Aortic Pulse wave velocity is greater in peritoneal dialysis patients with lower dual energy X-ray absorptiometry (DXA) femoral neck bone mineral density

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Compliance with Ethical Standards
Ethics: The study was undertaken according to the Helsinki accord, with appropriate informed consent and approvals (National research ethics committee project 129559, and trial registration ISRCTN70556765).
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Abstract

Background

Increased vascular stiffness is associated with low bone mineral density (BMD) in the general population, and both are risk factors for mortality. We wished to determine whether vascular stiffness is associated with BMD in peritoneal dialysis (PD) patients.

Methods

We measured vascular stiffness by aortic pulse wave velocity (aPWV), BMD by dual electron absorptiometry (DXA) scanning, and body composition using bioimpedance.

Results

We reviewed DXA scans in 125 PD patients, 56.8% male, mean age 64.4 ±15.3 years, mean aPWV, 10.2 ±2.6 m/s. We divided patients by aPWV (< 10 and >10 m/s), and there were no statistical differences in patient demographics, body composition, PD adequacy, peritoneal and urinary calcium losses. On univariate analysis aPWV was negatively associated with total body T score (r=-0.20, p=0.037).. On multivariable logistic regression patients with higher aPWV were prescribed fewer non-calcium containing phosphate binders, odds ratio (OR) 0.83, 95% confidence interval (CI) 0.70-0.99, p=0.039, more had lower 25 hydroxy-vitamin D_3 concentrations < 50 ng/L (OR 0.34, CI 0.12-0.93, p=0.035, and lower femoral BMD OR 0.03 (CI 0-0.3.4), p=0.029, but there was no association with total or lumbar spine BMD.

Conclusion

Our study reinforces the hypothesis of a link between bone disease and vascular disease in dialysis patients. As patients with higher aPWV were prescribed fewer non-calcium containing phosphate binders and fewer had higher 25 hydroxy-vitamin D_3 concentrations, then this raises the possibility that differences in clinical practice and drug prescribing may help to reduce vascular stiffness, which will require testing in future trials.

Background

Peritoneal dialysis (PD) patients have an increased risk for both cardiovascular and bone mineral disease, typified by vascular calcification, increased fracture risk and mortality. In general population studies, increased vascular calcification has been reported to be directly related to mortality and inversely related to bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) [1]. Calcification of arteries increases arterial stiffness, which can then be measured by pulse wave velocity (PWV), and aortic stiffness is an important independent risk factor for cardiovascular mortality [2].

Studies in haemodialysis patients have reported varying associations between BMD and PWV [3], with reports linking PWV positively with lumbar spine BMD, and negatively with femoral neck BMD [4]. Whereas one previous study in PD patients observed no association with PWV and BMD of the lumbar spine but did report a negative association with femoral neck BMD [5]. These cross-sectional studies have included less than fifty patients. As, clinical practices have changed over time, with the introduction of lower calcium

containing dialysates, and vitamin D sterols, we wished to revisit whether there was an association between vascular stiffness and BMD in PD patients.

Patients and methods

We reviewed whole body DXA scans (Hologic QDR Discovery W (S/N47096) from adult PD patients attending a university peritoneal dialysis centre using a standardised technique, whereby PD fluid was drained out from the abdomen patients were then asked to pass urine. Dressed in a thin hospital gown were weighed and had height measured. DXA scans were then performed and analysed (APEX software version 4.5.2.1) and T scores calculated from the National Health and Nutrition Examination Survey (NHANES) III population data set, with a normal T-score of −1.0 or higher and osteopenia defined as a T score between −1.0 and −2.5, and osteoporosis with a T score lower than -2.5.

Patient demographic data, co-morbidity and prescribed medications were retrieved from hospital electronic records. Centre policy was to supplement vitamin D_3 inpatients with serum 25 hydroxy vitamin D_3 concentrations < 50 nmol/L with 20,000 IU cholecalciferol/week [6].

