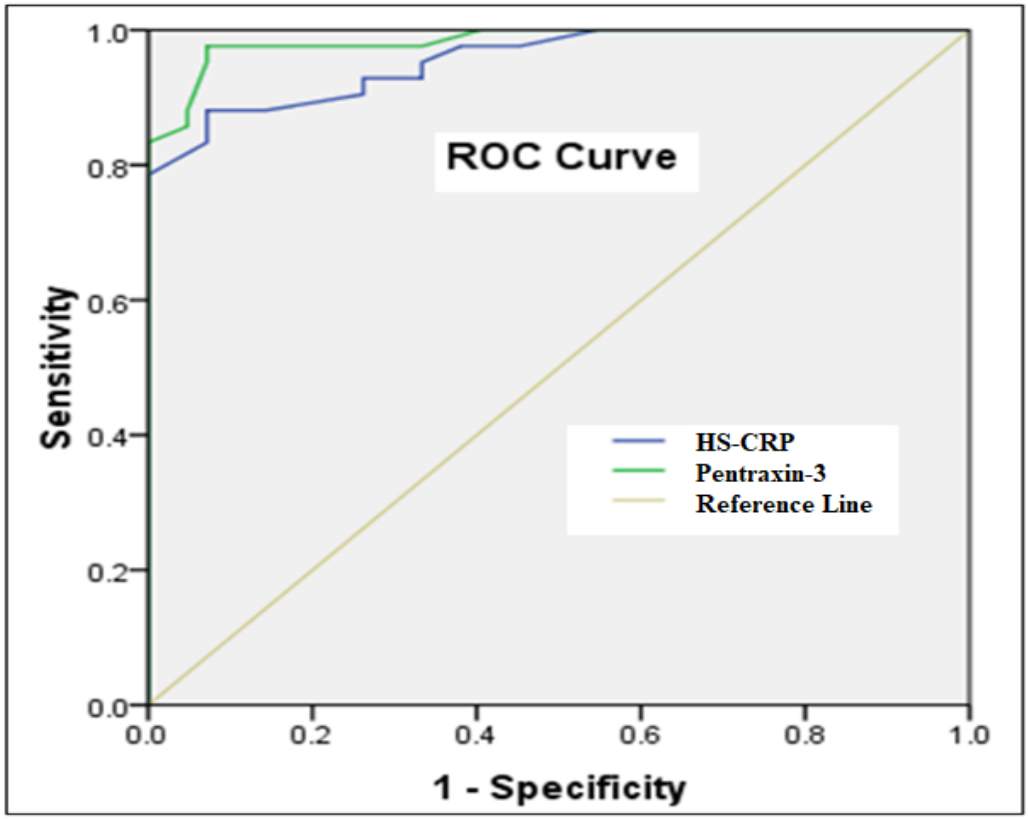

Figure (1): ROC Curve for the validity of HS-CRP and Pentraxin-3 levels for the detection of peripheral arterial disease (PAD) in HD patients

DISCUSSION

Thirteen percent of people over the age of 50 have peripheral artery disease (PAD) of the lower limbs, while 5% of people in Western nations between the ages of 55 and 74 have symptomatic PAD. Peripheral arterial disease (PAD) cannot be accurately diagnosed using the ankle-brachial index (ABI) alone [16]. The prognosis of HD patients can be improved by early PAD identification. ABI screening for PAD has a 100% specificity and a 29.9% sensitivity for identifying PAD in HD patients [17]. Acute-phase inflammatory protein pentraxin-3 (PTX3) alters the morphology and bioenergetics of human endothelial cells, which is detrimental to the vascular system [18].

Ašćerić *et al.* [19] stated that the prevalence of PAD was high among patients with ESRD on HD (35.3%), and the symptoms of PAD, elevation of C-reactive protein (CRP) levels, and Hickman vascular access were independent predictors of PAD in patients on HD. In this study, 42 ESRD patients on maintenance HD, all had PAD as diagnosed by Color Doppler Ultrasound criteria ,but only (88.1%) had PAD by ABI.

PAD is a systemic vascular illness that usually develops as a result of atherosclerosis and affects the aorta, iliac, and lower leg arteries. Compared to the general population (3%–10%), HD patients had a greater prevalence of PAD (26%–41%). The presence of inflammatory mediators, oxidative stress, hypercoagulability, vitamin D deficiency, or uremic toxins may be to blame for this [4].

In this study, the plasma levels of PTX3 were significantly higher in HD patients (6.87 ± 1.36 ng/ml) than healthy controls (1.47 ± 0.25 ng/ml). This is in agreement with other researchers, who found that PTX3 plasma levels were significantly higher in HD patients (5.8 ± 0.6 ng/ml) compared with peritoneal dialysis (PD) (1.5 ± 0.4 ng/ml), chronic kidney disease (CKD) (1.5 ± 0.4 ng/ml) and normal subjects (0.76 ± 0.2 ng/ml) [20].

