Evaluation of arterial stiffness in maintenance hemodialysis patients using pulse wave analysis and serum biomarkers of bone turnover

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Background
Vascular stiffness is common among patients with end-stage renal disease (ESRD). Circulating markers of bone formation play an important role in evaluating bone-mineral disease state as well as in predicting the risk of developing vascular calcification and hence, arterial stiffness.
Aims
This study aimed to assess arterial stiffness in maintenance hemodialysis patients using pulse wave analysis as an index of central and peripheral arterial stiffness and serum procollagen type I N-terminal propeptide (P1NP) as a marker for bone turnover.
Patients and methods
Fifty ESRD patients aged 18 years old or more who have been assigned to regular long-term hemodialysis were included in this study and subjected to complete history taking and physical examination and laboratory investigations including lipid profile, fasting plasma glucose level (mg/dl), serum creatinine, blood urea (mg/dl), serum phosphorus (mg/dl), serum calcium (mg/dl), P1NP (ng/ml), serum parathyroid hormone (PTH) (pg/ml), and serum bone-specific alkaline phosphatase (BALP) (U/l), and aortic pulse wave velocity.
Results
There was significant positive correlation between P1NP and PTH ($P \leq 0.01$) and between BALP and serum PTH ($P \leq 0.01$). There was significant difference between patients with low and high augmentation index regarding BALP ($P=0.018$).
Conclusion
ESRD patients have a high prevalence of vascular stiffness assessed by pulse wave analysis. There is a significant correlation between BALP and PTH and between P1NP and PTH. There is a relation between markers of bone formation and vascular stiffness.

Keywords:
arterial stiffness, hemodialysis, pulse wave analysis

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Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) is a worldwide public health problem with an increasing incidence and prevalence, poor outcomes, and high cost [1].

Chronic kidney disease-mineral and bone disease

Chronic kidney disease-mineral and bone disease (CKD-MBD) is a multisystem disorder consisting of overlapping entities. It is characterized by one or more of the following [2]:

(1) Abnormalities in laboratory tests including corrected serum calcium, organic phosphate, parathyroid hormone (PTH), and vitamin D derivatives.
(2) Abnormalities in bone (bone turnover, bone mineralization, and trabecular bone volume).
(3) Arterial walls and soft tissue calcifications.

Determination of bone turnover markers is important in clinical practice to evaluate bone turnover. KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommend measurement of PTH and bone-specific alkaline phosphatase (BALP) in the assessment of CKD-MBD [3,4].

So many markers have been developed and can be classified into markers of turnover, markers of bone formation, and markers of bone resorption [5].

Serum procollagen type 1 N-terminal propeptide (s-P1NP) is an indicator of the synthesis of type 1 collagen, which is a crucial step in bone formation [6].

The s-P1NP has little diurnal variation. Levels of s-P1NP may be also useful in ESRD, as they do not change during hemodialysis (HD) sessions [7].

Cardiovascular disease is the most common cause of morbidity and mortality in CKD and ESRD [8]. Premature vascular aging and arterial stiffening are observed with the progression of CKD [9–11].

A clear-cut contribution of the CKD-MBD to vascular stiffness has been established. Abnormalities of serum phosphorus, calcium, and PTH in the context of CKD-MBD are major determinants of vascular calcification, arteriosclerosis, and subsequent arterial stiffness in CKD patients [12].

Arterial stiffness of the aorta and its major branches can be estimated by measuring the aortic pulse wave velocity (PWV), which is the propagation velocity of the waveform from the proximal aorta toward peripheral vessels. Higher values than normal represent a stiffer aorta [13].

Various arterial parameters can be obtained including aortic PWV, augmentation index (AIx), central systolic blood pressure (SBP), and central pulse pressure (PP). These measurements have demonstrated their predictive value in ESRD patients being an indirect surrogate measure of arterial stiffness [14].

The aim of this study was to assess arterial stiffness in maintenance HD patients using pulse wave analysis as an index of central and peripheral arterial stiffness and s-P1NP as a marker for bone turnover.

Patients

Fifty patients were recruited from the HD units of Alexandria Main University Hospital and Al Mowasah University Hospital.

Inclusion criteria

(1) ESRD patients who have been assigned to regular long-term HD and perform thrice weekly, 4-h HD sessions for more than 3 months.
(2) Patients aged 18 years old or more.

