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Associations between parameters of peripheral quantitative computed tomography and bone material strength index

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ABSTRACT

Background: Bone material strength index (BMSi) is measured *in vivo* using impact microindentation (IMI). However, the associations between BMSi and other bone measures are not clear. This study investigated whether bone parameters derived by peripheral quantitative computed tomography (pQCT) are associated with BMSi.
Methods: Participants were men (n = 373, ages 34-96 yr) from the Geelong Osteoporosis Study. BMSi was measured using an OsteoProbe (Active Life Scientific, USA). Bone measures were obtained at both the radius (n = 348) and tibia (n = 342) using pQCT (XCT 2000 Stratec Medizintechnik, Germany). Images were obtained at 4% and 66% of radial and tibial length. Associations between pQCT parameters and BMSi were tested using Spearman's correlation and multivariable regression used to determine independent associations after adjustment for potential confounders. Models were checked for interaction terms.
Results: Weak associations were observed between total bone density (radius 4%; r = +0.108, p = 0.046, tibia 4%; r = +0.115, p = 0.035), cortical density (tibia 4%; r = +0.123, p = 0.023) and BMSi. The associations were independent of weight, height, and glucocorticoid use (total bone density: radius 4%; β = 0.020, p = 0.006, tibia 4%; β = 0.020, p = 0.027 and cortical density: radius 4%; β = 4.160, p = 0.006, tibia 4%; β = 0.038, p = 0.010). Associations with bone mass were also observed at the 66% radial and tibial site, independent of age, weight, and glucocorticoid use (β = 4.160, p = 0.053, β = 1.458, p = 0.027 respectively). Total area at the 66% tibial site was also associated with BMSi (β = 0.010, p = 0.012), independent of weight and glucocorticoid use. No interaction terms were identified.
Conclusion: There were weak associations detected between some pQCT-derived bone parameters and BMSi.

1. Introduction

The ability of bone to resist fracture is determined by its mass, structure and material properties [1]. Bone needs to be both stiff and flexible to allow weight bearing and deformation without cracking, while also being lightweight to facilitate movement [2]. Fractures can occur when a bone does not have sufficient strength. Dual energy X-ray absorptiometry (DXA) is currently the routine method of fracture risk assessment in a clinical setting. It provides information about the amount of mineral present in a given area of bone and is inherently associated with bone size, but provides no information about bone geometry, microarchitecture or material properties [3]. Consequently, many individuals who will sustain a fracture are not identified by DXA alone or in combination with clinical risk factors [4–6]; thus, other measures of bone are needed in order to improve fracture risk prediction.

Peripheral quantitative computed tomography (pQCT) is a potential technique for improving fracture risk prediction. It provides details of

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bone microarchitectural properties for the radius and tibia [7]. The measurement time is short (~3 min), and the radiation dose is small (<3 mSv per site). This technology can differentiate between cortical and trabecular bone, as well as provide a volumetric (three dimensional) rather than areal (two dimensional) bone mineral density (BMD). Previous studies have reported that the accuracy, precision and reproducibility of cortical and trabecular parameters of bone derived from pQCT are good [8–10] and are associated with incident fracture risk [11,12].

Another potential technique for clinical measurement of bone strength is known as impact microindentation (IMI), performed *in vivo* using a device called the OsteoProbe [13]. The measurement is performed on the surface of the mid-tibia (Fig. 1) and measures the indentation distance of the probe tip into the bone, comparing it with a reference material (polymethylmethacrylate). The output of the measurement is called bone material strength index (BMSi), a unitless value where a higher number represents a greater resistance to microfracture propagation [14]. However, relationships between BMSi and other bone measures have not been thoroughly explored [15]. For example, several studies have examined associations between BMSi and BMD (as measured by DXA), with several showing a positive correlation [16,17] whereas others showing no correlation [18–25]. We have also previously reported an association between BMSi and trabecular bone score [18]; however, no associations were detected between BMSi and measures of quantitative calcaneal ultrasound [18]. No associations between high-resolution(HR)-pQCT-derived parameters and BMSi were detected in a study including 35 postmenopausal women (16 with type 2 diabetes mellitus (T2DM) and 19 controls) [24]. However, another study reported that BMSi was correlated with some HR-pQCT derived bone parameters at the tibia, specifically measures of cortical bone (cortical porosity and cortical volumetric BMD) [26].

