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# Bone Density, Microstructure and Strength in Obese and Normal Weight Men and Women in Younger and Older Adulthood

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**Abstract**

Obesity is associated with greater areal BMD (aBMD) and considered protective against hip and vertebral fracture. Despite this, there is a higher prevalence of lower leg and proximal humerus fracture in obesity. We aimed to determine if there are site-specific differences in BMD, bone structure or strength between obese and normal weight adults. We studied 100 individually-matched pairs of normal (BMI 18.5-24.9 $kg/m^2$) and obese (BMI>30 $kg/m^2$) men and women, aged 25-40 or 55-75 years. We assessed aBMD at the whole body (WB), hip (TH) and lumbar spine (LS) with DXA, LS Tb.vBMD by QCT and vBMD, and microarchitecture and strength at the distal radius and tibia with HR-pQCT and micro-finite element analysis. Serum PINP and βCTX were measured by automated ECLIA. Obese adults had greater WB, LS and TH aBMD than normal adults. The effect of obesity on LS and WB aBMD was greater in older than younger adults ($p<0.01$). Obese adults had greater vBMD than normal adults at the tibia ($p<0.001$ both ages) and radius ($p<0.001$ older group), thicker cortices, higher cortical BMD and tissue mineral density, lower cortical porosity, higher trabecular BMD and greater trabecular number than normal adults. There was no difference in bone size between obese and normal adults. Obese adults had greater estimated failure load at the radius ($p<0.05$) and tibia ($p<0.01$). Differences in HR-pQCT measurements between obese and normal adults were seen more consistently in the older than the younger group. Bone turnover markers were lower in obese than normal adults. Greater BMD in obesity is not an artefact of DXA measurement. Obese adults have higher BMD, thicker and denser cortices and higher trabecular number than normal adults. Greater differences between obese and normal adults in the older group suggest obesity may protect against age-related bone loss, and also increase peak bone mass.

**Key words:** OBESITY, BONE MINERAL DENSITY, MICROARCHITECTURE, HR-pQCT, BONE TURNOVER

## Introduction

Most of the available evidence supports a lower overall risk of fracture and lower risk of proximal femur and vertebral fracture in obese adults, compared to adults with a normal body mass index (BMI) [1-8]. However, fracture risk in obesity is not lower at all skeletal sites; the risk of some non-spine fractures including proximal humerus, upper leg and ankle fracture is higher than in non-obese adults [3, 4, 7, 9]. Protection against fracture in obesity may be partly explained by the positive association between BMI and BMD [8, 10-12], while differences in fall characteristics and soft tissue padding at the hip have also been proposed as mechanisms to explain differences in fracture risk between normal BMI and obese adults [7, 8, 13]. The greater risk of lower limb fractures with obesity could result from differences in bone microarchitecture, bone quality or factors unrelated to bone strength such as greater impact during a fall.

The association of high BMD with obesity may be an artifact of the method used for measuring BMD. Dual energy X-ray absorptiometry (DXA) is affected by soft tissue overlying bone. Soft tissue thickness may cause a projection error affecting measurements of bone area and thus BMC [14-16]. The assumptions made about fat and lean tissue in a two-compartment model may be inaccurate in obesity, introducing further error. BMD by DXA may not be the best choice when comparing groups of different body weight. However, most previous studies have assessed areal BMD in obesity by DXA.

Quantitative computed tomography (QCT) allows the study of cortical bone and trabecular bone separately. Such technology allows us to understand whether higher bone density in obesity is a result of alterations in cortical bone and/or trabecular bone. Measurements of

bone density by QCT are less affected by overlying soft tissue than measurements by DXA [14].

Bone density is not the sole determinant of bone strength. Additional factors include bone geometry and bone microarchitecture. High resolution peripheral quantitative computed tomography (HR-pQCT) allows study of architectural properties of bone such as cortical thickness and trabecular number, and these measurements are less likely to suffer artefact due to variation in body composition. The composite effects of bone size, geometry, density and microarchitecture on bone strength can be evaluated by finite element models generated from HR-pQCT images. Few studies have investigated associations between obesity and measures of vBMD. Whether adiposity affects BMD and bone microstructure in men and women in younger and older adulthood in a consistent manner is unclear.

So far only one study has been designed to look at bone microarchitecture in obese individuals and that was restricted to older women [12]. It is not known whether associations between obesity and bone microarchitecture were the same in men and women, or whether differences between obese and normal weight groups are present in younger adults at peak bone mass. The results of a population-based study comprising men and women of a wide age span, suggested that there may indeed be differences in the associations between adiposity and bone density and microstructure by age, gender and menopausal status [17].

