



Full Length Article

Influence of soft tissue on bone density and microarchitecture measurements by high-resolution peripheral quantitative computed tomography



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ABSTRACT

High-resolution peripheral quantitative computed tomography (HR-pQCT) is a non-invasive method of measuring volumetric bone mineral density (vBMD) and microarchitecture at the distal radius and tibia. With increasing use of this technology, it is crucial to understand the potential impact of overlying soft tissue on the accuracy of HR-pQCT measures. Thus, we examined the effects of a simulated increase in adiposity (via 6- and 12-mm thick layers of overlying circumferential fat) on HR-pQCT measures of a hydroxyapatite (HA) phantom and in women ($n = 20$, aged 18–75 years). In the phantom, increasing the amount of overlying fat tissue led to a corresponding decrease in the mean measured density for each HA rod. In women, fat-layering led to a decrease in total vBMD (-2.9 to -3.7% , $p < 0.001$), cortical vBMD (-1.4% to -5.5% , $p < 0.001$), and estimated failure load (-1.4 to -5.7% , $p = 0.002$) at the radius, with similar changes in the tibia. Trabecular microarchitectural measurements were also impacted by simulated adiposity, with fat-layering leading to decreased trabecular thickness and separation and increased trabecular number at the radius (Δ 's = 5 to 12%) with more pronounced differences at the tibia (Δ 's = 14 to 40%). At the tibia, fat-layering also led to decreased cortical thickness and increased cortical porosity. Altogether, these results demonstrate that overlying adipose tissue can lead to artifacts in bone measurements by HR-pQCT, resulting in an underestimation of vBMD and generally, an overestimation of bone microarchitecture impairment. Therefore, soft tissue artifact should be considered when interpreting HR-pQCT results, particularly in those with high BMI and/or marked changes in adiposity.

1. Introduction

As the prevalence of obesity continues to rise, weight-related comorbidities such as diabetes, cardiovascular disease, and most recently bone fractures, are becoming a focus of medical care. Skeletal health in overweight individuals is of particular interest as high body mass index (BMI) was generally thought to protect against fractures. However, recent studies suggest this is not wholly accurate. Whereas a higher BMI is protective against osteoporotic fractures at the hip, forearm, and vertebrae, it is associated with an increased risk of extremity fractures, particularly at the humerus, elbow, ankle, and tibia [1–4], despite

higher dual-energy X-ray absorptiometry areal bone mineral density (DXA-aBMD) [1–5]. In addition, individuals with type 2 diabetes have a greater risk of fracture compared to non-diabetics despite normal to high aBMD and increased body weight [6,7], characteristics that are typically protective of fractures. These examples of aBMD-fracture discordance suggest that increased fracture risk in obese patients is due to factors other than aBMD, such as impaired bone microarchitecture or deficits in bone material properties [5,8–10]. Further complicating this issue, the accuracy of aBMD measurements in patients with high adiposity has been called into question [5,9,10].

DXA remains the most common method of diagnosing osteoporosis,

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¹ Body mass index (BMI), dual-energy X-ray absorptiometry areal bone mineral density (DXA-aBMD), computed tomography (CT), volumetric BMD (vBMD), high resolution peripheral quantitative CT (HR-pQCT), poly-methyl methacrylate (PMMA), total vBMD (Tot.vBMD), trabecular vBMD (Tb.vBMD), trabecular number (Tb.N), trabecular separation (Tb.Sp), and trabecular thickness (Tb.Th), total cross-sectional area (Tot.Ar), cortical area (Ct.Ar), cortical vBMD (Ct.vBMD), cortical tissue mineral density (Ct.TMD), cortical thickness (Ct.Th), cortical porosity (Ct.Po), failure load (N), micro-finite-element analysis (μ FEA), coefficient of variation (CV%).

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but DXA-aBMD measurements are known to be susceptible to accuracy errors in obese patients due to variations in surrounding soft tissue composition. For example, DXA-aBMD values of an anthropomorphic phantom increase after a simulated increase in adiposity by layering bags of vegetable shortening [11]. In studies on cadaveric animal bones, artificial increases in extraosseous fat led to both an underestimate and overestimate of DXA-aBMD [12]. Conversely, fat-layering over the lumbar spine in humans resulted in lower DXA-aBMD, whereas measurements of femoral neck and total hip aBMD were poorly reproducible but systematically unchanged [11].