Plasma PTX3 is related with the prevalence of cardiovascular disease and higher mortality, and it rises as glomerular filtration rate (GFR) declines [21]. High levels of PTX3 are produced in atherosclerotic arteries, mostly by macrophages and endothelial cells. Additionally, the generation of PTX3 by smooth muscle cells within atherosclerotic plaques is stimulated by oxidised LDL cholesterol [22].

Plasma PTX3 levels were markedly elevated in HD patients with PAD with highest value in severe, intermediate with moderate, lowest with mild PAD (mean±SD 10.93±2.29, vs. 6.81±0.89, vs. 4.93±1.15 ng/ml respectively). While HS-CRP could not differentiate case severity, although its levels were elevated.

These findings were in agreement with **Sjöberg *et al.*** [7], who found that PTX3 and HS-CRP could predict the presence of cardiovascular disease (CVD) as a complication in CKD patients. Additionally, PTX3 might be a more sensitive marker for the association of CVD than HS-CRP in patients with advanced CKD.

Plasma PTX-3 was negatively corrrelated with ABI, and Hb%, and positively corrrelated with cholesterol and triglycerides, but not correlated with age, serum calcium, phosphorous, blood urea or serum creatinine. On the other hand, HS-CRP was not corrrelated with ABI, or other laboratory tests. This indicates the importance of plasma PTX3 levels assessment in peripheral vascular diseases and atherosclerosis, especially in HD patients who are at greater risk for PAD.

Using the ROC analysis, for PTX3 at a cut-off value of 3.22 ng/ml, it had a higher sensitivity (95.2%), and specificity (92.9%), for predicting PAD in HD patients, than HS-CRP (88.1% sensitivity), and (86.7% specificity). Similarly, PTX3 had a diagnostic sensitivity and specificity in PAD (81% and 91.5%), respectively, while HS-CRP diagnostic sensitivity and specificity in PAD were only 57.1% and 56.8%, respectively [20]. These findings suggest that PTX3 may be a better predictor for PAD than HS-CRP, and independently correlated with PAD in HD patients.

Zhou *et al.* [5] found that higher levels of plasma PTX3 in HD patients with PAD predicted mortality in these patients, and that PTX3 levels could have a prognostic predictive value in HD patients. The efefctive PAD diagnostic clinical approach in CKD patients may help improve its prognosis and outcome [2].

Muscle pain that is brought on by exertion and eased by rest is known as intermittent claudication. It can't be utilised to accurately identify PAD because it is only present in 10% to 15% of individuals with substantial PAD (ABI < 0.9) [1]. HD patients may experience restless legs syndrome, pruritis, neuropathy, and arthritis-related non-PAD leg symptoms. The clinical examination cannot rule out PAD in asymptomatic instances, and in symptomatic situations, the presence of chilly skin, an arterial bruit, and/or loss of pulses does not necessarily indicate PAD [23].

Interestingly, 5 patients of 42 HD patients (11.9%) in our study had normal ABI, but were proved to have PAD by Color Doppler ultrasound criteria. HD patients may have false normal ABI or supranormal high ABI, and both atherosclerotic PAD and medial arterial calcification maybe found, thus masking the true PAD prevalence [24]. Similarly, **Ishioka *et al.*** [12] reported that among 45 HD patients with PAD, only 31.1% had low ABI.

PTX3 is a more comprehensive inflammatory biomarker than traditional biomarkers, and it has links to renal fibrosis, cardiovascular disease, malnutrition, inflammation, and death prediction in HD patients. Targeting PTX3 may reduce the high morbidity and mortality rates associated with ESRD patients [25], but

clopidogrel should continue to be the backbone of treatment for PAD patients [26].

For HD patients to have a better prognosis and quality of life, PAD needs to be prevented and treated quickly. Due to its early lack of symptoms and resistance to treatment, PAD in HD patients is difficult to diagnose [27].

Consequently, it is important to screen patients for PAD. The ankle-brachial index (ABI), a measure of the ratio of the ankle to the brachial systolic blood pressure, has been used to evaluate PAD, but it is largely insensitive to detecting disease development [7]. Measuring skin perfusion pressure (SPP) is proven to be quite precise and helpful for identifying PAD early and treating it effectively [8, 9]. Although its function is not well understood, plasma PTX3 is a good predictor for PAD in HD, and additional research is merited [28].

Points of Strength: This study included a reasonable number of maintenance HD patients with PAD, also they were referred from different dialysis centers. In this study we used different diagnostic methods for PAD detection with different sensitivities and specificities , as Color Doppler ultrasound, ABI, HS-CRP , and plasma pentraxin-3. Plasma PTX3 showed a high sensitivity and specificity for diagnosis of PAD in HD patients, compared to other methods, and hence it can be used as an independent predictor of PAD in these patients.

Limitations of the study: Duration since the onset ESRD or the start of dialysis before inclusion to this study and its relation with plasma pentraxin was not explored. Follow-up of the same HD patients over time may allow better evaluation for the validity of plasma PTX3 in predicting PAD in such patients.

CONCLUSION

Plasma PTX3 level is increased in HD patients with PAD and can be used as a predictor for PAD with a high sensitivity and specificity.

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