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Reduction in Aortic Pulse Wave Velocity Is Associated with a Short-Term Reduction in Dual-Energy X-Ray Absorptiometry Lumbar Spine Bone Mineral Density T Score

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Keywords
Dual energy X-ray absorptiometry · Peritoneal dialysis · Bioimpedance calcium · Pulse wave velocity

Abstract
Introduction: Increased vascular stiffness is a risk factor for mortality. We wished to determine whether changes in vascular stiffness are associated with changes in bone mineral density (BMD) in peritoneal dialysis patients. ***Methods:*** We measured vascular stiffness by aortic pulse wave velocity (aPWV) and BMD by dual electron absorptiometry (DXA) scanning and compared T scores to compensate for differences in patient ages and gender. ***Results:*** Twenty-four patients had repeat aPWV measurements and DXA scans, median 12.4 months apart. aPWV decreased in 15 and increased in 9. As there were more women in the group with an increase in aPWV, we used gender-adjusted DXA T scores Total body T scores fell in both groups, but median T scores remained positive for those with an increase in aPWV, whereas negative T scores on both scans for those with a decrease in or stable aPWV. Lumbar spine T scores fell in those with a reduction in aPWV (–1.6 [–2.4 to 0.6] to –2.1 [–2.4 to 0.3], $p < 0.05$), whereas there was no significant decrease in those with an increase in aPWV (–0.5 [–1.1 to 0.15] to –0.7 [–1.7 to 0.6]). There were no changes in femoral neck T scores. ***Conclusions:*** Our study reinforces the hypothesis of a link between bone disease and vascular disease in dialysis patients. Lumbar spine DXA includes imaging of the aorta and will include aortic calcification, and as such a reduction in lumbar spine T score without a change in femoral neck T score suggests a reduction in aortic calcification. Although our study requires additional confirmation, our data would suggest that changes in aPWV could be used as a surrogate for changes in vascular calcification in the investigation of interventions designed to reduce vascular calcification.

Background

In the general population, vascular calcification has been shown to be a risk factor for mortality and inversely related to bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) [1]. Vascular calcification increases arterial stiffness, which can reliably be measured by pulse wave velocity (PWV), and aortic stiffness is an independent risk factor for cardiovascular mortality [2].

Cross-sectional studies in dialysis patients have reported that PWV is positively associated with lumbar spine BMD, and negatively with femoral neck BMD [3,

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4]. We wished to determine whether changes in PWV in peritoneal dialysis (PD) were associated with changes in BMD by DXA.

Patients and Methods

PWV was measured prospectively in a cross-sectional cohort of PD patients attending for peritoneal membrane testing. Repeat PWV measurements were made in 66 patients, median 12.4 months apart, and 24 had repeat whole body DXA scans (Hologic QDR Discovery W [S/N47096], APEX software version 4.5.2.1) with T scores calculated from the National Health and Nutrition Examination Survey III population data set.

Patient demographic data and medications were retrieved from electronic medical records – PD adequacy as the weekly urea clearance (Kt/Vurea) from 24-h urine and peritoneal dialysate effluent collections. The daily calcium balance was estimated as the difference between the amount of calcium in the fresh daily dialysates and the calcium content of 24-h spent dialysate and 24-urine collections. Apart from icodextrin, all dialysate solutions contained 1.25 mmol/L calcium. Biochemical tests were measured by standard methods (Roche Integra, Roche diagnostics, Lewes, UK). Body composition was determined by multifrequency bioelectrical impedance assessments (InBody 720, Seoul, South Korea) using a standardised protocol [5].

We measured aortic-brachial PWV using the Tensio Clinic Arteriograph (TensioMed Kft., Budapest, Hungary), which has been validated against direct invasive measurements [6]. In keeping with standard practice aortic PWV (aPWV), measurements were corrected for heart rate.

Statistical Analysis

Statistical analysis was performed using standard analyses; D'Agostino-Pearson normality test along with *t* test and paired *t* test, Mann-Whitney U test and Wilcoxon rank sum pair test, as appropriate, and the Spearman rank sum was used for univariate correlation (Graph Pad Prism version 7.0, Graph Pad, San Diego, CA, USA) and SPSS version 24 (IBM corporation, Armonk, New York, NY, USA). Statistical significance was taken at or below the 5% level.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (National research Ethics Committee 129559) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written valid informed consent was obtained from all individual participants included in the study, and all patient data appropriately anonymised.