Peritoneal transport was calculated as the four-hour peritoneal dialysate effluent creatinine to serum ratio, peritoneal dialysis adequacy as the weekly urea clearance (Kt/Vurea) from 24-hour urine and peritoneal dialysate effluent collections. The daily calcium loss was estimated as the difference between the calcium content of fresh dialysates and the calcium content of spent dialysate and 24-urine collections. Biochemical tests were measured by standard methods

(Roche Integra, Roche diagnostics, Lewes, UK). Body composition was determined by multifrequency bioelectrical impedance assessments (MFBIA) (InBody 720, Seoul, South Korea) using a standardised protocol [7,8].

Aortic-brachial pulse wave velocity was prospectively measured using the Tensio Clinic Arteriograph (TensioMed Kft., Budapest, Hungary) which has been validated against direct invasive measurements [9], and also been shown to be the most reproducible of the currently available devices for measuring PWV [10]. In keeping with standard practice aortic PWV (aPWV) measurements were corrected for heart rate. PWV measurements were not able to be recorded in patients with atrial fibrillation, other arrhythmias, and patients with no recordable upper arm blood pressure recordings. As PWV normally increases with age, we reviewed the age distribution of our cohort and the normal PWV reference values reported by the reference values for arterial stiffness' collaboration [11].

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Statistical analysis

Data was checked using the D'Agostino & Pearson normality test, and results expressed as mean ± standard deviation, median and interquartile range, or percentage. Student's t test and Mann Whitney U test, and Chi square (X2), with appropriate corrections used to compare groups, and non-parametric data

was log transformed if required for further analysis. Step backwards logistic regression models were analysed, using variables which correlated with aPWV ($p<0.1$) by univariate analysis, and those which differed between higher and lower aPWV groups. Variables were then removed or retained in the models if the 95% confidence intervals for the estimate did not include zero or there was an improvement in model fit. Statistical analysis was performed using Graph Pad Prism (version 7.0, Graph Pad, San Diego, CA, USA) and SPSS version 24 (IBM corporation, Armonk, New York, USA). Statistical significance was taken at or below the 5% level.

Results

One hundred and twenty-five PD patients had DXA scans, aPWV and MFBIA measurements along with assessments of peritoneal membrane function and dialysis adequacy. Between August 2015 and July 2017 our centre treated 215 patients with peritoneal dialysis. Twenty-five patients did not have bioimpedance or PWV measurements due to the presence of implantable cardiac devices, amputation, or incapacitating stroke, or irregular cardiac output, and 56 patients did not have corresponding DXA scans (Figure 1), Their mean age was 64.4 ±15.3 years, 56.8% male, with a mean aPWV 10.2 ±2.6 m/s, when adjusted to a heart rate of 70 beats/min. The median whole-body T score was -0.2 (-1.1 to +0.8), the T score for lumbar spine 1.02 (0.88 to 1.11) and the T score for femoral neck was -1.8 (-2.5 to -1.05). As such 24.6% of patients had osteopenia and 5.3% osteoporosis based on whole body T scores, 47.2% osteopenia and

12.8% osteoporosis based on lumbar spine BMD, and 79.2% osteopenia and 21.6% osteoporosis at the femoral neck.

To ensure generalisability we compared those patients excluded without corresponding DXA scans to our final study group. There were no statistically significant differences in terms of patient gender ($X2=4.0$, $p=0.052$), mean age 61 ±15 years ($p>0.05$), Davies co-morbidity grade ($X2=2.7$, $p=0.45$), or mean arterial pressure of 101.8±12.7 mmHg, and aPWV 10.1 ±3.1 m/s ($p>0.05$).

We found no correlation between aPWV and gender, patient age or duration of PD therapy, peritoneal dialysis adequacy, residual renal function, or daily calcium losses. On univariate analysis aPWV was associated with systolic blood pressure ($r=0.21$, $p=0.025$), pulse pressure ($r=0.28$, $p=0.002$), and negatively with the total body T score ($r=-0.20$, $p=0.037$).

We divided patients into those with a lower and higher aPWV (< 10 and >10 m/s), according to the expected PWV for the age of our cohort [11] (table 1). Patients with higher aPWV were marginally older, but well matched for body composition, residual renal function and total urea clearance. Patients with higher aPWV were prescribed more calcium containing phosphate binders, although the total calcium content of these tablets and peritoneal dialysate and urinary calcium losses were not statistically different.

