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Original Article

The different correlations between obesity and osteoporosis after adjustment of static mechanical loading from weight and fat free mass

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Abstract

Objectives: To explore complex correlations between obesity (OB) and osteoporosis (OP) after adjustment of static mechanical loading from weight and fat free mass (FFM). **Methods**: A total of 3749 Chinese aged ≥65 years were selected from our ongoing cohort study. OB indices and bone mineral density (BMD) were measured for each subject. Linear regression analyses were performed to explore the correlations between OB indices and OP under three adjustment models (unadjusted, adjusted with weight and adjusted with FFM). **Results**: Under no adjustment, three general obesity indices (body mass index: BMI, fat mass: FM, and percentage FM: PFM) were positively associated with BMD at three skeletal sites (P<0.001) in the regression analyses. However, after the adjustment with weight, these associations were mostly significant but reverse i.e., negatively in direction. After adjustment with FFM, the three indices were still positively and significantly (P<0.001) associated with BMD but regression coefficients were smaller compared to the unadjusted associations. Similar associations were observed for central adiposity and lower limb adiposity indices. **Conclusions**: The combined relation of OB to OP due to the physiological factors secreted from adipose tissues and the static mechanical loading from FM is positive in direction.

Keywords: Bone Mineral Density, Fat Free Mass, Obesity, Osteoporosis

Introduction

Osteoporosis (OP) is a serious systemic bone disease especially in the elderly, whose main characteristics are low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, which lead to increased risk of osteoporotic fractures[1]. The estimated prevalence of OP will increase double from 6.6% in 1997 to 13.6% in 2050 in China[2]. OP in China has affected more than one-third of people aged 50 years and older[3]. Obesity (OB) is caused by abnormal or excessive fat accumulation and could lead to an increasing risk on health. China has the largest number of obese people in the world and the prevalence of overweight and OB are 38.7% in men and 33.1% in women in 2014[4].

OB has complex effects on OP. Excessive fat accumulation imposes a greater static mechanical stress on bone, and it represents a straightforward and important positive effect of fat mass (FM) on bone[5,6]. Bone can sense the mechanical forces brought by external loading and generates adaptive response in quality and structure. Osteocytes, osteoblasts and osteoclasts constitute complex cell network (bone

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multicellular unit, BMU) in response to mechanical stimuli. BMU can transform physical stimuli to biochemical signals by boosting or inhibiting the mechanosensors on cell surface, mainly including integrins and focal adhesions[7-12]. Then, intracellular Ca^{++} increases to respond mechanical loading[13]. From physiological point, adipose tissues affect bone metabolism by expressing and secreting a variety of biologically active factors. For example, leptin promotes the proliferation of osteoblasts through activation of leptin receptor[14], but its effects through sympathetic nervous system favor bone resorption[15]. Similarly, adiponectin increases osteoblastogenesis and inhibit osteoclastogenesis through the RANK/RANKL/OPG axis. On the contrary, adiponectin promotes RANKL and inhibit the expression of OPG in osteoblasts[16]. In summary, the effects of OB on bone include two parts (static mechanical loading, and physiological function). Since the two diseases tend to concurrently be observed in the elderly, it is important and urgent to detect their relation clearly especially in the elderly[17].

Previous epidemiological analyses have extensively investigated their correlations, but the results are still inconsistent or controversial. Previous studies reported their positive correlations[18-24], negative correlations[25-30], and sometimes the reversible correlations after adjustment[31-34]. Therefore, it is necessary to further clarify the relationship between OB and OP. These studies have used different covariates (e.g., BMI, weight) as adjustment of static mechanical loading effect in the regression model when studying the associations between OB and OP. Some studies have demonstrated that the positive correlations between FM and bone mass under no adjustment were reversed (negative) when the static mechanical loading effects due to body weight on bone mass were adjusted[31-34]. Since weight include FM, lean mass (LM) and bone mass, such adjustment with weight or BMI could exclude the loading effects not only from fat-free mass (FFM: including LM and bone mass) but also from fat mass when studying OB and OP.

This study evaluated the systemic correlations between three types of OB indices (general, central and lower limb) and OP under three adjustment models (unadjusted, adjusted with weight and adjusted with FFM. The results would improve our understanding on their relation, and provide helpful directions on the adjustment of mechanical loading on association study between OB and OP.

Materials and Methods

Study Subjects

A total of 4689 Chinese aged ≥65 years were enrolled in our ongoing Osteoporosis Preventive Project (OPP). All participants were recruited from community health centers in Suzhou, Jiangsu province in the Southeastern China. A total of 940 subjects were excluded from analyses by adopting the following exclusion factors: 1) The history of endocrine diseases, including parathyroidism, hypothyroidism, hyperthyroidism; major gastrointestinal operations; renal inadequacy; anemia; depression and malignant tumors etc. and 2) Use of corticosteroids. The project was approved by the Institutional Research Ethic Board, and all participants provided written informed consents.