Results

We divided patients into those who had an increase in aPWV, median 1.6 (0.5–2.9) cm/s and those who had a fall in aPWV, median –1.2 (–2.7 to –0.6) cm/s (Table 1), measured a median of 12.4 months apart, when patients reattended for their annual assessment of peritoneal membrane assessment. Patients with a fall in aPWV initially had higher aPWV, but there was no statistical association between the starting aPWV and the change in aPWV (r = 0.11–0.0, p = 0.6), more women had an increase in aPWV (X^2 = 5.2, p = 0.022). However, there was no difference in the mean arterial blood pressure, or prescription of anti-hypertensive medications. There were no differences in weekly peritoneal and urinary urea clearances, or urine volumes. Serum calcium and phosphate, and parathyroid hormone were not different, as was the prescription of calcium containing phosphate binders. Native vitamin D_3 concentrations were initially lower in those patients starting with a higher aPWV, and then increased as aPWV fell. Peritoneal and urinary calcium losses between groups were similar. On DXA scanning total body bone mineral content (BMC) and BMD fell in both groups ($p < 0.05$). Although BMD fell in 80% of those with a fall in aPWV, there was no statistical difference in the change in BMD (Table 1) or annualised change in BMD (–0.03 [–0.06 to –0.01] vs. 0 [–0.08 to 0.03] g/cm^2/year). As BMC and BMD vary with age and gender, we calculated T scores to enable comparison between patients. Total T scores fell in the group with increased aPWV (Fig. 1). BMD and T scores of the lumbar spine fell only in those with a fall in aPWV. No patient was reported to have vertebral fractures. There were no changes in absolute femoral neck BMD or when annualised (0.01 [0–0.03] vs. 0.01 [0–0.03] gm/cm^2/year) or T scores. There was no overall change in the ratio of extracellular water to total body water; 0.391 ± 0.015 vs. 0.394 ± 0.06, $p > 0.05$, and no statistical association between the change in ECW/TBW and aPWV (r = –0.19, p = 0.40).

Discussion

Greater PWV and vascular calcification are both associated with an increased risk of mortality [1, 2], and osteoporosis is a risk for increased arteriosclerotic vascular calcification [7]. Osteoporosis, arterial calcification and cardiovascular disease all share common risk factors, but also pathophysiological pathways linking vascular disease and osteoporosis [8].

Previous cross-sectional studies in dialysis patients have reported an association between PWV and DXA BMD or T score [4, 9]. Our study is the first to compare pairs of DXA scans and aPWV measurements. We chose to measure aPWV, as this is a measure or aortic PWV, whereas other PWV devices measure a composite of carotid-aortic

Table 1. PD patients were divided to those who did not increase (Stable) aPWV and those with an increase in aPWV