Other studies have also investigated correlations with *ex vivo* measurements of bone. Rokidi et al. measured BMSi for transiliac bone biopsies from a group of 12 participants [27] and reported that BMSi was associated with local mineral content, nanoporosity and pyridinoline (a collagen crosslinking compound) content at the subperiosteal site. BMSi has also been reported to be more strongly associated with the Young's modulus (stiffness) and damage constant than with the compressive yield stress and viscosity constant [28]. Ly et al. have reported that BMSi is significantly correlated with Vickers hardness and Rockwell hardness (r values >0.90), measured using a series of different materials [29].

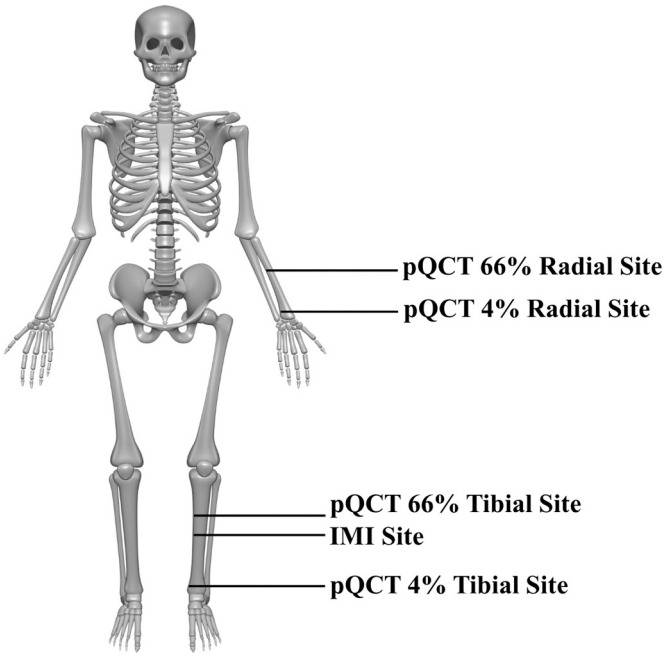

Fig. 1. Diagram showing the location of the impact microindentation (IMI) and peripheral quantitative computed tomography measurements (pQCT).

Although several studies have investigated associations between BMSi and some other bone measures, further information is needed to assist in advancing an understanding of how the IMI measurement might improve fracture risk predictions [30]. Few studies have examined correlations between pQCT-derived parameters of bone and BMSi, and to our knowledge, none have included men. Previous studies have indicated that BMSi may provide details about the properties of the surface of the bone; that is, cortical bone rather than trabecular bone. Since the pQCT technology can distinguish between cortical and trabecular bone, correlations with BMSi can be assessed for each type of bone separately. Additionally, BMSi and pQCT measurements are performed at similar tibial sites. Therefore, the aim of this study was to investigate associations between pQCT-derived parameters of bone and BMSi in a sample of men. If no associations are observed, this would suggest that the two provide complementary information and may both be useful for improving fracture risk predictions.

2. Methods

2.1. Participants

Participants for this study were residents of the Barwon Statistical Division in south-eastern Australia who were enrolled in the Geelong Osteoporosis Study [31]. The data for this study were generated at the 15-year follow-up assessment phase for men (2016–2020), as this was the first visit where IMI and pQCT assessments were performed. At this visit, 378 men provided data for both IMI and pQCT techniques.

Barwon Health Human Research Ethics Committee approved the study (project 00/56).

2.2. Impact microindentation (IMI)

An OsteoProbe device (Active Life Technologies, Santa Barbara, CA, USA) was used to perform IMI to determine BMSi. Measurements were performed on the anterior surface of the mid-tibia, determined by measuring the midpoint from the medial border of the tibial plateau to the distal edge of the medial malleolus. The area was disinfected and local anaesthesia was applied. Following this, operator inserted the probe tip through the skin and rest it on the bone surface. Then the outer housing of the device was pressed down, initiating the measurement. The measurements were conducted according to the recommended international guidelines [32]. As we have previously described [33], participants reported minimal discomfort during the measurement.