The aims of this study were to evaluate using DXA, QCT and HR-pQCT the effect of obesity on 1) cortical and trabecular bone density of the spine, distal radius and distal tibia and 2) bone structure and strength of the distal radius and distal tibia, in healthy younger and older

men and women. We also sought to characterise bone turnover in obese adults compared to adults with a normal BMI.

## Materials and Methods

**Study design and participants:** We conducted a cross-sectional case-control study of 200 community-dwelling men and women from South Yorkshire, UK, aged 25 to 40 years (n=80) or 55 to 75 years (n=120). Participants were recruited through general practitioners, university and hospital staff and students, and poster advertisements. Cases were obese individuals (BMI≥30 kg/m²) and controls were normal weight individuals (BMI 18.5 to 24.9 kg/m²) based on the WHO BMI classifications. Controls were recruited to be individually matched to an obese participant by sex, age (±3years), height (±5 cm), smoking status (current smoker or non-smoker) and postcode.

All women aged 25 to 40 years were pre-menopausal, and those aged 55 to 75 years were at least five years post-menopausal. Participants were excluded if they had pre-diagnosed conditions (including diabetes) or were taking medications known to affect bone metabolism (including hormonal contraceptives and hormone replacement therapy), had fractured or undergone orthopaedic surgery within the last 12 months, were highly physically active (≥7 hours per week), consumed above 21 units of alcohol per week or were actively trying to lose weight. All participants provided written informed consent. Ethical approval was obtained from Sheffield Research Ethics Committee.

Height (cm) and weight (kg) were measured using a wall mounted stadiometer (Seca 242, Seca, Birmingham, UK) and electronic balance scale (Seca, Birmingham, UK). BMI was

calculated using Quetelet's index ((weight kg/(height m)$^2$). Dietary calcium was determined from weekly milk, cheese and yoghurt intake reported in a questionnaire.

**DXA**

Bone density (g/cm$^2$) at the whole body, lumbar spine (LS) and total hip (TH) was measured by DXA (Hologic Discovery A, Bedford, MA, USA). Whole body fat mass (FM) was determined by DXA.

**QCT** (55 to 75 age group only)

QCT of the lumbar spine (L1-3) was obtained using the LightSpeed VCT XT device (GE Healthcare, Milwaukee, WI, USA). We obtained data for L1, L2 and L3 and then the total region L1-L3. Scans were performed in the axial plane, with a helical rotation and rotation time of 0.8 seconds and a table height of 155. The scan pitch was 0.969 for each scan. All scans had a noise index of 30 and a slice thickness of 0.625mm. The modulated Ma was at a maximum 140, minimum 80, with a mean assumed tube current of 120mA and a tube voltage of 80 kilovolt peak. Scans were attained from 5mm above the superior end plate of L1 (inclusive of the T12-L1 joint space) to 5mm below the end plate of L3 (inclusive of the L3-4 joint space). QCT scans were analysed using the QCTPro software (Version 5.0.3, Mindways Software Inc. Austin, TX, USA).

**HR-pQCT**

HR-pQCT images of the distal radius and distal tibia (non-dominant, non-fractured limb) were obtained using the XtremeCT device (Scanco Medical AG, Zurich, Switzerland) with standard protocols. HR-pQCT images were analysed with standard software and extended cortical measures software provided by Scanco Medical AG (version 6) [9,10]. This software

identifies the periosteal and endosteal boundaries, enabling assessment of cortical micro-structural bone properties, including apparent cortical thickness (Ct.Th, mm), cortical tissue mineral density (TMD, mgHA/cm$^3$) and cortical porosity (Ct.Po, %).

Radial images from one pair of women were excluded from analysis due to movement. Extended cortical measures outcomes from one pair of men were excluded due the obese participant exhibiting outlying results (Ct.Po = 0.737, Ct.Po.Dm = 2.388µm). Tibial images from two pairs of women were excluded from analysis due to subject movement and data loss.

Micro-finite element analysis (version 1.13, Scanco Medical AG, Zurich, Switzerland) was applied to the HR-pQCT images to obtain measures of stiffness and ultimate failure load. The model parameters were set as: material properties isotropic and elastic, cortical bone Young's modulus 20 GPa, trabecular bone Young's modulus 17 GPa, Poisson's ratio 0.3. The proximal end of the section was fixed and a compression strain of 1% was applied to the distal surface of the section.

**Bone Turnover Markers**

Blood samples were collected from all participants between 08:00 and 10:00, following an overnight fast. Serum was stored frozen at -80°C. Bone turnover markers (BTMs) serum collagen type 1 C-telopeptide (CTX) and type 1 procollagen N-terminal peptide (PINP) were measured using the Cobas e411 automated electrochemiluminescence immunoassay (Roche Diagnostics, Germany). The inter-assay coefficients of variation (CVs) were <5%.