Exclusion criteria

(1) Patients with a history of diabetes mellitus.
(2) Patients with a history of collagenic disorders.
(3) Patients with known severe valvular heart disease.
(4) Patients with a history of aortic surgery/prosthetic aorta.
(5) Patients with known cardiac rhythm irregularity.
(6) Patients with clinical hepatic decompensation.

Patents and methods

The study was conducted in compliance with the Declaration of Helsinki; the ethical committee of our faculty was requested to approve the protocol and the patients were requested to give informed consent. All patients included in the study were subjected to the following:

(1) Detailed history taking including personal and family histories, smoking habits, and previous history of cardiovascular disease with emphasis on the cause of ESRD and the duration of HD.
(2) Thorough physical examination.
(3) Investigations:
    (a) Laboratory (midweek predialysis samples were collected).
        (1) P1NP (ng/ml) measured by immunoassay (Cobas 6000 analyzer series) [6].
        (2) Lipid profile:
            (1) Serum triglycerides (TGs) (mg/dl) [15].
            (2) Total cholesterol (mg/dl) [16].
    (b) Fasting plasma glucose level (mg/dl) [17].
    (c) Serum creatinine and blood urea (mg/dl) [18].
    (d) Serum phosphorus (mg/dl) and serum calcium (mg/dl) [19].
    (e) Serum PTH (pg/ml) [20].
    (f) Serum BALP (U/l) [21].

Pulse wave analysis using Mobil-O-Graph device

(1) The Mobil-O-Graph (I.E.M. GmbH, Stolberg, Germany) is an electronic blood pressure monitoring system equipped with three different sized arm cuffs, connecting tube, recorder, bluetooth, laptop, and a software tool for pulse wave analysis [22].
(2) A computerized brachial oscillometric ambulatory blood pressure monitor device that has been validated according to the European Society of Hypertension recommendations [23]. Several hemodynamic parameters can be obtained including peripheral blood pressure, aortic SBP, aortic diastolic blood pressure (DBP), central PP, and most importantly aortic PWV and AIx.

Statistical analysis of data

Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0. (IBM Corp., Armonk, New York, USA). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, SD, median, and interquartile range. Significance of the obtained results was judged at the 5% level.

The used tests were:

Student's t test

For normally distributed quantitative variables to compare between two studied groups.

F test (analysis of variance)

For normally distributed quantitative variables, to compare between more than two groups.

Pearson coefficient

To correlate between two normally distributed quantitative variables.

Mann–Whitney test

For abnormally distributed quantitative variables to compare between two studied groups.

Kruskal–Wallis test

For abnormally distributed quantitative variables, to compare between more than two studied groups and post-hoc test (Dunn's multiple comparisons test) for pairwise comparisons.

Spearman coefficient

To correlate between two abnormally distributed quantitative variables.

Linear regression

To detect the most affecting factor affecting different factors.

Results

This study was performed on 50 ESRD patients on maintenance HD in HD units of Alexandria Main University Hospital and Al Mowasah University Hospital.

The baseline criteria of the patients are illustrated in Table 1.

Laboratory investigations

Table 2 shows the distribution of the studied cases according to laboratory investigations.

Table 1 Baseline criteria of the patients (*N*=50)

	n (%)
Sex	
Male	27 (54)
Female	23 (46)
Age (years)	
Median (minimum–maximum)	47.5 (26–60)
Mean±SD	47.34±9.89
BMI (kg/m^2)	
Median (minimum–maximum)	29 (18–35)
Mean±SD	28.82±3.7
Cause of ESRD	
Hypertension	22 (44)
Unknown	12 (24)
Adult polycystic kidney disease	6 (12)
Pyelonephritis	3 (6)
Congenital	3 (6)
Chronic glomerulonephritis	2 (4)
Interstitial	1 (2)
Analgesic	1 (2)
Duration of dialysis (years)	
Median (minimum–maximum)	9 (1–28)
Mean±SD	9.48±5.8
Type of dialysis access	
Arteriovenous fistula	43 (86)
Catheter	7 (14)

ESRD, end-stage renal disease.

Table 2 Descriptive analysis of the studied cases according to laboratory data (*N*=50)

	Median (minimum–maximum)	Mean±SD
Urea (mg/dl)	143 (95–225)	142.1 ±25.47
Creatinine (mg/dl)	10.2 (5–12)	10.53±2.98
Calcium (mg/dl)	8.60 (7.0–10.80)	8.55±0.89
Phosphorus (mg/dl)	6.05 (2–9)	5.96±1.54
FBG (mg/dl)	86.0 (70–115)	85.76±9.23
Cholesterol (mg/dl)	174.5 (107–303)	179.7 ±40.56
Triglycerides (mg/dl)	153.5 (39–532)	170.7±99

FBG, fasting blood glucose.