Computed tomography (CT) images are theoretically less susceptible to soft-tissue imaging artifacts than DXA, yet studies have reported errors in CT-based bone density measurements due to adiposity. One study found that fat-layering did not influence phantom volumetric BMD (vBMD) measures, but resulted in an increased vBMD measurement at the spine in humans [11].

High resolution peripheral quantitative CT (HR-pQCT) is a 3D non-invasive, high resolution, X-ray based imaging modality that measures compartment specific vBMD and bone microarchitecture at the distal radius and tibia with minimal ionizing radiation exposure [13]. Given the high risk of fractures at peripheral sites among individuals with high BMI [1,3], assessment of vBMD and bone microarchitecture via this method may be of particular interest in this population. Yet, the effects of overlying soft tissue on HR-pQCT measurements have not been well characterized. Thus, the goal of the current investigation is to examine effects of simulated adipose tissue on vBMD and bone microarchitecture parameters as assessed by HR-pQCT, using both a phantom and healthy female volunteers. We also sought to assess whether or not the degree of soft tissue-induced artifacts varied according to aBMD.

2. Materials and methods

2.1. Anthropomorphic phantom

We used the QC1 Phantom (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) to conduct the anthropomorphic phantom trials. This phantom contains four hydroxyapatite rods, with densities of 100 mg-HA/ccm, 200 mg-HA/ccm, 400 mg-HA/ccm, and 800 mg-HA/ccm, embedded in poly-methyl methacrylate (PMMA) plastic. Adipose tissue was simulated by filling 12 × 18 cm rectangular plastic bags with vegetable shortening (0.8 g/mL) to a mean thickness of 6 mm or 12 mm to correspond to a thin or thick layer of fat, respectively, and placing either 6 mm or 12 mm bags in a single circumferential layer around the phantom (Fig. 1A). HR-pQCT scans were repeated three times in each condition (e.g., no fat-layering (baseline), thin layer and thick layer) and mean density measurements were calculated for each HA rod.

2.2. Human volunteers

We enrolled 20 women, aged 18–75, who had participated in prior Partners approved research studies, had received a posterior-anterior (PA) spine, femoral neck (FN), and total hip (TH) DXA (QDR45000A; Hologic Inc., Bedford, MA, USA) aBMD (g/cm²) assessment within the past 24 months and given consent to be contacted for future research studies. Women were recruited based on hip bone density T-scores into 2 groups: normal aBMD ($T > -1.0$ in the femoral neck or total hip) or low aBMD ($T \leq -1.0$ in the femoral neck or total hip) ($n = 10$ per group). All subjects self-identified as White/Caucasian, had a BMI of < 26.0 kg/m², and no self-reported history of bilateral radius/wrist or tibia/ankle fractures, as all of these factors can influence measurements of bone density and microarchitecture. Participants who were not postmenopausal completed a urine pregnancy test prior to undergoing HR-pQCT scans. This study was approved by the Partners Human Research Committee and all subjects provided written informed consent.

2.3. HR-pQCT scan protocol

We assessed cortical and trabecular vBMD and microarchitecture at the non-dominant distal radius and tibia by HR-pQCT (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) at baseline (e.g., no fat-layering), with 6 mm (thin), and with 12 mm (thick) layers of fat. Adipose tissue was simulated by placing either 6 mm or 12 mm bags in a single circumferential layer around each scan site (Fig. 1B and C). Scans were acquired with an isotropic voxel size of 82 μm³ with a standard scan region of 110 computed tomography slices (9.02 mm) located 9.5 mm and 22.5 mm proximal to the distal radius and tibia endplates, respectively. The QC1 Phantom was scanned daily as per the manufacturer's protocol to ensure quality control. All scans were inspected for motion artifact by one operator and repeated if significant motion artifact was noted. We graded each scan on a 5-point scale, with 1 = no motion artifact and 5 = severe motion artifact [14]. We included all scans with grades 1–3 in our analysis and excluded four scans that had a motion artifact score > 3 (three radius scans: 1 at baseline, 1 at the 6 mm fat-layer, 1 at the 12 mm fat-layer; and one tibia scan at the 12 mm fat-layer). We used the manufacturer's two-dimensional region-matching software to determine the shared volume of interest (VOI) between paired scans before and after fat-layering [15,16]. We achieved a minimum of 88% matching between paired HR-pQCT scans from pre- and post-fat-layered scans.