The first measurement is often affected by insufficient penetration through the periosteum and was thus systematically removed for all participants. Following this, at least 10 indentations were performed; in two rows of five indentations. Each indentation was separated by approximately 2 mm, as the probe tip was moved between each measurement. At the time of data collection, there was no automated system for exclusion of invalid measurements. Therefore, we followed the previously reported guidelines [32], where measurements were removed if they lay outside the “green zone” area flagged by the software, or if the operator reported abnormal bone “texture” (*e.g.* a sensation of indenting a “cork-like” texture) during indentations. All indentations that were within the “green zone” area were considered valid and used to calculate a mean BMSi value for each participant. Three trained operators conducted the measurements, however, most (88.0%) were performed by one operator (PR-M). The intraoperator coefficient of variation (CV) for microindentation was 2% for repeated measures. Precision was calculated as the mean (expressed as %) of SD/mean for two sets of indentations for 10 participants.

2.3. Peripheral quantitative computed tomography measurements

Standard transverse scans were performed at 4% and 66% of radial and tibial length (Fig. 1) using a peripheral computed tomography instrument (XCT 2000, Stratec Medizintechnik, Pforzheim, Germany). BonAlyse software (BonAlyse Oy, Jyvaskyla, Finland) was then used for analysis of the scans and bone parameters were calculated (Table 1).

Each scan was assessed by at least two authors based on published protocols [34,35]. Of the 378 men, 375 completed a scan at the radius. Of these, 27 were excluded due to movement ($n = 2$) or measurement error ($n = 25$). There were 370 men who completed a tibial scan and of these, 28 were excluded due to movement (n = 2) or measurement error ($n = 26$). Thus, a total of 348 radial scans and 342 tibial scans were available for assessment for a total of 373 men.

2.4. Other data

Weight was measured to the nearest 0.1 kg using electronic scales and height to the nearest 0.1 cm using a Harpenden stadiometer. Body mass index was calculated as weight(kg) / height(m)^2. Other data for clinical risk factors were also documented by self-report. Prior low trauma fractures were reported by participants and confirmed using radiological reports where possible. Trauma level was determined and fractures resulting from high trauma were excluded. Fractures of the skull, face, fingers and toes were also excluded. Parental history of hip fracture and health behaviours were collected by questionnaire. Mobility was self-reported using a seven point scale as previously described [31] and included: very active, active, sedentary, limited, inactive, chair or bedridden and bedfast. These were then categorised into "high" mobility, including very active and active, and "low" mobility including the remaining groups. Current smoking status was categorised as current or not. Alcohol consumption was ascertained using a Food Frequency Questionnaire, developed by the Victorian Cancer Council [36] and categorised as "low" (<30 g/day) or "high" (≥30 g/day) consumption. Medication data, including anti-fracture agents (*e.g.* bisphosphonates, denosumab, anabolic agents), calcium and vitamin D supplements and glucocorticoids were self-reported. Data were collected and managed by the Research Electronic Data Capture (REDCap) tool, hosted by Barwon Health [37].

2.5. Statistical analyses

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range (IQR)), as appropriate. A Shapiro-Wilk test was used to determine if the continuous variables were normally distributed. Age, body mass index and BMSi were non-parametric, while the other variables, weight and height were normally distributed. Spearman's correlations were performed to investigate associations between BMSi and risk factors for fracture (age, weight, height, prior fracture, parental history of hip fracture, mobility, smoking, alcohol consumption and medication use (anti-fracture, calcium/vitamin D supplements and glucocorticoids)).

Spearman's correlation was used to determine unadjusted associations between pQCT-derived parameters of bone and BMSi. With BMSi as the dependent and the pQCT parameter as the independent variable, backward stepwise multivariable regression was used to investigate associations after adjustment for other variables; age, weight, height, prior fracture, parental history of hip fracture, mobility, smoking, alcohol consumption and medication use (anti-fracture, calcium/vitamin D supplements and glucocorticoids). These variables were tested in the models and excluded if $p \geq 0.05$. Models were checked for interaction terms between BMSi and other variables listed above; none were identified. Homoscedasticity of residuals was assessed using the White's and Breusch-Pagan tests, as well as a visual inspection of residual plots. All models met homoscedasticity assumptions. A p value of <0.05 was used to indicate statistical significance. Analyses were completed using Minitab (Minitab, version 18, State College, PA, USA) and STATA (Version 15.1. StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