Variable	Stable aPWV		Increased aPWV	
	first aPWV	follow-up	first aPWV	follow-up
n	15		9	
Gender, male	12 (75)		3 (33.3)*	
Age, years	51.5±14.4		43.8±11.2	
PD treatment months	24.6±21.1		25.8±16.9	
DXA scan interval months	14.3 (13.3 to 20.5)		16.4 (16.0 to 18.6)	
aPWV, m/s	9.6±3.1	9.0±2.0	6.9±2.1*	8.8±2.6
Weight, kg	72.7±17.5	72.7±17.4	73.8±16.0	72.6±16.1
BMI, kg/m^2	24.9 ±4.6	25.0±4.4	28.0±3.7	27.3±3.1
Weekly kt/Vurea	1.93±0.47	1.90±0.66	1.99±0.49	1.96±0.66
24-H urine volume, L/day	0.98 (0.59 to 1.16)	0.82 (0.16 to 1.07)	0.64 (.49 to 0.77)	0.49 (0.1 to 0.88)
Icodextrin, L/day	2.0 (0–2.5)	2.0 (0 to 2.5)	1.5 (0.9 to 2.0)	1.8 (0.7 to 2.8)
Protein nitrogen appearance, g/day	0.91±0.17	0.96±24	0.84±0.26	0.82±0.30
Net calcium loss, mmol/day	0.6 (0 to 1.6)	0.6 (0.2 to 0.9)	0.3 (–0.8 to 0.8)	0.7 (–0.3 to 1.0)
Serum calcium, mmol/L	2.31±0.19	2.28±0.16	2.42±0.10	2.39±0.14
Serum phosphate, mmol/L	1.68±0.56	1.72±0.44	1.63±0.44	1.50±0.26
Serum magnesium, mmol/L	0.82±0.14	0.86±0.2	0.95±0.20	0.91±0.27
Parathyroid hormone, pmol/L	38 (20 to 80)	31 (19 to 67)	28 (27 to 29)	24 (15 to 31)
25 OH vitamin D_3, nmol/L	64 (26 to 100)	87 (65 to 103)	82 (78 to 109)*	82 (67 to 91)
Alkaline phosphatase, U/L	100 (83 to 151)	108 (89 to 168)	77 (66 to 95)	75 (65 to 99)
Serum albumin, g/L	38.1±3.8	37.9±3.3	40.8±3.9	39.6±2.5
C reactive protein, mg/L	5 (2 to 22)	3 (2–3)	1 (1 to 3)	3 (1 to 6)
Serum bicarbonate, mmol/L	24.9±3.0	23.9±3.0	24.7±2.9	24.0±3.3
Serum creatinine, umol/L	847 (359 to 944)	877 (717 to 1,080)	583 (513 to 701)	700 (546 to 806)
Haemoglobin, g/L	103.7±16.0	103.6±8.7	114.8±16.3	107.6±13.2
Haemoglobin A1c, mmol/mol	35.5 (33.3 to 44.3)	36.6 (35.5 to 41)	35.5 (34.4 to 39.9)	38.8 (35.5 to 41)
Glucose, mmol/L	5.6 (5.2 to 7.1)	5.6 (4.9 to 6.3)	5.2 (4.7 to 5.4)	5.0 (4.5 to 5.2)
Ferritin, ug/L	662 (353 to 944)	586 (408 to 828)	472 (328 to 714)	561 (368 to 1,064)
Mean arterial blood pressure, mm Hg	113.8±17.7	113.6±19.9	107.7±16.0	106.0±10.9
Patients prescribed antihypertensives, %	60	73.3	88.9	66.7
Number of classes of antihypertensives	1 (0 to 1)	1 (0 to 2)	1 (1 to 1.5)	1 (0 to 1)
Alphacalcidol prescribed, μg/week	0.75 (0 to 1.75)	0.75 (0 to 3.5)	0.75 (0.25 to 2.5)	0.75 (0.25 to 3.25)
Number of calcium binders/day	0 (0 to 1)	0 (0 to 3)	0 (0 to 3.5)	0 (0 to 3)
Total body bone mineral content, g	2,559±531	2,255±381±535	2,471±543	2,225±482
Total body bone mineral density, g/cm^2	1.21±0.17	1.18±0.07	1.19±0.09	1.16±0.09
Lumbar spine bone mineral density, g/cm^2	0.917 (826 to 1.16)	0.861 (0.806 to 1.16)	1.06 (0.955 to 1.1)	0.968 (0.922 to 1.14)
Femoral neck bone mineral density, g/cm^2	0.645 (0.601 to 0.733)	0.622 (0.575 to 0.774)	0.608 (0.542 to 0.802)	0.61 (0.524 to 0.776)

Results expressed as integer, percentage, mean ± SD, median (interquartile range).

* $p < 0.05$ versus stable aPWV.

PD, peritoneal dialysis; aPWV, aortic pulse wave velocity; BMI, body mass index; SMM, skeletal muscle mass; DXA, dual electron absorptiometry.

and femoral artery PWV. The prevalence of medial vascular calcification varies between arteries, this being greater for the aorta compared to the femoral artery, and the femoral artery greater than that of the carotid artery [10].

Aortic PWV fell in a group that started with a greater initial aPWV. There was no effect of the change in aPWV and the initial aPWV. The reduction in aPWV in this group was not associated with differences in blood pressure control, ECW/TBW or anti-hypertensive prescriptions. Similarly, there were no differences in serum chemistries, or prescription of calcium containing binders, estimates of peritoneal and urinary calcium losses, or prescription of active vitamin D analogues. This group started with lower native vitamin D_3 concentrations, which were then supplemented in keeping with clinical policy of the centre, and previous reports have suggested that native vitamin D_3 may play a role in preventing vascular calcification [11].