Serum parathyroid hormone, serum procollagen type 1 N-terminal propeptide, and serum bone alkaline phosphatase

Table 3 shows the distribution of the studied cases according to markers of bone turnover. Regarding PTH, it ranged from 7.30 to 1447.0 pg/ml with a mean of 376.3±341.0 pg/ml. Of the patients, 16 (32%) had a PTH level of less than 150 pg/ml, 20% (10 patients) from 150 to 300 pg/ml, and 48% (24 patients) above 300 pg/ml. Regarding P1NP, it ranged from 101.0 to 1200.0 µg/l with a mean of 655.5 ±433 µg/l. Thirteen (26.0%) patients had a P1NP of level less than 300 µg/l, 30% (15 patients) from 300 to 600 µg/l, 4% (two patients) from 600 to 900 µg/l, 8%

Table 3 Distribution of the studied cases according to bone alkaline phosphatase and procollagen type I N-terminal propeptide (*N*=50)

	n (%)
PTH (pg/ml)	
<150	16 (32.0)
150–<300	10 (20.0)
≥300	24 (48.0)
Median (minimum–aximum)	300 (7.30–1447)
Mean±SD	376.3±341
P1NP (μg/l)	
<300	13 (26.0)
300–<600	15 (30.0)
600–<900	2 (4.0)
900–<1200	4 (8.0)
≥1200	16 (32.0)
Median (minimum–maximum)	458 (101–1200)
Mean±SD	655.5±433.0
BAP (U/l)	
<10	0
10–<20	6 (12.0)
≥20	44 (88.0)
Median (minimum–maximum)	57.50 (11–389)
Mean±SD	105.2±106.8

BAP, bone alkaline phosphatase; P1NP, procollagen type I N-terminal propeptide; PTH, parathyroid hormone.

Table 4 Descriptive analysis of the studied cases according to pulse wave parameters (*N*=50)

	n (%)
Heart rate (b/min)	
Median (minimum–maximum)	82.5 (54–126)
Mean±SD	84.86±15.96
SBP (mmHg)	
Peripheral	
Median (minimum–maximum)	132.5 (85–195)
Mean±SD	135±25.52
Central	
Median (minimum–maximum)	121.5 (84–178)
Mean±SD	121.4±21.96
DBP (mmHg)	
Peripheral	
Median (minimum–maximum)	79.50 (40–126)
Mean±SD	81.98±17.26
Central	
Median (minimum–maximum)	83 (43–130)
Mean±SD	84.32±17.26
PP (mmHg)	
Peripheral	
Median (minimum–maximum)	51.5 (28–113)
Mean±SD	53.08±18.42
Central	
Median (minimum–maximum)	32.5 (20–83)
Mean±SD	36.68±13.75
Aortic PWV (m/s)	
Normal	21 (42)
Low	4 (8)
High	25 (50)
Median (minimum–maximum)	8.10 (4.40–10.90)
Mean±SD	7.80±1.52
Augmentation index (%)	
Normal	30 (60)
Low	5 (10)
High	15 (30)
Median (minimum–maximum)	27.0 (4.0–61.30)
Mean±SD	27.89±13.21

DBP, diastolic blood pressure; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

(four patients) from 900 to 1200 μg/l, and 32% (16 patients) above 1200 μg/l. Regarding bone alkaline phosphatase (BAP), it ranged from 11.0 to 389.0 U/l with a mean of 105.2±106.8 U/l.

Pulse wave analysis

Table 4 shows the distribution of the studied cases according to pulse wave parameters.

Regarding aortic PWV, it ranged from 4.40 to 10.90 m/s with a mean of 7.80±1.52 m/s.

Twenty-one (42%) patients had a normal PWV measurement, four (8%) patients had a low PWV measurement, and 25 (50%) patients had a high PWV measurement.

Regarding AIx, it ranged from 4.0 to 61.30% with a mean of 27.89±13.21%.

Thirty (60%) patients had a normal AIx, five (10%) patients had a low AIx, and 15 (30%) patients had a high AIx.