**Statistical Analysis:**

Power calculation: We used data sets from a previous study of healthy women in Sheffield to estimate the difference and variability of the difference in hip BMD between normal weight and obese pairs. The standardised difference was 1.125 g/cm$^2$ and the standard deviation of the paired differences was 0.16. We set the effect size at 0.09 g/cm$^2$ as this is likely to represent a clinically significant difference. A sample size of 200 has 80% power to detect a 0.09 g/cm$^2$ difference at $p < 0.05$ based on a paired sample t-test.

As frequency distributions of CTX and PINP were non-normal, a log transformation was applied prior to analysis. Standard deviation scores for PINP and CTX were calculated by subtracting the mean of the normal BMI, age and gender matched group from each individual result and dividing by the standard deviation of the normal BMI age and gender matched group. Uncoupling index was calculated to assess the relative balance of bone formation and resorption, as described by Eastell et al. [18] as the difference in the standard deviation scores for PINP and CTX ($Z_{PINP} - Z_{CTX}$), where $Z_{PINP}$ = (observed PINP − mean PINP)/SD and $Z_{CTX}$ = (observed CTX − mean CTX)/SD. Uncoupling index has previously been shown to be correlated with postmenopausal BMD bone loss [19].

Paired samples t-tests were used to determine significant differences between normal BMI and obese adults. Paired samples t-tests were performed for men and women combined, as after considering the results both by gender and in combination, the direction and categorised degree of significance remained the same for all outcomes. Standard deviation scores were calculated by standardising the mean difference between normal BMI and obese groups for each variable against the standard deviation of the normal weight, gender and age matched group. Univariate general linear models (GLM) were used to identify whether age group, gender and BMI had an effect on bone outcomes and GLM interaction terms were used to determine any interaction of age or gender with the relationship between obesity and bone

outcomes. Analysis was performed using IBM SPSS Statistics for Windows (Version 21.0. Armonk, NY: IBM Corp.). Significance was accepted when $p<0.05$.

**Results**

The total sample consisted of 200 individuals. The 25 to 40 years group consisted of 18 male and 22 female pairs and the 55 to 75 years group of 30 male and 30 female pairs. Characteristics of the study population are shown in Table 1. Obese and normal BMI individuals were well matched for age and height (Table 1). The obese group had significantly greater whole body fat mass than the normal group (Table 1).

**Areal bone density by DXA:**

Obese individuals had significantly greater mean aBMD than normal BMI individuals at the total hip ($p<0.001$ both age groups) and lumbar spine ($p=0.019$ younger, $p<0.001$ older). Whole body aBMD was also significantly greater in the obese older adults ($p<0.001$), but not in the obese younger adults ($p=0.158$).

There was an interaction between age group and the effect of obesity on aBMD at the lumbar spine ($p=0.001$) and whole body ($p=0.008$), but not at the total hip ($p=0.071$), with a greater effect of obesity on aBMD in the older adults than the younger adults. In the younger adults, aBMD was 0 to 1 SD scores greater in the obese group than in the normal weight group (Figure 1). In the older adults, aBMD was 1 to 2 SD scores greater in the obese group than in the normal weight group (Figure 1).

There was no interaction between gender and the effect of obesity on aBMD at the total hip, lumbar spine or whole body, in either age group.

**HR-pQCT:**

Volumetric bone density (vBMD) was significantly greater in obese adults compared to adults with a normal BMI at the distal tibia in both age groups ($p<0.001$) (Figure 2) and at the distal radius in the older adults ($p<0.001$) (Figure 3). There was an interaction between age group and the effect of obesity on vBMD at the distal radius ($p=0.005$) with a greater effect of obesity on vBMD in the older adults. There was no interaction between age group and the effect of obesity on vBMD at the distal tibia ($p=0.222$).There was no interaction between gender and the effect of obesity on vBMD at the distal radius or distal tibia in either age group.

Microstructure measurements showed that the higher vBMD in obesity was due to greater trabecular density in younger adults ($p=0.021$ radius, $p<0.001$ tibia) and greater trabecular and cortical density in older adults (all $p<0.001$) (Figure 2, Figure 3). The higher trabecular density in the obese adults was due to greater trabecular number (Tb.N) ($p<0.001$ all ages, all sites) and lower trabecular separation (Tb.Sp) ($p<0.001$ all ages, all sites) with no difference in trabecular thickness (Tb.Th) at the radius ($p=0.696$ younger, $p=0.056$ older) and tibia ($p=0.357$ younger, $p=0.205$ older) (Figure 2, Figure 3).

Cortical thickness was significantly greater in obese groups at the tibia ($p=0.001$ younger, $p<0.001$ older) (Figure 2) and at the radius in the older adults ($p<0.001$) (Figure 3). The higher cortical density in the older obese adults was due to higher cortical tissue mineral density (Ct.TMD) ($p=0.027$ radius, $p<0.001$ tibia) and lower cortical porosity ($p=0.017$ tibia).No differences between normal BMI and obese groups were observed in these cortical parameters in the younger adults (Figure 2, Figure 3).