Anthropometric Measurements and Questionnaire Survey

Each participant received a face-to-face interview to obtain basic information, including demographics, lifestyle, family history of disease, current medication. Standing height and weight were measured using standard procedures. Waist circumference (WC) was assessed at the level of umbilicus and hipline was determined at the level of the maximum extension of the buttocks posteriorly in a horizontal plane. BMI and waist-to-hip ratio (WHR) were calculated derived using the formulas: body weight/height squared (kg/m^2) and WC/hipline, respectively.

Measurements of BMD and Body Composition

BMD (g/cm^2) at total hip (TH), femur neck (FN) and lumbar spine (LS, L1–L4) were measured using dual-energy X-ray absorptiometry (DXA) bone densitometer (Hologic Inc., Waltham, MA, USA). The precision of BMD measurement was based on repeated measurements of thirty volunteers for three times, expressed as the root-mean-square percent coefficient of variation (RMS-CV). The RMS-CVs were 2.50%, 2.05% and 2.47% for BMD measurement at TH, FN and LS, respectively.

The body composition was measured using the bioelectrical impedance analyzer (MC 780A, TANITA, Tokyo, Japan). All participants were required to wear lighting clothing and take off shoes and socks. The following indices were obtained: FM (kg), FFM (kg), body weight (kg), percentage fat mass (PFM, %), trunk-PFM (T-PFM, %), trunk-FM (T-FM, kg), visceral fat rating (VFR), and trunk-weight (T-weight, kg). In addition, lower limp adiposity indices including lower limp FM (L-FM, kg), lower limp FFM (L-FFM, kg) and lower limp weight (L-weight, kg) were respectively the sum of right lower limp (RL) and left lower limp (LL) adiposity indices. Lower limp PFM (L-PFM, %) was calculated as follows: $(\text{RL-FM} + \text{LL-FM}) \div (\text{RL-weight} + \text{LL-weight}) \times 100$.

Statistical Analysis

Descriptive statistics were used to characterize the distribution of all indices. The continuous variables such as age, height and other adiposity indices were expressed as the mean and standard deviation (SD). T-tests or Wilcoxon Rank-Sum tests were used to compare the differences between males and females (two-sided $P<0.05$). The associations of BMD at the three regions and sex, age, as well as adiposity indices were investigated using linear regression analyses and bivariate Spearman's correlation analyses. The variables were statistically significant if the level of P values were less than 0.05 and those significant factors were admitted into multiple regression models. Multiple linear regression

Table 1. Basic characteristics of the studied subjects.

	Total (N=3749)		Male (N=1666)		Female (N=2083)		P
	Means	SD	Means	SD	Means	SD	
Age (year)	72.37	5.61	72.59	5.60	72.21	5.60	0.04
TH-BMD (g/cm²)	0.80	0.16	0.88	0.13	0.73	0.14	<0.001
FN-BMD (g/cm²)	0.67	0.14	0.74	0.12	0.61	0.13	<0.001
LS-BMD (g/cm²)	0.90	0.19	1.02	0.18	0.81	0.14	<0.001
WC (cm)	85.55	9.22	86.99	8.86	84.39	9.35	<0.001
WHR	0.91	0.65	0.91	0.08	0.92	0.87	0.79
Weight (kg)	60.31	10.34	65.37	9.60	56.27	9.06	<0.001
Height (m)	159.96	8.41	166.62	6.11	154.65	5.82	<0.001
BMI (kg/m²)	23.51	3.27	23.52	3.03	23.51	3.46	0.92
PFM (%)	27.61	8.39	21.77	5.83	32.28	7.11	<0.001
FM (kg)	16.84	6.42	14.56	5.36	18.65	6.61	<0.001
LM (kg)	41.03	7.72	48.05	5.49	35.43	3.52	<0.001
FFM (kg)	43.38	8.10	50.70	5.77	37.55	3.83	<0.001
VFR	10.62	3.98	13.52	3.21	8.33	2.89	<0.001
T-PFM (%)	28.08	8.76	23.41	6.80	31.78	8.36	<0.001
T-FM (kg)	9.80	3.90	8.75	3.31	10.64	4.12	<0.001
T-LM (kg)	23.14	3.75	26.42	2.79	20.53	1.93	<0.001
T-FFM (kg)	24.40	3.88	27.71	2.92	21.77	2.13	<0.001
T-weight (kg)	34.20	5.44	36.46	4.93	32.41	5.15	<0.001
L-PFM (%)	30.20	8.08	23.02	4.77	35.91	5.05	<0.001
L-FM (kg)	6.10	1.95	5.27	1.75	6.76	1.84	<0.001
L-LM (kg)	13.78	3.29	16.69	2.48	11.47	1.57	<0.001
L-FFM (kg)	14.18	3.40	17.16	2.58	11.82	1.67	<0.001
L-weight (kg)	20.28	4.00	22.43	3.94	18.57	3.13	<0.001