3. Results

Participant characteristics are presented in Table 2. The median age was 63.3 years, with a range of 34 to 96 years. Many participants were in the overweight category for body mass index (25.0 to 29.9 kg/m^2). There were approximately 11% of men with a parental history of hip fracture. A similar proportion also had a prior fracture (~11%). Approximately 20% of men had low mobility. A similar number of men reported a high alcohol consumption (~20%). Few men were current smokers (~6%) or used anti-fracture medications, calcium or vitamin D supplements or glucocorticoids (<10%). The median (IQR) BMSi value was 82.6 (78.5–87.1), with a range of 49.0 to 100.2. BMSi was weakly negatively associated with age ($r = -0.151$, $p = 0.004$) and negatively with body mass index ($r = -0.156$, $p = 0.003$) (Supplementary Table 1). No other associations were observed.

3.1. Radius

Table 3 shows the results for associations between pQCT-derived

Table 1
List of bone parameters included in this study that were derived from peripheral quantitative computed tomography scans for both the radius and tibia.

Radius and tibia 4% site
Bone mass (g/cm)
Bone total area (mm^2)
Bone total density (mg/cm^3)
Bone trabecular density (mg/cm^3)
Bone trabecular area (mm^2)
Bone cortical area (mm^2)
Bone cortical density (mg/cm^3)

Radius and tibia 66% site
Bone mass (g/cm)
Bone total area (mm^2)
Bone total density (mg/cm^3)
Bone cortical area (mm^2)
Bone cortical density (mg/cm^3)
Bone cortical thickness (mm)
Polar stress strain index (mm^3)

Table 2
Descriptive statistics of the participants. Data presented as mean ± SD, median (IQR) or n (%).

	Participants (n = 373)
Age (yr, median)	63.3 (52.4–72.5)
Weight (kg, mean)	82.2 ± 11.4
Height (cm, mean)	174.6 ± 7.0
Body mass index (kg/m^2, median)	26.9 (24.8–29.1)
Parental history of hip fracture	39 (11.2)
Prior low trauma fracture	42 (11.3)
Low mobility	79 (21.2)
Smoking	24 (6.4)
High alcohol consumption (≥30 g/day)	74 (19.8)
Anti-fracture medication[a]	7 (1.9)
Calcium supplements	16 (4.3)
Vitamin D supplements	34 (9.1)
Glucocorticoids	8 (2.1)
Bone Material Strength Index (BMSi, median)	82.6 (78.5–87.1)

Missing data: physical activity $n = 1$, alcohol consumption $n = 3$.
[a] Includes bisphosphonates, denosumab and anabolic agents.

Table 3
Association between Bone Material Strength Index (BMSi) and peripheral quantitative computed tomography (pQCT)-derived bone parameters at the radius ($n = 348$).

Radius 4% site	Correlation		Adjusted*			
	r value	p value	β coefficient	R squared	p value	Variables included in the model
Bone mass (g/cm)	+0.056	0.299	2.760	0.054	0.068	Weight ($p < 0.001$), height ($p = 0.013$), glucocorticoids ($p = 0.014$)
Bone total area (mm^2)	−0.080	0.140	−0.006	0.048	0.256	Weight (p = 0.003), height ($p = 0.002$), glucocorticoids ($p = 0.017$)
Bone total density (mg/cm^3)	+0.108	0.046	0.020	0.096	0.006	Weight (p < 0.001), height (p = 0.002), glucocorticoids (p = 0.017)
Bone trabecular density (mg/cm^3)	+0.097	0.073	0.019	0.057	0.032	Weight (p < 0.001), height ($p = 0.001$), glucocorticoids ($p = 0.019$)
Bone trabecular area (mm^2)	−0.080	0.140	−0.014	0.048	0.256	Weight (p = 0.003), height (p = 0.002), glucocorticoids ($p = 0.017$)
Bone cortical area (mm^2)	−0.080	0.141	−0.113	0.048	0.515	Weight (p = 0.003), height (p = 0.002), glucocorticoids (p = 0.017)
Bone cortical density (mg/cm^3)	+0.099	0.067	4.160	0.067	0.006	Weight (p = 0 < 0.001), height (p = 0.003), glucocorticoids ($p = 0.015$)