The difference between normal BMI and obese adults in Ct.vBMD (p=0.048 radius, p=0.008 tibia) and Ct.TMD (p=0.040 radius, p=0.003 tibia) was greater in women than in men. At the tibia, the difference in Ct.Th (p=0.017) and cortical area (p=0.012) was also greater in older women than older men. In the younger adults, differences in cortical or trabecular properties between normal BMI and obese adults were similar in men and women.

No difference was observed in bone size between normal BMI and obese adults, as assessed by total area or cortical perimeter (Figure 2, Figure 3).

Whilst patterns of bone microarchitecture were consistent between the distal radius and distal tibia in the older population, the differences between obese and normal BMI adults in the younger group were seen at the tibia, but less consistently at the radius.

**QCT:**

Lumbar spine Tb.vBMD was significantly greater in obese women compared to women with normal BMI (p=0.003). There was no difference in lumbar spine Tb.vBMD between normal BMI and obese groups in men (p=0.166). There was an interaction between gender and the effect of obesity on Tb.vBMD at the lumbar spine, with a greater effect of obesity on Tb.vBMD in women than in men (p=0.001).

**Bone Strength:**

Bone stiffness was greater in obese adults at the distal tibia in both age groups (p=0.001 younger, p<0.001 older) (Figure 2) and at the distal radius in the older adults (p<0.001) (Figure 2). In both age groups, obesity was associated with greater estimated failure load at

the distal radius ($p=0.048$ younger, $p<0.001$ older) and distal tibia ($p=0.001$ younger, $p<0.001$ older) (Figure 2, Figure 3).

Therefore, although in the younger group the differences in bone density and microarchitectural outcomes between obese and normal BMI adults were less pronounced, the differences appear to contribute to an overall increase in bone strength. There was no interaction between age group and the effect of obesity on stiffness or failure load at either site.

There was no interaction between gender and the effect of obesity on bone stiffness or estimated failure load at the distal radius or distal tibia, in either age group.

**Bone Turnover Markers:**

CTX was lower in the obese adults in both age groups ($p=0.024$ younger, $p<0.001$ older) and PINP was lower in obese older adults ($p=0.084$ younger, $p=0.008$ older) (Figure 4). GLM revealed no interaction between gender or age group and the effect of obesity on CTX or PINP. CTX and PINP were highly correlated ($r=0.779$, $p<0.001$). Obese adults had an uncoupling index on average 0.24 SD scores greater than normal BMI adults ($p=0.009$). The ratio of PINP to CTX was higher in young adults than older adults ($p=0.022$). Young obese adults had an uncoupling index on average 0.16 SD scores greater than normal BMI young adults ($p=0.342$). Older obese adults had an uncoupling index on average 0.29 SD scores higher than normal BMI older adults ($p=0.007$).

There was no effect of gender on uncoupling index.

Multiple linear regression adjusting for age and gender showed that CTX was a significant negative predictor of aBMD and vBMD (whole body aBMD p=0.002, TH aBMD p<0.001, LS aBMD p=0.002, radius vBMD p=0.010, tibia vBMD p=0.038, LS Tb.vBMD p=0.157). PINP was not a significant predictor of aBMD or vBMD.

## Discussion

Obese adults had greater BMD at all sites measured and favourable bone microarchitecture and greater bone strength at the distal radius and distal tibia, compared to normal adults. Greater differences in BMD and HR-pQCT measurements between obese and normal adults were observed in the older adults than the younger adults and suggest that obesity may protect against age-related bone loss, and also increase peak bone mass.

Our results are consistent with the existing literature that shows greater aBMD in obesity. High BMI has previously been positively associated with bone mass in adults [8, 11, 12, 20-28] and older adults [29, 30] of both sexes. Body weight and BMI have been positively associated with aBMD of the lumbar spine [12, 22, 23, 25, 28], femoral neck [22, 23, 28], distal radius [12], proximal femur and leg [8, 22, 25, 26, 28, 30]. Low body weight is associated with osteoporosis at the lumbar spine, proximal femur, total hip, femoral neck and trochanter [22].

This is the first study to address relationships between obesity, bone microarchitecture and micro finite element derived bone strength in an individually-matched case control study of younger and older men and women.

Sornay-Rendu et al. (2013) previously reported an assessment of bone microarchitecture in obese postmenopausal women, compared with a non-obese control group [12]. In agreement

with our findings, the authors reported greater vBMD at the distal radius and distal tibia in obesity. This greater vBMD resulted from greater cortical thickness, greater Tb.BMD (due to greater Tb.N and lower Tb.Sp), and greater Ct.BMD (due to lower Ct.Po). Also in agreement with our results, the authors reported no difference in total area or trabecular area in obesity [12]. Greater percentage differences in microarchitectural parameters were observed at the distal tibia compared to the distal radius in the obese group versus the non-obese group [12].