Notes: T- represents trunk-. L- represents lower limb-. TH: total hip; FN: femoral neck; LS: lumbar spine; BMD: bone mineral density; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; PFM: percentage fat mass; FM: fat mass; VFR: visceral fat rating; FFM: fat-free mass.

analyses were used to examine the independent associations of adiposity indices with LS-BMD, TH-BMD and FN-BMD after adjustment for significant confounding factors (age and/or sex) and loading-related indices (weight or FFM). A two-sided $P<0.05$ was considered as significance. Variance inflation factors (VIF) >10 represented the existence of collinearity between obesity-related phenotypes and covariates. All statistical analyses were performed using SAS version 9.4.

Results

As shown in Table 1, significant differences for the studied indices were observed between different sexes ($P<0.05$) except for WHR and BMI. Sex and age were two confounding factors that were significantly associated with TH-BMD and FN-BMD ($P<0.05$). As we expected, compared to females, males have higher BMD and VFR, heaver weight and lean mass than females, but have lower FM and PFM of the whole body, trunk and lower limbs. Thus, sex and age were used as two covariates to adjust the confounding effects in the following multiple linear regression analyses. To systematically investigate the relations between OB indices and OP, we divided these indices into three types (general, central and lower limb OB indices), and we performed the analyses under three conditions (unadjusted, adjusted with corresponding weight and adjusted with corresponding FFM).

General Adiposity Indices and BMD

The results of multiple linear regression analyses between general, central and lower limp adiposity indices and BMD were shown in Table 2. Under no adjustment, the three general OB indices (BMI, FM, and PFM) were significantly ($P<0.001$) and positively associated with BMD at three skeletal sites (TH, FN, and LS), which were consistent with the observations from previous studies. However, after the adjustment with weight, these associations at three skeletal sites were still significant but reverse i.e., negatively in direction (e.g., PFM, $\beta= -0.185$, $P<0.001$ for FN-BMD), except for the association between BMI and TH-BMD (Table 2). After the adjustment with FFM, the three indices were still positively and significantly ($P<0.001$)

Table 2. Standardized regression coefficients between OB indices and BMD under three adjustment conditions.

