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Aortic vascular calcification is inversely associated with the trabecular bone score in patients receiving dialysis☆,☆☆

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ABSTRACT

Introduction: Progressive chronic kidney disease (CKD) confers a marked increase in risk for vascular calcification, cardiovascular disease, fracture and mortality, with likely contributing factors including dysregulated bone metabolism and mineral homeostasis. In general population studies, increased vascular calcification is directly related to mortality and inversely related to bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA). In patients with CKD, abnormalities in turnover, mineralization and bone volume reduce the ability of DXA to predict fracture. The trabecular bone score (TBS) obtained from lumbar spine DXA images, provides a surrogate measure of microarchitectural integrity not captured by BMD. This study aimed to examine the association of the TBS to prevalent abdominal aortic calcification (AAC) in patients with CKD receiving dialysis.

Methods: We performed a cross-sectional study of dialysis patients awaiting transplantation. All patients underwent laboratory testing, lateral spinal radiographs including the abdominal aorta, DXA imaging and TBS assessment. AAC scores were determined using the Kauppila method. Correlations and linear regression models were used to determine predictors of AAC scores.

Results: 146 patients (60% male, mean age 48 ± 13 years) were included, of whom 49% had prevalent calcification with an AAC score ≥ 1. Of those with calcification, the mean AAC score was 7 ± 5.5 and 42 patients had scores ≥ 6, considered to indicate severe AAC. TBS values corresponding to intermediate or high risk for fracture (< 1.31) were present in 35% of patients. TBS values correlated inversely to AAC scores ($\beta = -0.206$, $p = 0.013$) and remained significant in multivariable linear regression, adjusting for age, BMI and time on dialysis (-0.160, $p = 0.031$). There was no significant correlation of AAC scores to any BMD parameter.

Conclusion: There is a high prevalence of AAC in relatively young dialysis patients awaiting transplantation and their AAC scores are inversely related to the TBS but not to DXA-derived BMD parameters. In patients with CKD on dialysis, TBS assessment reflects microarchitectural abnormalities of bone not captured by DXA. The inverse relationship of TBS to vascular calcification may provide insights into bone-vascular interactions in CKD.

1. Introduction

Mortality is increased in patients with chronic kidney disease (CKD), with cardiovascular disease the predominate cause of death [1,2]. In addition to traditional risk factors of age, smoking, dyslipidaemia and hypertension, abnormal bone and mineral metabolism and accelerated vascular calcification are important contributors to cardiovascular risk in these patients [3].

Vascular calcification is a marker of cardiovascular disease and mortality [4,5]. The prevalence of abdominal aortic calcification (AAC) detected by radiographs in the Framingham study was 50% for women and 55% for men aged 51–60 years, increasing to 84% for men and 89%

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for women aged 72–80 years [6]. Importantly, AAC has been associated with an increased risk for adverse cardiovascular outcomes, including acute coronary syndromes, stroke and peripheral vascular disease, as well as an increased risk for mortality [4,7–9]. The incidence and prevalence of vascular calcification is higher in patients with CKD, increasing with progressive renal decline with a reported prevalence up to 80–90% in those requiring dialysis [10].

Although osteoporosis, vascular calcification and cardiovascular disease share common risk factors, direct pathophysiological pathways coupling these entities have also been demonstrated [11]. In the general population, vascular calcification has been linked to dysregulated bone and mineral metabolism, reduced bone mineral density (BMD) and increased fracture rates [12–14]. Ageing, dyslipidaemia, inflammation and oxidative stress, amongst other conditions, induce vascular smooth muscle cells (VSMC) to undergo osteogenic transformation leading to osseous deposition and vascular calcification [15].

Perturbations of the bone-vascular axis are well recognized in patients with CKD and are described by the term CKD mineral and bone disorder (CKD-MBD) [16]. This encompasses the interplay of declining kidney function and abnormalities of bone and mineral homeostasis that increase fracture risk, cardiovascular risk and mortality in patients with CKD far above that of the general population [16–18].

In patients with CKD, pathophysiological mechanisms linking kidney, bone and the vasculature provide a rationale for the accelerated and severe vascular phenotype. The focus on hyperphosphataemia, hyperparathyroidism and traditional cardiovascular risk factors has expanded to include rising levels of fibroblast growth factor 23 (FGF-23), reduced expression of klotho and the contribution of inhibitors of the Wnt (wingless/integrated-1) signalling pathway that participate in early responses to kidney injury [19]. These concepts are redefining our understanding of cardiovascular risk in CKD-MBD.

The abdominal aorta, coronary and carotid arteries are principal vascular beds used to assess vascular calcification. Abdominal aortic calcification (AAC) can be readily quantified using lateral spinal radiographs that include the abdominal aorta or computed tomography (CT), and the 24-point scoring method employed by Kauppila et al. in the Framingham study [6] is the most widely used measure of AAC. In the general population, prevalent and incident vascular calcification has been consistently reported to be inversely associated with BMD measured using dual-energy X-ray absorptiometry (DXA) [20,21], which provides supportive evidence for a vascular-bone interplay.