Relations and correlations of markers of bone turnover

Tables 5 and 6 show the relations and correlations of bone turnover markers. There was a significant difference between patients with low and high AIx regarding BAP (P=0.018), while there was no significant difference between them regarding P1NP (P=0.227).

There was a significant positive correlation between BAP and serum creatinine (P=0.039), serum PTH ($P\leq0.01$), serum TGs (P=0.01), and serum P1NP ($P\leq0.01$) and a significant negative correlation between BALP and age (P=0.08) and serum phosphorus (P=0.026).

There was a significant positive correlation between P1NP and PTH ($P\leq0.01$), serum TG (P=0.017), and serum BALP ($P\leq0.01$).

Table 5 Relation between bone alkaline phosphatase, procollagen type I N-terminal propeptide, and different parameters (*N*=50)

		BAP		P1NP	
	N	Median (minimum–maximum)	Mean±SD	Median (minimum–maximum)	Mean±SD
Sex					
Male	27	48 (11–389)	95.93±103.5	385 (101–1200)	624.3±455.7
Female	23	68 (11–382)	116.09±111.9	542 (138–1200)	692.2±411.74
U (*P*)		262.0 (0.345)	274.0 (0.476)		
Cause of ESRD					
Hypertension	22	37.50 (11–189)	59.77±55.03	366.5 (101–1200)	530.7±442.7
Unknown	12	113.5 (46–389)	196.83±150.9	936.5 (344–1200)	873.8±351.3
Adult polycystic kidney disease	6	139 (14–242)	135±102.37	981 (104–1200)	816.7±468.7
Pyelonephritis	3	48 (45–135)	76.0±51.12	346 (342–528)	405.3±106.3
Congenital	3	115 (62–218)	131.67±79.32	1200 (1022–1200)	1140.7±102.8
Chronic glomerulonephritis	2	46.50 (45–48)	46.50±2.12	235.5 (184–287)	235.5±72.83
Interstitial	1[#]	26[#]	301[#]		
Analgesic	1[#]	31[#]	305[#]		
H (*P*)		262.0 (0.345)	13.140 (0.069		
Aortic PWV (m/s)					
Normal	21	48 (11–389)	116.43±118.2	394 (121–1200)	633.3±448.97
Abnormal	29	60 (11–384)	97.07±99.14	465 (101–1200)	671.6±428.27
U (*P*)		304.0 (0.992)	276.0 (0.569)		
Normal	21	48 (11–389)	116.43±118.2	394 (121–1200)	633.3±448.97
Low	4	41 (35–47)	41.0±5.89	267.5 (193–344)	268±86.61
High	25	63 (11–384)	106.04±104.2	721 (101–1200)	736.2±426.1
H (*P*)		1.826 (0.401)	324.0 (0.569)		
Augmentation index (%)					
Normal	30	49.50 (11–389)	98.63±104.15	432.5 (101–1200)	599.2±416.3
Abnormal	20	64 (11–384)	115.05±112.7	721.5 (151–1200)	740±454.3
U (*P*)		259.50 (0.442)	240.0 (0.227)		
Normal	30	49.50 (11–389)	98.63±104.2	432.5(101–1200)	599.2±416.26
Low	5	65 (35–175)	76.80±57.02	542 (193–1200)	697.2±475.34
High	15	63 (11–384)	127.80±124.9	901 (151–1200)	754.3±463.4
H (*P*)		16.900[*] (0.018*)	1.459 (0.227)		

BAP, bone alkaline phosphatase; ESRD, end-stage renal disease; *H*, *H* for Kruskal–Wallis test; P1NP, procollagen type I N-terminal propeptide; PWV, pulse wave velocity; *U*, Mann–Whitney test. *P*: *P* value for comparing between the different categories. [#]Excluded from the comparison due to small number of cases (*N*=1). [*]Statistically significant at $p \leq 0.05$.

Relations and correlations of augmentation index and pulse wave velocity

Tables 7 and 8 show the relations and correlations of AIx and aortic PWV.

There was a significant positive correlation between AIx and heart rate (*P*=0.02).

There was a significant positive correlation between PWV and age (*P*≤0.01), serum phosphorus (*P*≤0.01), peripheral SBP (*P*≤0.01), central SBP (*P*=0.01), peripheral DBP (*P*=0.040), central DBP (*P*=0.018), peripheral PP (*P*=0.01), and central PP (*P*=0.037).