We used Scanco analysis software version 5.11 to assess total and trabecular vBMD (Tot.vBMD, Tb.vBMD, mgHA/cm³), trabecular number (Tb.N, 1/mm), trabecular separation (Tb.Sp, mm), and trabecular thickness (Tb.Th, mm). We performed extended cortical analysis using a semi-automated technique to determine total cross-sectional and cortical area (Tot.Ar, Ct.Ar, mm²), cortical vBMD (Ct.vBMD, mgHA/cm³), cortical tissue mineral density (Ct.TMD, mgHA/cm³), cortical thickness (Ct.Th, mm), and cortical porosity (Ct.Po, %) [16,17]. We calculated estimated failure load (N) at the radius and tibia under axial compression using micro-finite-element analysis (μFEA), as previously described [18,19].

2.4. Statistical analysis

For scans involving the anthropomorphic phantom, we report mean percent change in density measurements with each fat-layer compared to baseline. The precision of the density measurements for each fat-layering condition was determined by calculating the coefficient of variation (CV%) for three repeated scans. For the human studies, we performed paired, repeated-measures analyses to determine median percent change in vBMD, microarchitecture, and estimated failure load with each fat-layering condition compared to baseline. We included data from all available paired radius and tibia scans ($n = 18$ pairs for baseline-6 mm and baseline-12 mm comparisons at the radius, and $n = 20$ pairs for baseline-6 mm, $n = 19$ pairs for baseline-12 mm comparisons at the tibia). We used Wilcoxon Signed Ranks tests to evaluate differences before and after fat-layering. We performed two-tailed independent *t*-tests to determine whether differences in HR-pQCT parameters due to fat-layering differed for subjects with normal and low hip aBMD. For all tests, differences with a *p*-value < 0.05 are reported as statistically significant. We used R version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 1.1.414 (RStudio, Inc., Boston, MA) for all statistical analyses.

3. Results

3.1. Fat-layering and anthropomorphic phantom

The mean measured density decreased for each hydroxyapatite (HA) rod with increasing fat-layers (Fig. 2A). The effect of increasing soft tissue on density measurements was most pronounced for the 800 mg HA/ccm rod, where the density decreased by 2.6% and 6.3%