Similarly, in a study of young obese men, BMI was positively associated with Tb.N and inversely associated with Tb.Sp [31]. Using pQCT, BMI was also positively associated with tibial Tb.BMD in both pre- and postmenopausal women [28].

A recent study examined the effect of fat mass and lean mass on HR-pQCT derived bone microarchitecture in obese individuals with metabolic syndrome [32]. The study reported positive associations between lean mass and Tb.N and Tb.Sp at the radius, and vBMD, Tb.vBMD, BV/TV, Tb.N, Tb.Sp and Ct.Th at the distal tibia [32]. No significant associations between fat mass and microarchitectural outcomes were observed [32]. However, because there was no control group, and metabolic syndrome may have effects on bone metabolism, it is difficult to compare these findings directly with our results.

It was perhaps surprising that there was no difference in bone size between normal and obese adults. We speculate that this indicates a minimal effect of habitual loading on bone structure in obesity, and that the differences observed reflect alterations in the hormonal milieu associated with greater adiposity. The observation of no difference in bone size might be the result of inhibition of periosteal apposition due to greater circulating oestrogen in obesity, associated with increased aromatisation of androgens [33].

Obese adults have lower bone turnover than individuals with a normal BMI, with lower CTX and PINP. By calculating an uncoupling index, as described by Eastell et al. [18], we were able to demonstrate a positive balance of bone formation to bone resorption in obese adults. These findings are consistent with the existing literature which shows lower makers of resorption and formation with high BMI in premenopausal women [34], through the menopausal transition [35] and in postmenopausal women [12, 34, 36-38]. Studies in obese men are lacking, although a recent study of young men and women by Viljakainen et al. showed lower PINP, CTX, TRAP, total OC and carboxylated OC in obese adults compared to non-obese age and gender matched controls [39]. In further agreement with our results Viljakainen et al. found no difference in uncoupling index between young obese and non-obese men and women [39]. Despite bone turnover typically increasing with age, we found no effect of age on bone resorption in the present study. This may be explained by the age stratification of our young adults, as bone turnover markers remain elevated until age 35 years [40]. Younger adults had higher bone formation than older adults, possibly associated with the period of consolidation in early adulthood.

Fat distribution may affect associations between adiposity and bone microarchitecture [17, 31, 41, 42]. Premenopausal women with greater central adiposity have been shown to have lower trabecular bone volume, bone stiffness and bone formation on bone biopsy [41]. The inverse relationship between trunk fat and trabecular bone volume remained significant after controlling for age and BMI [41] . Ng et al. reported differences in the association between subcutaneous and visceral adipose compartments and bone density and microstructural parameters, differences which were also age and gender dependent [17]. A key limitation of the present study is the lack of assessment of body fat compartments, which should be addressed in future work.

Sornay-Rendu et al suggested that the greater BMD observed in obesity does not appear to be proportional to the greater body weight, so that adaptation of bone in obesity may not be sufficient to withstand the greater falls force [12]. Fractures often occur in obese individuals despite normal or high aBMD [9, 10]. In particular, tibial vBMD and estimated failure load are greater in obese people, so lower bone density is not the cause of the increased risk of lower limb or ankle fracture observed in obesity [2, 6, 8, 43]. Simple linear scaling may not be sophisticated enough to fully determine appropriate bone strength for body size. Further development of finite element models that account for body weight in the forces acting may provide a better understanding of fracture risk in obesity. Bone is more likely to adapt to daily forces and loads, which differ from forces acting in a fall impact. Therefore it may not be surprising that obese individuals continue to fracture at some sites despite greater BMD than normal weight individuals.

Whilst the greater BMD at the hip and lumbar spine may explain obesity being protective against hip and vertebral fracture, non-skeletal factors, such as greater soft tissue thickness at the greater trochanter may also contribute to fracture risk in obesity [44]. Obese individuals may be at greater risk of falls due to impaired muscular function, sarcopenic obesity, and/or fat infiltration of skeletal muscle [45-47]. Different fall direction and fall forces in obesity could also contribute to the greater risk of lower limb and proximal humerus fractures.

The cross-sectional design of this study must be acknowledged as a limitation. BMI may be considered too crude a measure of obesity, as body fat distribution could be a determinant of bone density and microarchitecture, but our obese group did have significantly higher fat mass than the normal weight group. Whilst the most likely confounding differences between

obese and normal weight individuals (age, body size, smoking, exercise and socioeconomic status) were controlled for as much as possible, any remaining differences may have affected the results.