Discussion

The present study included 50 patients on maintenance HD. The mean age was 47.82±10.64 years. This is different from data that showed that the mean age of ESRD is 54.4±13.7 [24]. Data from the United States Renal Data System in 2016 showed a similar trend toward older dialysis population in the United States with 45% of the patients being over the age of 65 years [25]. The difference in age in this study is due to the exclusion of patients older than 60 years old as these patients have higher AIx and PWV in comparison to younger patients and have different reference range that makes comparison and interpretation of data difficult.

Regarding the etiology of ESRD, hypertensive nephropathy was the most common cause of ESRD in the studied sample representing 44% (22 patients). Twelve (24%) patients have an unknown cause of ESRD. Hypertension and diabetes are known to be the most common causes of CKD and ESRD [26]. This is not reflected in our study because we excluded diabetic patients as PWV, PP, and AIx are significantly increased in diabetic patients when adjusted for age, sex, and heart rate in mean aortic pressure [27,28].

Table 6 Correlation between different parameters (*N*=50)

	BAP		P1NP	
	r_s	*P*	r_s	*P*
Age (years)	–0.370*	0.008*	–0.117	0.418
BMI (kg/m^2)	–0.090	0.534	–0.067	0.642
Duration of dialysis (years)	0.251	0.079	0.098	0.497
Urea	0.01	0.993	–0.074	0.608
Cr	0.293*	0.039*	0.159	0.270
Ca	0.118	0.416	0.241	0.092
PO_4	–0.315*	0.026*	–0.062	0.670
PTH	0.699*	<0.001*	0.671*	<0.001*
FBG	0.032	0.828	–0.081	0.578
Cholesterol	0.252	0.077	0.126	0.382
TG	0.441*	0.001*	0.335*	0.017*
Heart rate (b/min)	0.039	0.789	0.028	0.847
SBP (mmHg)				
Peripheral	–0.068	0.638	0.027	0.851
Central	–0.027	0.851	0.055	0.704
DBP (mmHg)				
Peripheral	–0.026	0.858	–0.079	0.586
Central	–0.058	0.691	–0.093	0.521
PP (mmHg)				
Peripheral	–0.147	0.309	0.03	0.985
Central	–0.058	0.691	0.082	0.569
Aortic PWV (m/s)	–0.082	0.572	0.144	0.318
Augmentation index (%)	0.083	0.568	0.170	0.238
P1NP	0.859*	<0.001*		

BAP, bone alkaline phosphatase; DBP, diastolic blood pressure; FBG, fasting blood glucose; P1NP, procollagen type I N-terminal propeptide; PP, pulse pressure; PTH, parathyroid hormone; PWV, pulse wave velocity; r_s, Spearman coefficient; SBP, systolic blood pressure; TG, triglyceride. *Statistically significant at *P* value less than or equal to 0.05.

In our study, we found that the mean TG level was 170.7±99.0 mg/dl with around 50% of patients having an elevated TG level. The mean cholesterol level was 179.7±40.56 mg/dl with around 20% of patients having an elevated cholesterol level. Cofan *et al*. [29] analyzed characteristics of dyslipidemia in 1824 HD patients in Catalonia and reported that the prevalence of dyslipidemia was high (63%) with the most frequent lipid alterations being decreased high-density lipoprotein cholesterol (HDL) (40%), hypertriglyceridemia (31%), and hypercholesterolemia (19%). Total cholesterol/HDL ratio was elevated in 23%. Attman and Samuelsson [30] and Pennell *et al*. [31] also found that hypertriglyceridemia is one of the most common lipid abnormality in patients with CKD in association with decreased HDL concentrations. Maheshwari *et al*. [32] identified hyperlipidemia as a main risk factor of atherosclerosis in HD patients characterized by hypertriglyceridemia without cholesterol accumulation. Kronenberg *et al*. [33] and Vaziri *et al*. [34] stated that low HDL cholesterol is often already present in an early stage of CKD and could be considered one of the factors that accelerate atherosclerosis in patients on dialysis.