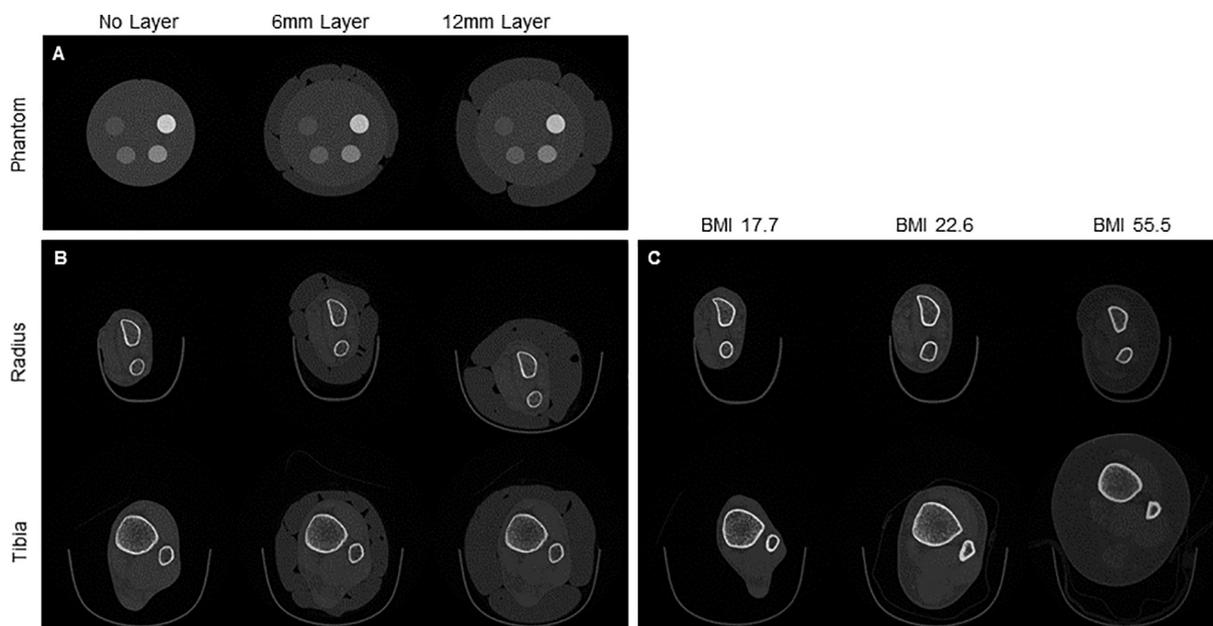


Fig. 1. Representative HR-pQCT images of fat-layered phantom and adult volunteers, and patients with increasing BMI. (A) Cross-section of hydroxyapatite calibration phantom without fat-layering, and wrapped with a 6 mm or 12 mm fat-layer. (B) Most proximal cross-sectional slice of distal radius and tibia scans of adult volunteers, with and without fat-layering. (C) Most proximal cross-sectional slice of distal radius and tibia scans of patients with increasing BMI.

with 6 mm and 12 mm fat-layers, respectively. Successive fat-layering increased the mean standard deviation of each HA rod density by approximately 20% in the 6 mm layer and 40% in the 12 mm layer of fat (Fig. 2B), but fat-layering did not have a large effect on the precision of the repeat measurements; the coefficient of variation for three repeated phantom density scans ranged between 0.07 and 0.37% without fat-layering, and between 0.10 and 0.36% and 0.16–0.52% with the 6 mm and 12 mm thick fat-layers, respectively.

3.2. Fat-layering and human volunteers

Women in the low vs. normal hip aBMD group were similar in age, height, weight and BMI. As expected, compared to women with normal hip aBMD, women in the low aBMD group had lower aBMD at the PA spine, total hip, and femoral neck as measured by their most recent DXA scan (Table 1). Women with low aBMD also had similar total bone area at both the radius and tibia compared to those with normal aBMD.

Sequential fat-layering caused a significant decrease in Tot.vBMD, Ct.vBMD and Ct.TMD at both the radius and tibia (Fig. 3A and C), with greater differences with increasing fat thickness (Fig. 3A and C). Tb.vBMD was minimally impacted by the fat-layering. In particular,

whereas the 6 mm fat-layer caused a slight decline (−1.3%; $p = 0.02$) in Tb.vBMD at the radius, there was no effect of the 12 mm layer on Tb.vBMD at the radius, or with either fat-layer thickness at the tibia. Failure load decreased with sequential fat-layering compared to baseline with the greatest changes seen with the 12 mm layer (−5.7% for the radius, −8% for the tibia; $p < 0.005$ for both).

Sequential fat-layering also influenced measurements of trabecular bone microarchitecture at the radius and tibia. In particular, at both the radius and tibia, Tb.Th and Tb.Sp decreased with sequential fat-layering compared to baseline, while Tb.N increased (Fig. 3B, D), though the changes in Tb.Sp (−10.7%; $p = 0.004$) and Tb.N (12.0%; $p = 0.003$) at the radius only reached statistical significance with the 12 mm fat-layer thickness. There were no statistically significant differences in cortical parameters with the 6 mm fat-layer at the radius. However, the 12 mm fat-layer caused a decline (−2.9%, $p = 0.009$) in Ct.Th and an increase (16.3%, $p = 0.005$) in Ct.Po at the radius, but had no effect on Ct.Ar ($p = 0.5$). Sequential fat-layering successively also led to decreased Ct.Th (6mm: −1.9%; $p < 0.001$, 12mm: −4.0%; $p < 0.001$) and successively increased Ct.Po measurements (6mm: 6.5%; $p < 0.001$, 12mm: 16.7%; $p < 0.001$) at the tibia.