CT density measurements may be affected by the soft tissue thickness effects of increasing BMI measures, for example beam hardening due to greater adiposity. While bone density measurements might be affected in obesity, it is less likely that microarchitectural outcomes would be affected.

Our finding of greater bone strength in young obese adults despite less pronounced differences in bone density and microarchitecture between normal and obese groups could be due to unmeasured factors rather that the cumulative effect of non-significant differences in bone structure. It is possible that the absence of an interaction between age and the effect of obesity on failure load could exist when there is no effect in young adults, a small effect in older adults, and insufficient power to detect a difference.

The HR-pQCT finite element analysis model used in this study does not take into account individual loads upon falling and this approach would increase the sophistication of the model. The current model simulates a direct compression force on the distal tibia which may not be the most suitable strength test for the prediction of ankle fracture which is affected by torsion forces and contribution of ligaments.

In conclusion, obese individuals had greater bone density than their normal weight counterparts, at all sites measured. The greater density in trabecular bone was due to greater trabecular number, but trabecular thickness did not differ between obese and normal weight

people. Cortical thickness and cortical tissue mineral density were also higher in obese people, and cortical porosity was lower. Bone size at the radius and tibia did not differ between obese and normal weight people. The magnitude of the difference in bone density observed between obese and normal weight individuals using DXA was comparable to that observed using HR-pQCT suggesting that greater bone density in obesity is not solely an artefact resulting from greater soft tissue thickness.

The differences in bone turnover and BMD between obese and normal weight groups manifest by young adulthood, suggesting that obesity has positive effects on peak bone mass acquisition. The greater differences between obese and normal groups in the older adults suggest obesity may also be protective against age-related bone loss.

The identification of mechanisms responsible for greater bone density in obesity will improve our understanding of the pathophysiology of osteoporosis and could lead to new therapeutic targets. Understanding why some fractures are increased in obesity may require more sophisticated models for the assessment of bone strength, which may lead to further insights into the site-specific mechanisms of fractures.

**Disclosures**

The authors state that they have no conflicts of interest.

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## References

1. Armstrong ME, Spencer EA, Cairns BJ, Banks E, Pirie K, Green J, et al. Body mass index and physical activity in relation to the incidence of hip fracture in postmenopausal women. J Bone Miner Res. 2011;26(6):1330-8.
2. Armstrong ME, Cairns BJ, Banks E, Green J, Reeves GK, Beral V. Different effects of age, adiposity and physical activity on the risk of ankle, wrist and hip fractures in postmenopausal women. Bone. 2012;50(6):1394-400.
3. Prieto-Alhambra D, Premaor MO, Fina Aviles F, Hermosilla E, Martinez-Laguna D, Carbonell-Abella C, et al. The association between fracture and obesity is site-dependent: a population-based study in postmenopausal women. J Bone Miner Res. 2012;27(2):294-300.
4. Premaor MO, Compston JE, Fina Aviles F, Pages-Castella A, Nogues X, Diez-Perez A, et al. The association between fracture site and obesity in men: a population-based cohort study. J Bone Miner Res. 2013;28(8):1771-7.
5. De Laet C, Kanis JA, Oden A, Johanson H, Johnell O, Delmas P, et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int. 2005;16(11):1330-8.
6. Johansson H, Kanis JA, Oden A, McCloskey E, Chapurlat RD, Christiansen C, et al. A meta-analysis of the association of fracture risk and body mass index in women. J Bone Miner Res. 2013.
7. Gnudi S, Sitta E, Lisi L. Relationship of body mass index with main limb fragility fractures in postmenopausal women. J Bone Miner Metab. 2009;27(4):479-84.
8. Beck TJ, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the women's health initiative-observational study. J Bone Miner Res. 2009;24(8):1369-79.
9. Compston JE, Watts NB, Chapurlat R, Cooper C, Boonen S, Greenspan S, et al. Obesity is not protective against fracture in postmenopausal women: GLOW. Am J Med. 2011;124(11):1043-50.
10. Premaor MO, Pilbrow L, Tonkin C, Parker RA, Compston J. Obesity and fractures in postmenopausal women. J Bone Miner Res. 2010;25(2):292-7.
11. Morin S, Leslie WD, Manitoba Bone Density P. High bone mineral density is associated with high body mass index. Osteoporos Int. 2009;20(7):1267-71.
12. Sornay-Rendu E, Boutroy S, Vilayphiou N, Claustrat B, Chapurlat RD. In obese postmenopausal women, bone microarchitecture and strength are not commensurate to greater body weight: the Os des Femmes de Lyon (OFELY) study. J Bone Miner Res. 2013;28(7):1679-87.
13. Nielson CM, Bouxsein ML, Freitas SS, Ensrud KE, Orwoll ES, Osteoporotic Fractures in Men Research G. Trochanteric soft tissue thickness and hip fracture in older men. J Clin Endocrinol Metab. 2009;94(2):491-6.