In our study, we found that the mean PTH level was 376.3±341.0 pg/ml with values ranging between 7.30 and 1447.0 pg/ml, with 54% (27 patients) having PTH values of more than 300 pg/ml, 32% (16 patients) having PTH values between 150 and 300 pg/ml, and 14% (seven patients) having a PTH of less than 150 pg/ml. A high PTH (>300 pg/ml) is associated with high bone turnover and osteitis fibrosa on bone biopsy. A low PTH (<150 pg/ml) is more likely found in adynamic bone disease (ABD) [35]. Cavalier *et al*. [36] observed a relatively high proportion of secondary hyperparathyroidism according to Salusky *et al*. [37] with 32 patients (44%) having levels of intact PTH above 250–300 pg/ml. The patient population was separated into three groups according to PTH levels (group 1: <100 pg/ml; group 2: ≥100 to <300 pg/ml and group 3: ≥300 pg/ml). Bone formation markers were significantly ($P<0.01$) higher in group 3 than in the other groups. Bone resorption markers were significantly lower ($P<0.05$) in group 1 than in group 2, and also lower ($P<0.01$) in group 2 than in group 3.

In our study, we found that the mean BALP level was 105.2±106.8 U/l with values ranging between 11.0 and

Table 7 Relation between augmentation index (%), aortic pulse wave velocity (m/s), and different parameters (*N*=50)

		Augmentation index (%)		Aortic PWV (m/s) (pulse wave velocity)	
	N	Median (minimum–maximum)	Mean±SD	Median (minimum–maximum)	Mean±SD
Sex					
Male	27	28.0 (4.0–61.30)	28.69±14.99	8.10 (5.70–10.90)	7.90±1.39
Female	23	27.0 (6.0–49.0)	26.95±11.01	7.90 (4.40–10.50)	7.68±1.69
t (*P*)		0.462 (0.646)		0.510 (0.612)	
Cause of ESRD					
Hypertension	22	27.90 (4.0–61.30)	28.01±15.59	8.40 (5.70–10.40)	8.20±1.31
Unknown	12	27.0 (7.0–50.0)	29.27±13.80	7.90 (4.60–9.10)	7.28±1.50
Adult polycystic kidney disease	6	26.0 (13.0–42.0)	26.90±9.92	8.65 (6.30–10.50)	8.58±1.38
Pyelonephritis	3	23.0 (21.60–31.0)	25.20±5.07	7.90 (4.40–8.0)	6.77±2.05
Congenital	3	31.0 (13.0–44.0)	29.33±15.57	6.30 (5.50–10.90)	7.57±2.91
Chronic glomerulonephritis	2	23.0 (18.0–28.0)	23.0±7.07	7.10 (6.40–7.80)	7.10±0.99
Interstitial	1[#]	19.0[#]		6.90[#]	
Analgesic	1[#]	37.0[#]		6.60[#]	
F (*P*)		0.193 (0.985)		1.058 (0.407)	
		Aortic PWV (m/s)		Augmentation index (%)	
Normal	21	24.0 (4.0–60.0)	26.82±14.11	30 7.95 (4.40–10.10)	7.49±1.52
Abnormal	29	28.0 (6.0–61.3)	28.67±12.71	20 8.40 (6.0–10.90)	8.27±1.44
t (*P*)		0.484 (0.631)		1.805 (0.077)	
Normal	21	24.0 (4.0–60.0)	26.82±14.11	30 7.95 (4.40–10.10)	7.49±1.52
Low	4	21.30 (9.20–36.0)	21.95±10.97	5 8.20 (6.0–10.40)	7.92±1.85
High	25	28.80 (6.0–61.30)	29.74±12.83	15 8.60 (6.40–10.90)	8.38±1.34
F (*P*)		0.234 (0.631)		3.258 (0.077)	

ESRD, end-stage renal disease; *F*, *F* analysis of variance test; PWV, pulse wave velocity; *t*, Student's *t* test. *P*: *P* value for comparing between the different categories. [#]Excluded from the comparison due to the small number of cases (*N*=1).

389.0 U/l (normal range: up to 90 U/l), while the mean P1NP level was 655.5±433.0 ng/ml with values ranging between 101.0 and 1200.0 ng/ml (normal range: up to 58 ng/ml).

Recently, the role of alkaline phosphatase (ALP) as an inducer of vascular calcification in CKD has been demonstrated [38]. Shantouf *et al*. [39] reported a significant association of serum ALP with coronary artery calcification in maintenance HD patients. Lomashvili *et al*. [40] reported that ALP activity and protein were significantly increased in the aorta of uremic rats. Studies further showed that increased ALP lead to hydrolysis and inactivation of inorganic pyrophosphate [39,41–43], which was a potent inhibitor of vascular calcification, in the aorta of uremic rats [40].