The effect of fat-layering on HR-pQCT parameters was largely

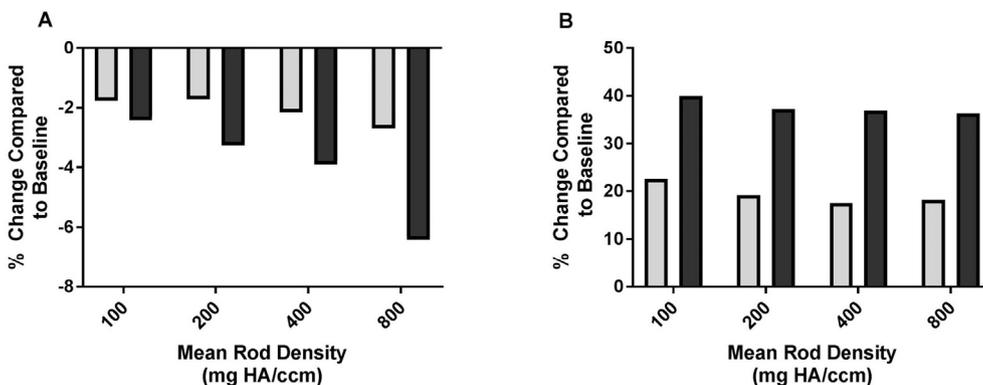


Fig. 2. Percent change in mean hydroxyapatite rod density (A) and mean standard deviation of hydroxyapatite rod density (B) with a 6 mm (light gray bars) or a 12 mm (dark gray bars) layer of fat. Data given as mean percent change compared to baseline for three repeated measures.

Table 1
Descriptive characteristics of adult volunteers. Values given as mean ± SD.

	Low hip aBMD (n = 10)	Normal hip aBMD (n = 10)	p
Age (years)	62.6 ± 9.0	50.4 ± 20.8	0.1
Height (cm)	160.1 ± 5.3	165.7 ± 8.2	0.09
Weight (kg)	55 ± 7.6	62.6 ± 8.5	0.05
BMI (kg/m ²)	21.4 ± 2.4	22.7 ± 1.5	0.2
PA spine aBMD (g/cm ²)	0.785 ± 0.063	1.028 ± 0.102	< 0.001
PA spine T-score	-2.3 ± 0.6	-0.1 ± 0.9	< 0.001
Total Hip aBMD (g/cm ²)	0.668 ± 0.047	0.953 ± 0.062	< 0.001
Total Hip T-score	-2.2 ± 0.4	0.1 ± 0.5	< 0.001
Femoral neck aBMD (g/cm ²)	0.546 ± 0.029	0.834 ± 0.052	< 0.001
Femoral neck T-score	-2.7 ± 0.3	-0.2 ± 0.5	< 0.001
Radius total area (mm ²)	232 ± 40	257.1 ± 64.3	0.3
Tibia total area (mm ²)	628.3 ± 70	641.9 ± 107.9	0.7