Radius 66% site	Correlation		Adjusted*			
	r value	p value	β coefficient	R squared	p value	Variables included in the model
Bone mass (g/cm)	+0.022	0.698	4.160	0.042	0.053	Weight ($p = 0.016$), glucocorticoids ($p = 0.007$)
Bone total area (mm^2)	+0.012	0.832	0.023	0.029	0.127	Weight ($p = 0.127$), glucocorticoids ($p = 0.008$)
Bone total density (mg/cm^3)	−0.004	0.944	0.001	0.022	0.875	Weight ($p = 0.073$), glucocorticoids (p = 0.008)
Bone cortical area (mm^2)	+0.021	0.705	0.050	0.032	0.061	Weight (p = 0.017), glucocorticoids (p = 0.008)
Bone cortical density (mg/cm^3)	+0.052	0.350	0.009	0.024	0.368	Weight ($p = 0.076$), glucocorticoids (p = 0.007)
Bone cortical thickness (mm)	−0.007	0.901	0.878	0.024	0.332	Weight ($p = 0.048$), glucocorticoids ($p = 0.009$)
Polar stress strain index (mm^3)	+0.042	0.448	0.005	0.026	0.223	Weight ($p = 0.040$), glucocorticoids (p = 0.008)

* Variables tested in the models included: age, weight, height, parental history of hip fracture, prior fracture, mobility, smoking, alcohol consumption and medication use (anti-fracture, calcium/vitamin D supplements and glucocorticoids). These were retained if $p < 0.05$.

parameters of bone and BMSi at the radial 4% and 66% sites. For the 4% site, in unadjusted analyses, higher total density was associated with greater BMSi. This association was sustained following adjustments for other variables: age, weight, height and glucocorticoid use. In analyses adjusted for weight, height and glucocorticoid use, an association was also observed for both cortical and trabecular density. For the 66% site, an association between bone mass and BMSi was observed in analyses adjusted for weight, height and glucocorticoid use. No other associations were observed between pQCT-derived bone measures and BMSi at the 66% radial site.

3.2. Tibia

Table 4 shows the results for the tibia at the 4% and 66% sites. Scatterplots showing associations between pQCT parameters and BMSi are shown in Supplementary Figs. 1 and 2. At the 4% site, higher total density and cortical density were associated with greater BMSi in unadjusted analyses and after adjustment for weight, height and glucocorticoid use.

At the 66% site, higher bone mass, total area and polar strain index was associated with greater BMSi in analyses adjusted for age, weight,

Table 4
Association between Bone Material Strength Index (BMSi) and peripheral quantitative computed tomography (pQCT)-derived bone parameters at the tibia ($n = 342$).

Tibia 4% site	Correlation		Adjusted*			
	r value	p value	β coefficient	R squared	p value	Variables included in the model
Bone mass (g/cm)	+0.016	0.770	−0.077	0.014	0.894	Height ($p = 0.201$), glucocorticoids ($p = 0.0018$)
Bone total area (mm^2)	−0.105	0.053	−0.005	0.054	0.061	Weight (p = 0.014), height ($p = 0.005$), parental hip fracture ($p = 0.028$), glucocorticoids (p = 0.015)
Bone total density (mg/cm^3)	+0.115	0.035	0.020	0.033	0.027	Weight ($p = 0.034$), glucocorticoids (p = 0.016)
Bone trabecular density (mg/cm^3)	+0.074	0.173	0.012	0.024	0.192	Weight ($p = 0.049$), glucocorticoids (p = 0.014)
Bone trabecular area (mm^2)	−0.106	0.052	−0.005	0.035	0.277	Weight ($p = 0.126$), parental hip fracture ($p = 0.026$), glucocorticoids (p = 0.008)
Bone cortical area (mm^2)	−0.105	0.053	−0.005	0.035	0.277	Weight (p = 0.126), parental hip fracture (p = 0.026), glucocorticoids (p = 0.008)
Bone cortical density (mg/cm^3)	+0.123	0.023	0.038	0.147	0.010	Weight ($p = 0.029$), glucocorticoids ($p = 0.018$)