BMD is also predictive of fracture risk in the general population [22,23]. Although some studies demonstrate prognostic value for DXA-derived BMD to predict fractures in patients with CKD G3-5D (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 to dialysis) [24,25], and recently updated guidelines recommend its use for screening in patients with CKD, it remains less predictive of fracture risk in these patients and accounts for a limited proportion of observed fractures [16,17]. Surprisingly, although there is a strong physiological basis for the inverse relationship of BMD to vascular calcification in patients with CKD, this is also less established than in the general population with studies showing conflicting results [10,26]. In part this may reflect the complex changes of renal osteodystrophy, including high and low bone turnover, impaired mineralization and volume, and differences in these effects on cortical and cancellous compartments that cannot adequately be measured using areal BMD alone.

The trabecular bone score (TBS) is a novel grey level textural measurement taken from anterior-posterior lumbar spine (LS) DXA images [27,28]. It requires no additional scanning time or radiation exposure, is inexpensive and readily accessible on exisiting DXA machines. The TBS provides a surrogate measure of bone microarchitecture, with high resolution peripheral quantatative CT (HR-pQCT) and micro-CT studies showing correlation of the TBS to trabecular volume, thickness, connectivity and stiffness [29,30]. Lower TBS values are associated with an increased risk for major osteoporotic fractures in post-menopausal women and men [31,32] and the TBS provides additive fracture risk prediction to BMD using the FRAX tool [33]. For patients with CKD, some studies have reported lower values of the TBS [34,35] and for patients on dialysis, lower values of the TBS have correlated to microarchitectural abnormalities detected by HR-pQCT and to prevalent non-vertebral fractures [36,37]. To date, no studies have assessed associations of the TBS to measures of vascular calcification in patients with CKD. In this study of patients with CKD receiving dialysis, we examine associations of the TBS to vascular calcification.

2. Methods

2.1. Cohort

Patients included in the study had CKD G5-5D and were waitlisted for kidney or simultaneous kidney-pancreas (SPK) transplant by the Department of Renal Medicine, Westmead Hospital, Sydney, between January 2015 and December 2016. All patients transplanted during this time were included and there were no study exclusions. Demographic information, relevant clinical data and use of prior bone modifying medications [calcium, vitamin D, calcitriol, bisphosphonates, cinacalcet or hormone replacement therapies (HRT)] were recorded during a structured clinic visit within 4 weeks of transplantation. The study was approved by the Human Research Ethics Committee of the Western Sydney Local Health District. All patients commencing dialysis in Australia are informed that de-identified data are collected for research purposes and given an opportunity to opt out.

2.2. Biochemical parameters

Fasting blood samples were collected within the 24 h prior to transplantation on all patients. Serum calcium, phosphate, magnesium, creatinine and alkaline phosphatase (ALP) were assayed using the Siemens Vista platform (Siemens Healthcare GmbH, Germany), and for 10 patients with CKD G5 not on dialysis, eGFR was calculated using the CKD-EPI formula [24]. Serum 25(OH)D was measured using the Liaison assay (DiaSorin Inc., Stillwater, MN, USA) and 1,25(OH)2D by radioimmunoassay (DiaSorin Inc., Stillwater, MN, USA) using an in-house reference range. The testing laboratory is enrolled in the Royal College of Pathologists Australasia Quality Assurance and the Vitamin D External Quality Assessment Scheme. Intact parathyroid hormone (PTH) was measured using the Abbott Architect (Abbott Diagnostics, Illinois USA) and procollagen type 1 N-terminal propeptide (P1NP) and beta C-terminal cross-linking telopeptide of type I collagen (β-CTx) were analysed on the Roche COBAS e411 (Roche Diagnostics, Indianapolis, USA).

2.3. Vascular calcification

Lateral spinal radiographs that included the abdominal aorta were obtained within 2–4 weeks of transplantation on all patients. The AAC score was derived using the method described by Kauppila et al. [6]. In brief, the anterior and posterior aspects of the aorta are divided into four segments bound by the first four lumbar vertebrae giving a total of 8 segments. For each segment, the anterior and posterior walls of the aorta are assessed separately, and the degree of vascular calcification is graded 0, 1, 2 or 3 corresponding to vascular calcification being absent, present in less than one third of the aortic wall, greater than one third but less than two thirds, or greater than two thirds of the aortic wall. Each of the 8 segments is scored from 0 to 3 so that the total score can range from 0 to 24 (Fig. 1). For rescored X-rays, we have reported the correlation coefficient between assessors' scores to be 0.91 [38] and others have reported intra-class correlation for intra-rater agreement as 0.90 or higher [6,10,39].