Our study found a significant positive correlation between BALP and serum creatinine (P=0.039), serum PTH ($P\leq$0.01), serum TG (P=0.01) and serum P1NP ($P\leq$0.01), and a significant negative correlation between BALP and age (P=0.08) and serum phosphorus (P=0.026). Regarding P1NP, there was a significant positive correlation between P1NP and PTH ($P\leq$0.01), serum TG (P=0.017), and serum BALP ($P\leq$0.01). There was a significant difference between patients with low and high AIx regarding BALP (P=0.018), while there was no significant difference between them regarding P1NP (P=0.227).

In a study by Cavalier *et al*. [36], 62% had a BALP level more than 10 µg/l, and the patients belonging to this group were younger, had higher levels of P1NP and carboxyterminal collagen crosslinks (2.0× higher), and tartrate-resistant acid phosphatase (1.5×). The correlation between BALP and P1NP levels explained 90.8% of the variability in BALP. In addition to P1NP, other parameters [bone markers, serum calcium, wPTH/non-(1–84) PTH ratio, intact PTH, and wPTH] were included as independent variables in a multiple regression analysis with BALP as the dependent variable. The results, however, show that these factors do not contribute any more than P1NP alone in the diagnosis of ABD. This strict correlation between BALP and P1NP is interesting and means that both markers observe a closely related phenomenon. Ueda *et al*. [44] have already shown the usefulness of P1NP as a marker of osteoblast function in hemodialyzed patients and its usefulness for predicting radical bone loss.

Table 8 Correlation between different parameters (*N*=50)

	Augmentation index (%)		Aortic PWV (m/s) (pulse wave velocity)	
	r	*P*	*r*	*P*
Age (years)	0.127	0.380	0.627*	<0.01*
BMI (kg/m^2)	0.082	0.572	0.121	0.402
Duration of dialysis (years)	0.063	0.662	0.147	0.48
Urea	–0.180	0.210	–0.048	0.743
Cr	0.08	0.958	–0.152	0.292
Ca	0.158	0.275	0.108	0.454
PO_4	0.094	0.514	0.487*	<0.01*
PTH	–0.021	0.885	–0.102	0.481
Cholesterol	0.088	0.545	–0.206	0.151
TG	0.09	0.952	–0.032	0.827
Heart rate (b/min)	0.422	0.02*	–0.152	0.295
SBP (mmHg)				
Peripheral	0.056	0.698	0.531*	<0.01*
Central	0.018	0.903	0.466*	0.01*
DBP (mmHg)				
Peripheral	0.101	0.484	0.292*	0.040*
Central	0.101	0.487	0.334*	0.018*
PP (mmHg)				
Peripheral	–0.016	0.914	0.463*	0.01*
Central	–0.070	0.628	0.296*	0.037*
P1NP	0.120	0.408	0.134	0.355
Augmentation index (%)			0.267	0.061
Aortic PWV (m/s)	0.267	0.061		

DBP, diastolic blood pressure; P1NP, procollagen type I N-terminal propeptide; PP, pulse pressure; PTH, parathyroid hormone; PWV, pulse wave velocity; *r*, Pearson coefficient; SBP, systolic blood pressure; TG, triglyceride. *Statistically significant at *P* value less than or equal to 0.05.

Bervoets *et al*. [45] found that low levels of BALP (≤10 μg/l) were a good index for the presence of ABD in HD patients. They found BALP to be a useful diagnostic marker to differentiate between ABD/normal bone. Combining a low PTH (<150 pg/ml) and a low BALP (<27 IU/l) improved the specificity of diagnosing ABD in 103 dialysis patients with bone biopsy results [46]. Low bone turnover is linked to vascular calcification and is also associated with mortality [47].

Increased serum BALP in HD patients may represent, in part, osteoblastic transformation of vascular smooth muscle cells [48]. Ishimura *et al*. [48] reported that BALP was significantly independently associated with the presence of vascular calcification after adjustment for the duration of HD, diabetes, and PTH. This result also indicated that BALP exhibited a distinct, independent association with vascular calcification, and that higher BALP not only represents a bone turnover, but also a significant factor associated with vascular calcification.

Alterations in collagen turnover that favor collagen type I synthesis are related to increased aortic stiffness [49]. P1NP reflects the synthesis and conversion of type I collagen and is another bone formation marker [50].

An additional aim of the present study was to assess the presence of arterial stiffness commonly found in ESRD patients. We recorded peripheral pressure waveforms using a cuff-based device applied over the brachial artery and generated central aortic waveform using the pulse wave analysis software.