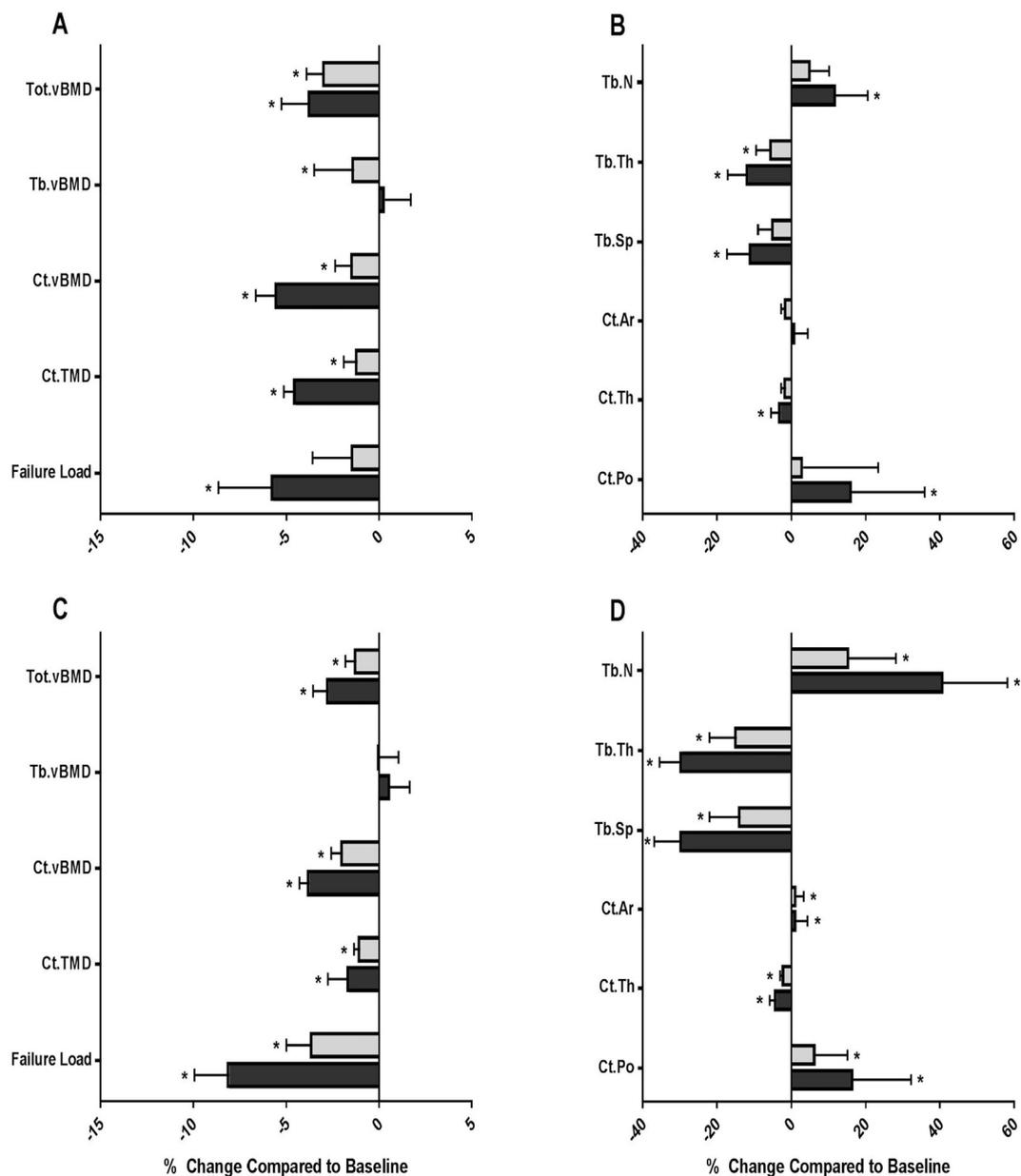


Fig. 3. Median (IQR) percent change in vBMD and failure load at the distal radius (A) and distal tibia (C) and in bone microarchitecture at the distal radius (B) and distal tibia (D) with a 6 mm (light gray bars) or 12 mm (dark gray bars) layer of fat. *Indicates p < 0.05 for percent change compared to baseline.

independent of subjects' hip aBMD, although we found that the effects of fat-layers (the 12 mm layer in particular) on Ct.BMD (at the radius and tibia), Tt.vBMD (at the tibia only), and Ct.Po (at the radius only) were greater in normal aBMD than low aBMD subjects ($p < 0.05$), although the direction of fat-layer artifact was the same in both groups. In particular, with a 12 mm fat-layer radius Ct.BMD decreased by $-4.4 \pm 3.0\%$ versus $-6.5 \pm 1.9\%$ in the low versus normal aBMD group ($p < 0.05$). Similarly, tibia Ct.BMD declined more in the normal hip aBMD ($-4.3 \pm 1.0\%$) compared to the low hip aBMD group ($-3.2 \pm 1.0\%$, $p < 0.005$). The decline in Tot.BMD at the tibia was also greater in the normal versus low hip aBMD group ($-3.2 \pm 0.9\%$ vs. $-1.8 \pm 1.3\%$, $p < 0.01$); as was the increase in radius Ct.Po which increased significantly in the normal aBMD group with fat-layering ($31.4 \pm 36.4\%$, $p = 0.006$), but was unchanged in the low aBMD group.

4. Discussion

The present investigation examined the influence of increasing adipose tissue on vBMD and bone microarchitecture measurements as assessed by HR-pQCT by fat-layering of a hydroxyapatite phantom and of women with low or normal hip aBMD. We found that incremental fat-layering led to stepwise declines in HR-pQCT measurements of total and cortical density, as well as altered bone microarchitecture measurements. Wrapping the phantom with thin and thick layers of fat (6 mm and 12 mm, respectively) resulted in a stepwise decrease in the mean density of each hydroxyapatite rod, indicating a reduced accuracy of HR-pQCT measurements with increased adiposity. The precision of the phantom measurements was unaffected, suggesting a consistently reliable under-ascertainment of vBMD with increased layers of soft tissue. Our findings in the phantom align with others that found a decrease in cortical and trabecular vBMD by HR-pQCT with increased fat-layering in an idealized tibia phantom [20], but contrast with findings in DXA, where increased fat-layering led to increased aBMD in a spine phantom [11].