14. Yu EW, Thomas BJ, Brown JK, Finkelstein JS. Simulated increases in body fat and errors in bone mineral density measurements by DXA and QCT. J Bone Miner Res. 2011.
15. Blake G, Wahner H, Fogelman I. The Evaluation of Osteoporosis: Dual Energy X-ray. Absorptiometry and Ultrasound in Clinical Practice. London, UK: Taylor & Francis; 1999.
16. Nelson L, Gulenchyn KY, Atthey M, Webber CE. Is a fixed value for the least significant change appropriate? J Clin Densitom. 2010;13(1):18-23.
17. Ng AC, Melton LJ, 3rd, Atkinson EJ, Achenbach SJ, Holets MF, Peterson JM, et al. Relationship of adiposity to bone volumetric density and microstructure in men and women across the adult lifespan. Bone. 2013;55(1):119-25.
18. Eastell R, Robins SP, Colwell T, Assiri AM, Riggs BL, Russell RG. Evaluation of bone turnover in type I osteoporosis using biochemical markers specific for both bone formation and bone resorption. Osteoporos Int. 1993;3(5):255-60.
19. Rogers A, Hannon RA, Eastell R. Biochemical markers as predictors of rates of bone loss after menopause. J Bone Miner Res. 2000;15(7):1398-404.
20. Zhao LJ, Liu YJ, Liu PY, Hamilton J, Recker RR, Deng HW. Relationship of obesity with osteoporosis. J Clin Endocrinol Metab. 2007;92(5):1640-6.
21. Bakker I, Twisk JW, Van Mechelen W, Kemper HC. Fat-free body mass is the most important body composition determinant of 10-yr longitudinal development of lumbar bone in adult men and women. J Clin Endocrinol Metab. 2003;88(6):2607-13.
22. Morin S, Tsang JF, Leslie WD. Weight and body mass index predict bone mineral density and fractures in women aged 40 to 59 years. Osteoporos Int. 2009;20(3):363-70.
23. Albala C, Yanez M, Devoto E, Sostin C, Zeballos L, Santos JL. Obesity as a protective factor for postmenopausal osteoporosis. Int J Obes Relat Metab Disord. 1996;20(11):1027-32.
24. Meyer HE, Sogaard AJ, Falch JA, Jorgensen L, Emaus N. Weight change over three decades and the risk of osteoporosis in men: the Norwegian Epidemiological Osteoporosis Studies (NOREPOS). Am J Epidemiol. 2008;168(4):454-60.
25. Dogan A, Nakipoglu-Yuzer GF, Yildizgoren MT, Ozgirgin N. Is age or the body mass index (BMI) more determinant of the bone mineral density (BMD) in geriatric women and men? Arch Gerontol Geriatr. 2010.
26. Yu Z, Zhu Z, Tang T, Dai K, Qiu S. Effect of body fat stores on total and regional bone mineral density in perimenopausal Chinese women. J Bone Miner Metab. 2009;27(3):341-6.
27. Sodi R, Hazell MJ, Durham BH, Rees C, Ranganath LR, Fraser WD. The circulating concentration and ratio of total and high molecular weight adiponectin in post-menopausal women with and without osteoporosis and its association with body mass index and biochemical markers of bone metabolism. Clin Biochem. 2009;42(13-14):1375-80.
28. Sukumar D, Schlussel Y, Riedt CS, Gordon C, Stahl T, Shapses SA. Obesity alters cortical and trabecular bone density and geometry in women. Osteoporos Int. 2011;22(2):635-45.
29. Barrera G, Bunout D, Gattas V, de la Maza MP, Leiva L, Hirsch S. A high body mass index protects against femoral neck osteoporosis in healthy elderly subjects. Nutrition. 2004;20(9):769-71.
30. Kirchengast S, Peterson B, Hauser G, Knogler W. Body composition characteristics are associated with the bone density of the proximal femur end in middle- and old-aged women and men. Maturitas. 2001;39(2):133-45.
31. Bredella MA, Lin E, Gerweck AV, Landa MG, Thomas BJ, Torriani M, et al. Determinants of bone microarchitecture and mechanical properties in obese men. J Clin Endocrinol Metab. 2012;97(11):4115-22.