The mean heart rate was 84.86±15.96 b/min. The mean central SBP was 135.0±25.52 mmHg. The mean peripheral SBP was 121.4±21.96 mmHg. The mean central DBP was 84.32±17.26 mmHg. The mean peripheral DBP was 81.98±17.26 mmHg. The mean central PP was 36.68±13.75 mmHg. The mean peripheral PP was 53.08±18.42 mmHg.

Regarding aortic PWV, 21 (42%) patients had normal PWV readings while 25 (50%) patients had abnormally high readings and four (8%) patients had abnormally low readings. Regarding AIx, 30 (60%) patients had normal readings while 15 (30%) patients had abnormally high readings and five (10%) patients had abnormally low readings. The increased aortic PWV among the dialysis group indicates a stiffer aorta. Vascular stiffness is translated into higher conduction velocity of an impulse along the vessel length. Aortic stiffness is a feature of an accelerated arterial aging observed in ESRD patients [51,52]. These data are supported by other studies investigating aortic PWV in ESRD patients. Several studies have shown that aortic PWV values of patients undertaking HD are significantly worse compared with age-matched and sex-matched individuals in the general population [53–56]. In observational studies, change in progression of PWV by approximately 1 m/s each year is reported in patients with CKD, which represents an increased rate in the progression of arterial stiffness in comparison to the normal aging process [57].

AIx is a measure of the contribution made by the peripherally reflected pressure waves to the ascending aortic pressure waveform and, thus, provides a measure of systemic arterial stiffness. Data in the literature showed that abnormalities in the microcirculation of ESRD patients such as rarefaction of vessels, calcifications of small arterioles, and decreased endothelium-mediated vasodilation are largely responsible for the increased

peripheral reflectance [58,59]. Similarly, London *et al.* [60] found an increased AIx values in dialysis patients and extended his observations by reporting a value of 25% as a cutoff value of AIx for CV mortality. The all-cause mortality-adjusted odds ratio for each 1 m/s increase in PWV is 1.39 (95% confidence interval, 1.19–1.62], while for AIx every 10% increase has an adjusted risk ratio of 1.59 (95% confidence interval, 1.23–1.86) for all-cause mortality [61,62].

In our study, there was a significant positive correlation between AIx and heart rate (P=0.02) and a significant negative correlation between AIx and fasting blood glucose (P=0.036).

There was a significant positive correlation between PWV and age ($P\leq$0.01), serum phosphorus ($P\leq$0.01), peripheral SBP ($P\leq$0.01), central SBP (P=0.01), peripheral DBP (P=0.040), central DBP (P=0.018), peripheral PP (P=0.01), and central PP (P=0.037).

Aging comprises functional and structural arterial changes. Along with reduced arterial compliance, in the larger elastic arteries there is an increase in collagen content, covalent cross-linking of the collagen, elastin fracture, and calcification and reduction in the elastin content with aging. There are also changes in endothelial function, wall thickness media to lumen ratio, and arterial stiffness with aging. The endothelium changes arterial structure and function by producing vasoactive substances such as nitric oxide (potent vasodilator) and endothelin (potent vasoconstrictor and procoagulant). With age, endothelin production increases and nitric oxide production decreases. This favors a procoagulant state and promotes vascular smooth muscle growth. In disease states such as hypertension, diabetes, and CKD this sequence is exaggerated causing an increased risk of CV events [63]. Several studies have found that PWV positively correlated with age [64,65].

Studies have demonstrated a close link between elevated serum phosphorous, vascular calcification, and CV mortality in the CKD population and particularly HD patients [66]. Several mechanisms explain the link between elevated serum phosphate and arterial stiffness in CKD patients (including increased vascular calcification, increased oxidative stress, and increased expression of bone-forming transcription factors) [67]. Studies show conflicting results regarding the link between serum phosphorus and PWV. In a study by Krzanowski *et al.* [68] that included 57 patients on peritoneal dialysis, PWV did not correlate with serum phosphorus. However, Jung *et al.* [64] observed in 67 peritoneal dialysis patients a significant correlation (P=0.008) between serum phosphorus and PWV.

Conclusion

(1) ESRD patients have a high prevalence of vascular stiffness assessed by pulse wave analysis.
(2) There is a significant correlation between BALP and PTH and between P1NP and PTH.
(3) There is a relation between markers of bone formation and vascular stiffness.

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Conflicts of interest
No conflict of interest.

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