Tibia 66% site	Correlation		Adjusted*			
	r value	p value	β coefficient	R squared	p value	Variables included in the model
Bone mass (g/cm)	+0.062	0.259	1.458	0.058	0.027	Age (p = 0.004), weight ($p = 0.004$), glucocorticoids ($p = 0.024$)
Bone total area (mm^2)	+0.035	0.522	0.010	0.062	0.012	Age (p < 0.001), weight (p = 0.003), glucocorticoids (p = 0.028)
Bone total density (mg/cm^3)	+0.007	0.906	−0.005	0.058	0.315	Age (p = 0.002), weight ($p = 0.036$), glucocorticoids ($p = 0.055$), vitamin D supplements ($p = 0.034$)
Bone cortical area (mm^2)	+0.051	0.353	0.014	0.053	0.074	Age (p = 0.006), weight (p = 0.007), glucocorticoids (p = 0.026)
Bone cortical density (mg/cm^3)	+0.079	0.150	0.016	0.026	0.139	Weight ($p = 0.080$), glucocorticoids (p = 0.013)
Bone cortical thickness (mm)	+0.027	0.626	0.082	0.044	0.882	Age (p = 0.004), weight (p = 0.034), glucocorticoids (p = 0.028)
Polar stress strain index (mm^3)	+0.094	0.087	0.002	0.064	0.009	Age (p = 0.001), weight (p = 0.004), glucocorticoids (p = 0.027)

* Variables tested in the models included: age, weight, height, parental history of hip fracture, prior fracture, mobility, smoking, alcohol consumption and medication use (anti-fracture, calcium/vitamin D supplements and glucocorticoids). These were retained if $p < 0.05$.

and glucocorticoid use. No other associations were observed.

In summary, pQCT-derived parameters explained approximately 1–15% (1.4–14.7) and 2–6% (2.2–6.4) of the variation in BMSi at the 4% and 66% tibial sites respectively (Tables 3 and 4).

4. Discussion

In this study, weak associations were detected between some pQCT-derived bone parameters and BMSi. Higher total density and cortical density were associated with a greater BMSi at the 4% site for both the radius and the tibia. Associations were also detected for the 66% tibial site, showing a higher bone mass, bone total area and polar stress strain index were associated with greater BMSi. At the 66% radial site, only bone mass was associated with BMSi.

The BMSi value has been reported to be associated with subperiosteal bone properties [27], and the measurement is performed on the surface of the bone, therefore it seems reasonable that BMSi would be more strongly correlated with cortical rather than trabecular bone properties. In addition, IMI does not quantify the amount of bone present, thus it is not unexpected that BMSi was not consistently correlated with bone area. However, it is unclear why associations were observed with cortical bone parameters at the 4% sites, but not the 66% sites, particularly as the IMI measurement is performed near the 66% tibial site. However, associations were observed between bone mass, total bone area and polar stress strain index at the 66% tibial site. It is not clear why an association with polar stress strain index, a surrogate measure of bone strength, was observed at the tibia but not the radius. However, it may be related to the location of measurement, as IMI and pQCT are both performed on the tibia. It is also possible that an association was observed for the tibia as it is a weightbearing bone, whereas the radius is not.

It is possible that the observed associations could be a result of similar bone properties across multiple sites across the body, rather than due to similarities between the variables derived from IMI and pQCT. A person with poor bone properties may have lower values for both BMSi and pQCT-derived parameters, leading to the detection of a correlation between the two. A study by Davis et al. [38] performed bone densitometry measurements in women (age range 47–82 years) at four sites: spine, calcaneus, distal radius and proximal radius and reported that approximately half (56%) of the women had low bone mass for at least one site, and often at more than one site. However, there was a subgroup of women (~15%) with heterogeneity across the skeletal sites examined, indicating that low bone mass could occur at regional locations, or across the skeleton as a whole. Nordin et al. [39] also reported that primary postmenopausal osteoporosis appeared to affect the skeleton as a whole, rather than only at specific sites. Heterogeneity between trabecular density at the radius and tibia measured using pQCT has also been reported, whereas cortical parameters are more homogeneous across different skeletal sites [40–42]. Using pQCT measured at nine skeletal sites (femur, proximal and distal tibia, third metatarsal, humerus, ulna, radius, third metacarpal, and vertebrae), Chirchir et al. [43] also showed that there were no correlations between the skeletal sites for trabecular density, indicating bone heterogeneity across the skeleton. However, Turner et al. [44] have shown using acoustic microscopy and Berkovich's nanoindentation that mechanical properties of trabecular and cortical bone are similar, and thus although bone architecture is heterogeneous, tissue properties are likely to be more homogeneous.