On multivariable logistic regression those patients with higher aPWV were prescribed fewer non-calcium containing phosphate binders, odds ratio (OR) 0.83, 95% confidence interval (CI) 0.70-0.99, β-0.18, standard error (StE) 0.09, Wald 4.3, $p=0.039$. fewer had 25 hydroxy-vitamin D_3 concentrations > 50

ng/L OR 0.34, CI 0.12-0.93, β-1.1, StE 0.5, Wald 4.5, p=0.035, and faster aPWV was associated with lower femoral neck bone mineral density (BMD) OR 0.03, CI 0-0.3.4, β-10.4, StE 4.8, Wald 4.8, p=0.029.

Discussion

Both PWV and vascular calcification are associated with an increased mortality risk for dialysis patients [1,2], and in the general population low bone mineral density (BMD) is associated with increased arteriosclerotic vascular calcification [12]. Although osteoporosis, aortic and conduit artery calcification and cardiovascular disease share common risk factors, direct pathophysiological pathways linking vascular disease and osteoporosis have been demonstrated [13]. However, several earlier studies in haemodialysis patients have reported variable results, with some studies reporting an association between PWV and BMD or T score measured by DXA scanning and others not [3,14,15]. Similarly, studies have variably reported an association between aortic calcification and lumbar spine BMD, where greater aortic calcification was associated with lower lumbar spine trabecular bone scores, but vascular calcification was not associated with lumbar spine or femoral neck BMD [14]. These differences may relate to differences in aortic and conduit artery calcification, as dialysis patients are reported to have more aortic medial calcification than carotid or superficial femoral artery calcification [4].

We found that higher PWV was associated with a lower total body T score, and on multivariate analysis those patients with a higher aPWV had a

lower femoral neck BMD, in keeping with an earlier smaller study in PD patients [5]. We measured aortic PWV, whereas other studies have measured PWV from the carotid artery down to the superficial femoral artery, and as such measured a composite of aortic and conduit artery PWV [3,4], and as vascular calcification differs between these vessels this may account for the different findings reported between studies.

There has been a debate as to the accuracy of lumbar spine BMD measurements, as anterior to posterior scanning will include the aorta and also part of the gastrointestinal tract, so lumbar spine BMD could be increased by aortic calcification and ingestion of heavy metals, including lanthanum containing phosphate binders [14,15]. As such, some investigators have advocated lateral lumbar spine DXA scanning [14,16], or quantitative computerised tomographic scanning (CT) [17,18].

We found that fewer patients with higher aPWV had normal 25 hydroxy-vitamin D_3 concentrations, supporting previous observations linking low levels with increased vascular calcification [19]. Vitamin D is recognised to protect against vascular and soft-tissue calcification by its effects on increasing klotho and osteopontin, and also by preventing osteoblastic transformation of vascular smooth muscle cells [20,21], and reduced vitamin D levels with increased risk of bone fracture [22]. On the other hand the administration of large doses of activated vitamin D_3 may conversely increase vascular calcification and vessel stiffness [23,24].

In our study patients with lower aPWV were prescribed more non-calcium containing phosphate binders raising the possibility that increased oral calcium may contribute to an increased net calcium gain and increased soft tissue calcification. There was no difference in the amount of calcium lost in dialysates or urine between the groups, and studies in haemodialysis patients have differed as to whether dialysate calcium contributes to vascular calcification and vascular stiffness [24,25]. However, we were unable to estimate the dietary calcium intake, as such were not able to estimate overall calcium balance in our patients. Due to the increased fracture risk, several agents have been proposed to improve bone mineral density or bone structure. None of our patients had received bisphosphates, denosumab, teriparatide, romosozumab or raloxifene [26], and as such we are unable to comment on whether these agents have any effects on aPWV. We excluded a number of patients without DXA scans but these patients did not differ from the study group in terms of age, gender, co-morbidity or aPWV.

We report an observational cohort study, and as such can only report associations and not apportion causality. Even so, our large study provides information which can be used to plan future studies designed to test hypotheses. In keeping with earlier studies, we suspect that lumbar spine DXA measurements in older adult chronic kidney disease patients can be confounded by vertebral osteoarthritis and aorta calcifications [17,18].