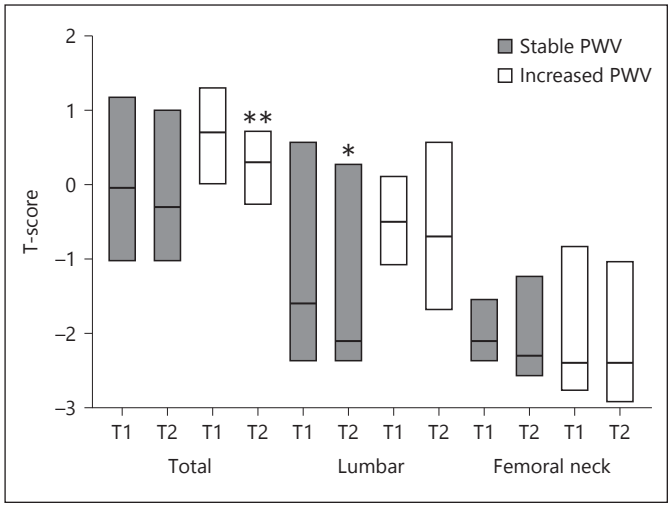

Fig. 1. T scores derived from DXA total body, lumbar spine and femoral neck BMD. Median (interquartile range) * $p < 0.05$, ** $p < 0.01$ second scan (T2) vs. first scan (T1). Patients divided into those in whom aPWV did not increase (Stable) and those with an increase in aPWV. PWV, pulse wave velocity.

Although DXA scanning has not been shown to be predictive of the type renal bone mineral disease, reduced BMD on DXA scanning is associated with increased fracture risk for kidney dialysis patients [12], and fracture risk is not only increased for PD patients [13], but also with both greater over-all mortality and cardiovascular mortality [13, 14].

Total body BMC was greater in the group with a fall in aPWV, but as this group contained more men, we reviewed T scores to overcome confounders of gender and age. While the median T scores on DXA scans were negative for the group with a fall in aPWV, they were positive on both scans for those with an increase in aPWV. T scores were similar for the femoral neck for both groups, and did not change between scans.

However, T scores for the lumbar spine fell only in those with a reduction in aPWV. DXA scans of the lumbar spine include the aorta, and as such additionally measure aortic calcification. Thus, the fall in aPWV and lumbar spine T score could reflect a reduction in aortic calcification and thus a reduction in aortic stiffness as measured by aPWV, whereas there was no reduction in lumbar T score in those patients with an increase in aPWV. On the other hand, at the femoral neck, which has no overlying artery, there was no change in T score on repeat DXA scanning and no association between T score and aPWV.

As such, our study supports previous reports of an association between PWV and vascular calcification [15], and more recent studies have shown that a reduction in vascular calcification following parathyroidectomy is associated with a reduction in vascular stiffness, measured by PWV [16].

We report a short-term study, as PWV tends to increase with patient age. There may be errors in PWV measurement, but to overcome these, all measurements were made by the same observer. Calcification of conduit arteries may reduce PWV, particularly when measuring PWV over a longer distance, such as brachial artery-ankle PWV [17]. To reduce this potential artefact, we restricted our measurements to aPWV. Recent studies have observed an association between the regulators of vascular calcification and PWV [18]. However, we were only able to measure standard biochemical variables.

Patients with chronic kidney disease have a much greater rate of increase in aortic stiffness, and a faster increase in aPWV compared to patients with normal kidney function [19]. Dialysis patients have disorders of bone and mineral metabolism, resulting in greater risk of vascular calcification. We report that a fall in aPWV in PD patients was associated with a fall in lumbar spine T score, which most likely reflects a reduction in the adjacent aortic calcification, reinforcing the hypothesis of a link between bone disease and vascular disease in dialysis patients. Although our study requires additional confirmation, our data would suggest that changes in aPWV could be used as a surrogate for changes in vascular calcification in the investigation of interventions designed to reduce vascular calcification.

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Disclosure Statement

The authors have no conflict of interest. The data in this paper has not been previously presented or published.

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