In humans, fat-layering introduced artifact in vBMD and microarchitecture parameters at both the distal radius and tibia. Increased layers of fat generally led to an underestimation of total and cortical vBMD, cortical tissue mineral density, failure load, cortical and trabecular thickness, and trabecular separation; and an overestimation of trabecular number, cortical porosity, and cortical area, though trabecular vBMD and total area were relatively unaffected. Altogether, these findings suggest that HR-pQCT measurements of bone density and strength may be artificially low in obese patients and/or may artificially decline in subjects who gain adipose tissue from baseline to follow-up measurements. Our results are consistent with a previous study that showed a decrease in spine aBMD by DXA with increased fat-layering [11], but contrast with reported increases in vertebral trabecular vBMD by QCT following fat-layering [11]. Notably, subjects with normal hip aBMD tended to exhibit greater changes in HR-pQCT measured density and microarchitecture values with increased fat-layering compared to subjects with low aBMD.

Our results have important implications for the interpretation of HR-pQCT outcomes when studying skeletal health in obese individuals and/or in patients undergoing significant changes in body composition. In particular, the observed accuracy errors in HR-pQCT measures with increasing adipose tissue thickness will make bones appear weaker than they are in reality: vBMD and failure load are underestimated, while cortical and trabecular microarchitecture is generally less favorable. Thus, cross-sectional studies showing better vBMD, microarchitecture and μ FEA-estimated strength at the tibia and/or radius of individuals with obesity as compared to normal-weight controls may be underestimating the positive impact of obesity on these parameters [5,9,10,21,22]. Notably, patients with type 2 diabetes, who generally have higher body mass and increased adiposity compared to non-diabetic controls, are reported to have normal to high trabecular density,

but often a slight increase in cortical porosity [23–26]. Although results in studies comparing type 2 diabetics to non-diabetic controls use statistical adjustments to account for differences in BMI, the current study indicates that some of the observed increase in cortical porosity may be due to imaging artifact. Conversely, in very low-weight individuals, such as those with anorexia nervosa, HR-pQCT measurements may be underestimating deficits in skeletal health compared to normal weight individuals [27–29]. Further, individuals undergoing rapid weight loss and a concurrent decrease in adipose tissue may show an artificial improvement in HR-pQCT-derived vBMD, bone microarchitecture and failure load compared to baseline. Notably, these results suggest that HR-pQCT may be underestimating deficits in the appendicular skeleton that have been documented to occur after bariatric surgery [20,30–33]. Moreover, changes in lean mass, possibly due to aging or exercise, may also influence HR-pQCT measures in a similar fashion and should be considered in interpreting study results.

To our knowledge, this is the first study to examine the effect of a sequential, simulated increase in adipose tissue on HR-pQCT measurements in human volunteers. Previous studies were exclusively performed in cadaver bones or on anthropomorphic phantoms [11,12,20]. An important strength of this study is that the vegetable fat used in fat-layering has a similar density to human adipose tissue, and was applied at thicknesses that are typical of the levels of soft tissue seen in patients with a high BMI (Fig. 1). Limitations to this study include the small number of human volunteers that were scanned. It is possible that enrolling additional subjects with high quality HR-pQCT scans would have resulted in sequential and statistically significant differences in failure load and bone microarchitecture parameters at the radius, since a larger number of radius scans were excluded from analyses due to movement artifact. To limit radiation exposure in enrolled subjects and due to the potential of motion artifact between scans, we did not test the precision of HR-pQCT measurements with fat-layering in human volunteers. However, repeated measures of the QC1 anthropomorphic phantom across a range of hydroxyapatite densities suggested that, while adipose tissue impairs accuracy, it has a minimal effect on scan precision. Further studies are necessary to determine how changes in lean mass or subcutaneous edema may affect the accuracy and precision of HR-pQCT measurements.

5. Conclusion

In summary, our results indicate that increased adipose tissue reduces the accuracy of in vivo bone measurements by HR-pQCT, resulting in an underestimation of vBMD and an overestimation of bone microarchitecture impairment. Baseline BMD modulates these effects, disproportionately reducing the accuracy of measurements in patients with normal versus low hip aBMD. These findings suggest that clinical studies using HR-pQCT to examine bone health in individuals with obesity or in patients undergoing significant changes in body composition need to consider soft tissue artifact when interpreting results.

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Conflicts of interest

The authors have no conflicts of interest to disclose. The results of this study do not constitute endorsement by Bone.

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