32. Madeira E, Mafort TT, Madeira M, Guedes EP, de Oliveira Moreira R, de Mendonca LM, et al. Lean mass as a predictor of bone density and microarchitecture in adult obese individuals with metabolic syndrome. Bone. 2013.
33. Callewaert F, Sinnesael M, Gielen E, Boonen S, Vanderschueren D. Skeletal sexual dimorphism: relative contribution of sex steroids, GH-IGF1, and mechanical loading. J Endocrinol. 2010;207(2):127-34.
34. Rico H, Arribas I, Casanova FJ, Duce AM, Hernandez ER, Cortes-Prieto J. Bone mass, bone metabolism, gonadal status and body mass index. Osteoporos Int. 2002;13(5):379-87.
35. Sowers MR, Zheng H, Greendale GA, Neer RM, Cauley JA, Ellis J, et al. Changes in bone resorption across the menopause transition: effects of reproductive hormones, body size, and ethnicity. J Clin Endocrinol Metab. 2013;98(7):2854-63.
36. Cifuentes M, Johnson MA, Lewis RD, Heymsfield SB, Chowdhury HA, Modlesky CM, et al. Bone turnover and body weight relationships differ in normal-weight compared with heavier postmenopausal women. Osteoporos Int. 2003;14(2):116-22.
37. Papakitsou EF, Margioris AN, Dretakis KE, Trovas G, Zoras U, Lyritis G, et al. Body mass index (BMI) and parameters of bone formation and resorption in postmenopausal women. Maturitas. 2004;47(3):185-93.
38. Revilla M, Villa LF, Sanchez-Atrio A, Hernandez ER, Rico H. Influence of body mass index on the age-related slope of total and regional bone mineral content. Calcif Tissue Int. 1997;61(2):134-8.
39. Viljakainen H, Ivaska KK, Paldanius P, Lipsanen-Nyman M, Saukkonen T, Pietilainen KH, et al. Suppressed bone turnover in obesity - a link to energy metabolism? A case-control study. J Clin Endocrinol Metab. 2014:jc20133097.
40. Glover SJ, Garnero P, Naylor K, Rogers A, Eastell R. Establishing a reference range for bone turnover markers in young, healthy women. Bone. 2008;42(4):623-30.
41. Cohen A, Dempster DW, Recker RR, Lappe JM, Zhou H, Zwahlen A, et al. Abdominal fat is associated with lower bone formation and inferior bone quality in healthy premenopausal women: a transiliac bone biopsy study. J Clin Endocrinol Metab. 2013;98(6):2562-72.
42. Bredella MA, Torriani M, Ghomi RH, Thomas BJ, Brick DJ, Gerweck AV, et al. Determinants of bone mineral density in obese premenopausal women. Bone. 2011;48(4):748-54.
43. Ong T, Sahota O, Tan W, Marshall L. A United Kingdom perspective on the relationship between body mass index (BMI) and bone health: A cross sectional analysis of data from the Nottingham Fracture Liaison Service. Bone. 2014;59:207-10.
44. Bouxsein ML, Szulc P, Munoz F, Thrall E, Sornay-Rendu E, Delmas PD. Contribution of trochanteric soft tissues to fall force estimates, the factor of risk, and prediction of hip fracture risk. J Bone Miner Res. 2007;22(6):825-31.
45. Binkley N, Krueger D, Buehring B. What's in a name revisited: should osteoporosis and sarcopenia be considered components of "dysmobility syndrome?". Osteoporos Int. 2013;24(12):2955-9.
46. Marcus RL, Addison O, Dibble LE, Foreman KB, Morrell G, Lastayo P. Intramuscular adipose tissue, sarcopenia, and mobility function in older individuals. J Aging Res. 2012;2012:629637.
47. Himes CL, Reynolds SL. Effect of obesity on falls, injury, and disability. J Am Geriatr Soc. 2012;60(1):124-9.

**Table Legend:**

Table 1: Study population characteristics by age and gender group (Mean (SD)).

**Figure Legends:**

Figure 1: Mean standard deviation score (95% CI) of obese groups calculated against normal weight groups for aBMD at the total hip, lumbar spine and whole body, by age and gender.

Zero line indicates the mean of the age and gender matched normal group. Y=Younger adults, O=Older adults. The p-value refers to the comparison between obese and normal BMI groups, where *p<0.05, **p<0.01, ***p<0.001

Figure 2: Mean standard deviation score (95% CI) of obese groups calculated against normal groups for total and cortical parameters at the distal tibia, by age and gender. Zero line indicates the mean of the age and gender matched normal group. Y= Younger adults, O= Older adults. The p-value refers to the comparison between obese and normal BMI groups, where *p<0.05, **p<0.01, ***p<0.001.

Figure 3: Mean standard deviation score (95% CI) of obese groups calculated against normal groups for microarchitectural parameters at the distal radius, by age and gender. Zero line indicates the mean of the age and gender matched normal group. Y= Younger adults, O=Older adults. The p-value refers to the comparison between obese and normal BMI groups, where *p<0.05, **p<0.01, ***p<0.001

Figure 4: Box and whisker plots for serum CTX and PINP in obese and normal, younger and older adults.