There is increasing awareness that BMD in kidney dialysis patients is a condition not just simply limited to biochemical abnormalities [27]. We report

that lower BMD, evaluated by DXA, at the femoral neck but not at the lumbar spine were associated with greater aPWV, reinforcing the hypothesis of a link between bone disease and vascular disease in dialysis patients.

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Figure 1. Consort diagram of patient recruitment

Table 1. Peritoneal dialysis (PD) patients were divided to those with an aortic pulse wave velocity (aPWV) ≤10 m/s and > 10 m/s. Results expressed as integer, percentage, mean ±SD, median (interquartile range). * p <0.05.

variable	aPWV ≤10 m/s	aPWV > 10 m/s
number	57	68
Gender (male)	28 (49.1%)	43 (63.2%)
Age years	62 ±16	66 ±14
Months of PD treatment	17 (9-28)	12 (4-27)
Weight kg	72.0 ±16.3	73.9 ±16.8
Skeletal muscle mass kg	26.5 ±9.1	26.4 ±6.5
Extracellular water/height L/m	8.35 ±2.01	8.57 ±1.92
Weekly Kt/Vurea	1.93 (1.5-2.37)	2.03 (1.61-2.22)
24-hour urine volume L/day	0.74 (0.43-1.24)	0.83 (0.27-1.29)
4-hour dialysate/serum creatinine ratio	0.75 ±0.11	0.72 ±0.12
Protein nitrogen appearance g/day	62.8 ±17.8	60.9 ±15.7
Net calcium loss mmol/day	0.76 ±1.04	0.77 ±1.06
Serum calcium mmol/L	2.32 ±0.21	2.32 ±0.16
Serum phosphate mmol/L	1.70 ±0.51	1.65 ±0.45
Calcium phosphate product $mmol^2/L^2$	3.88 ±1.32	3.77 ±1.92
Serum magnesium mmol/L	0.81 (0.71-0.92)	0.84 (0.74-0.96)
Parathyroid hormone pmol/L	34.7 (19.8-53.3)	38.5 (35.5-42)
25 OH Vitamin D_3 nmol/L	66 (50-84)	63 (40-82)
Alkaline phosphatase U/L	108 (81-141)	91 (72-122)
Serum albumin g/L	38.3 ±4.2	38.4 ±4.3
C reactive protein mg/L	4.5 (2.0-11.0)	3.0 (2.0-7.5)

Haemoglobin g/L	108.6 ±14.1	110.0 ±14.8
Haemoglobin A1c mmol/mol	36.6 (30.1-47.0)	41.0 (34.4-58.5)
Ferritin ug/L	806 (461-1064)	636 (440-928)
Mean arterial blood pressure mmHg	101.0 ±15.8	100.5 ±14.4
Patients prescribed antihypertensives	29 (50.9%)	48 (70.6%)*
Alphacalcidol prescribed ug/week	1.5 (0.25-3.5)	1.0 (1.0-3.0)
Number of non-calcium binders/day	0 (0-3)	0 (0-0) *
Calcium based binders G calcium/day	0 (0-1.5)	0.5 (0-2.3)
Number of calcium binders/day	0 (0-3)	1 (0-3) *
Total bone mineral g	2384 ±543	2302 ±535
Total bone mineral density g/cm^2	1.19 ±0.14	1.14 ±0.13
Total T score	0.3 (-0.9 to 1.0)	-0.5 (-1.3 to 0.5)*
Total body osteopenia/osteoporosis %	21.8/3.6	27.1/6.8
Total lumbar spine mineral g	60.9 ±17.1	59.5 ±18.9
Lumbar spine bone mineral density g/cm^2	1.03 ±0.17	0.99 ±0.19
Lumbar spine T score	-0.7 (-1.6 to -0.1)	-1.0 (-2.2 to 0.2)
Lumbar spine osteopenia/osteoporosis %	45.6/8.8	48.5/16.2
Femoral neck bone mineral g	3.84 ±1.05	3.63 ±0.78
Femoral neck bone mineral density g/cm^2	0.73 ±0.18	0.68 ±0.13
Femoral neck T score	-1.7 (-2.4 to -0.7)	-1.9 (-2.8 to -1.3)
Femoral neck osteopenia/osteoporosis %	73.7/19.3	83.8/23.5