The associations observed in this study are consistent for total and cortical density at both the radial and tibial 4% sites. The observed associations are also independent of other risk factors for fracture such as age, weight, height and prior fracture, and are consistent with other studies that suggest cortical and/or surface parameters of bone are being assessed using IMI.

Although we report only weak associations, these small but important differences might be relevant in populations where current methods do not accurately distinguish individuals who will or will not sustain a fracture. The results also suggest that BMSi and pQCT-derived parameters provide complementary information and may both be useful for improving fracture risk predictions. Two previous studies have reported correlations between HR-pQCT derived bone parameters and BMSi, though investigation of correlations was not the primary aim. One included 35 postmenopausal women, 16 of whom had T2DM and the remaining 19 were controls [24]. The study reported no association between HR-pQCT parameters and BMSi, however a small sample size as well as the combination of participants selected on the basis of a disease and healthy samples may be the reason for this null finding. The other study included a larger sample of older women ($n = 202$, mean age 78.2 $\pm$ 1.1 years) from Sweden [26]. The authors reported that BMSi was correlated with cortical porosity and cortical volumetric BMD at the distal tibia. This correlation was sustained after adjustment for a range of covariates including age, height, weight, oral glucocorticoid use, bisphosphonate use, calcium intake, walking speed, smoking status and OsteoProbe operator. While pQCT and HR-pQCT do not provide the same level of information about bone parameters due to differences in resolution, this previous study does indicate that BMSi is more closely associated with cortical rather than trabecular properties of bone, similar to what we have reported in the current study.

We have previously reported that BMSi is associated with some risk factors for fracture and in particular, prior fracture status [45]. We, along with others, have also reported that BMSi is lower in individuals at high risk of fracture such as T2DM [23,24,46–49], glucocorticoid users [50], chronic kidney disease [51] and human immunodeficiency virus [52]. Additional studies have also reported that BMSi is lower in individuals who have sustained a fracture [16,22,25,53]. Overall, these previous studies indicate that BMSi may detect important bone parameters that have an impact on fracture risk.

This study has some strengths and limitations. A strength is that participants were randomly selected from the population, not on the basis of disease status. This was a study of men, which has not been reported in the literature previously, however, future studies with sufficient sample sizes are necessary to investigate these associations in women. The IMI and pQCT measurements were not conducted at the same skeletal sites, although the 66% site for pQCT is similar to the region where measurements were conducted for IMI. Although the age and body mass index ranges for participants in this study were wide (34–96 years and 18.6–39.8 kg/m^2, respectively), there were some participants who were unable to complete the IMI measurement due to excessive soft tissue around the mid-tibia region. Thus, we were unable to explore associations for the full range of weight and body mass index represented within the sample of participants in this study. There were also several participants excluded from pQCT analyses due to inability to assume the correct position as well as inability to remain still for the duration of the scan (~3 min), resulting in excessive movement in the images. We did not adjust for multiple comparisons; however, associations with measures of bone density were consistently observed at both the radius and tibia, indicating that these are unlikely to be the result of chance. Future work could investigate combining BMSi with indicators of bone geometry to determine how this would influence the associations observed.

5. Conclusion

There were weak associations detected between pQCT-derived cortical bone parameters at both the radius and tibia and BMSi. Additional work is required to explore associations between pQCT-derived parameters of bone and BMSi in women.

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CRediT authorship contribution statement

Kara L. Holloway-Kew: Conceptualisation, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft. **Pamela Rufus-Membere:** Data curation, Investigation, Methodology, Writing – review & editing. **Kara B. Anderson:** Data curation, Investigation, Methodology, Writing – review & editing. **Monica C. Tembo:** Data curation, Methodology, Writing – review & editing. **Sophia X. Sui:** Data curation, Methodology, Writing – review & editing. **Natalie K. Hyde:** Data curation, Methodology, Supervision, Writing – review & editing. **Adolfo Diez-Perez:** Methodology, Supervision, Writing – review & editing. **Mark A. Kotowicz:** Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. **Julie A. Pasco:** Conceptualisation, Data curation, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

AD-P owns shares of Active Life Scientific, Inc., the manufacturer of the reference point indentation device.

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