	TH-BMD			FN-BMD			LS-BMD		
	Unadjusted	Adjusted corresponding weight	Adjusted corresponding FFM	Unadjusted	Adjusted corresponding weight	Adjusted corresponding FFM	Unadjusted	Adjusted corresponding weight	Adjusted corresponding FFM
General adiposity indices in all subjects									
PFM (%)	0.212***	-0.137***	0.138***	0.181***	-0.185***	0.104***	0.225***	-0.118***	0.157***
FM (kg)	0.234***	-0.182***	0.127***	0.215***	-0.232***	0.100***	0.249***	-0.167***	0.140***
BMI (kg/m^2)	0.265***	0.056*	0.159***	0.219***	-0.100***	0.093***	0.253***	-0.035	0.140***
Central adiposity indices in all subjects									
T-PFM (%)	0.192***	-0.086***	0.180***	0.170***	-0.127***	0.157***	0.197***	-0.078***	0.192***
T-FM (kg)	0.219***	-0.132***	0.168***	0.203***	-0.185***	0.147***	0.228***	-0.125***	0.177***
VFR	0.345***	0.144***	0.270***	0.306***	0.022	0.217***	0.321***	0.053	0.249***
WC (cm)	0.185***	-0.013	0.113***	0.187***	0.003	0.113***	0.222***	0.043***	0.154***
WHR	0.017	0.012	0.014	0.008	0.003	0.005	0.021	0.016	0.018
Lower limp adiposity indices in all subjects									
L-PFM (%)	0.208***	-0.067*	0.131***	0.199***	-0.071*	0.123***	0.301***	0.052*	0.234***
L-FM (kg)	0.239***	-0.092**	0.106***	0.232***	-0.092**	0.101***	0.286***	0.025	0.178***
General adiposity indices in males									
PFM (%)	0.223***	-0.075*	0.144***	0.177***	-0.113***	0.1***	0.181***	-0.073*	0.124***
FM (kg)	0.295***	-0.132**	0.152***	0.248***	-0.194***	0.101***	0.258***	-0.124**	0.132***
BMI (kg/m^2)	0.372***	0.172***	0.234***	0.282***	-0.058	0.106***	0.309***	0.071	0.172***
Central adiposity indices in males									
T-PFM (%)	0.209***	-0.075*	0.197***	0.168***	-0.112**	0.156***	0.171***	-0.052	0.176***
T-FM (kg)	0.274***	-0.124**	0.197***	0.232***	-0.179***	0.153***	0.234***	-0.089*	0.176***
VFR	0.359***	0.146**	0.266***	0.291***	-0.013	0.184***	0.312***	0.149***	0.244***
WC (cm)	0.255***	-0.032	0.127***	0.232***	-0.032	0.099***	0.265***	0.055	0.165***
WHR	0.091***	-0.023	0.020	0.075**	-0.032	0.002	0.099***	-0.007	0.031
Lower limp adiposity indices in males									
L-PFM (%)	0.182***	-0.049	0.088***	0.142***	-0.075*	0.053*	0.205***	0.019	0.132***
L-FM (kg)	0.291***	-0.13**	0.089**	0.247***	-0.17***	0.047	0.296***	-0.008	0.148***
General adiposity indices in females									
PFM (%)	0.168***	-0.173***	0.1***	0.147***	-0.221***	0.075***	0.245***	-0.158***	0.166***
FM (kg)	0.227***	-0.315***	0.111***	0.217***	-0.364***	0.091***	0.316***	-0.311***	0.178***
BMI (kg/m^2)	0.262***	0.003	0.149***	0.226***	-0.153***	0.097***	0.308***	-0.159***	0.169***
Central adiposity indices in females									
T-PFM (%)	0.181***	-0.097**	0.166***	0.166***	-0.142***	0.150***	0.247***	-0.108**	0.230***
T-FM (kg)	0.222***	-0.176**	0.173***	0.215***	-0.239***	0.158***	0.301***	-0.210***	0.236***
VFR	0.255***	0.089*	0.206***	0.238***	0.021	0.182***	0.273***	-0.077*	0.212***
WC (cm)	0.183***	0.001	0.130***	0.197***	0.034	0.146***	0.268***	0.047	0.204***
WHR	0.019	0.018	0.019	0.007	0.006	0.008	0.029	0.028	0.030
Lower limp adiposity indices in females									
L-PFM (%)	0.121***	-0.048	0.095***	0.133***	-0.035	0.108***	0.239***	0.054*	0.213***
L-FM (kg)	0.225***	-0.113*	0.112***	0.237***	-0.076	0.132***	0.343***	0.055	0.243***

*Note: * P<0.05, ** P<0.01, *** P<0.001. T- represents trunk-. L- represents lower limb-. TH: total hip; FN: femoral neck; LS: lumbar spine; BMD: bone mineral density; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; PFM: percentage fat mass; FM: fat mass; VFR: visceral fat rating; FFM: fat-free mass.*

associated with BMD but the regression coefficients of these associations had changed smaller when compared to the unadjusted associations.

Central Adiposity Indices and BMD

Due to the complex and important effects of adipose tissue when accumulated in the abdomen, this study investigated the associations between BMD and five central OB indices (T-PFM, T-FM, VFR, WC, and WHR). Table 2 showed a higher T-PFM, T-FM, VFR and WC tended to increase TH-BMD, FN-BMD and LS-BMD without control of loading ($P<0.001$). When adjusted with T-weight, T-PFM and T-FM were inversely correlated with BMD in all sites, but for the other two indices (VFR and WC), the level of significance for the associations has decreased and some associations became insignificant (e.g., VFR and FN-BMD, WC and FN-BMD). Similar with the results for general OB indices, after adjusted with trunk-FFM (T-FFM), the four indices (T-PFM, T-FM, VFR, and WC) were still positively and significantly (*P*<0.001) associated with BMD but the regression coefficients of these associations have changed smaller when compared to the unadjusted associations. The associations between WHR and BMD were insignificant under three conditions (unadjusted, adjusted with T-weight and adjusted with T-FFM).

Lower Limb Adiposity Indices and BMD

We further analyzed the associations between lower limb OB indices and BMD. Similar results were observed under three conditions (unadjusted, adjusted with L-weight, and adjusted with L-FFM) except for LS-BMD adjusted with weight. As shown in Table 2, L-PFM and L-FM were positively associated with TH-BMD, FN-BMD and LS-BMD under no adjustment. The adjustment of L-weight reversed the direction of associations except for the associations with LS-BMD. L-PFM and L-FM were positively correlated with BMD at all regions when L-FFM was as covariate (*P*<0.001).

Adiposity Indices and BMD Stratified by Sex

We further performed the above similar analyses in sex-stratified groups (males and females). We found that after adjusting for body weight and FFM, the detected results in both males and females were generally similar to those in the total population (Table 2). The regression coefficients of males were slightly higher than that of females (Table 2).

Discussion

This study represents our first efforts in comprehensively investigating the complex relation between OB indices and OP after adjustment of static mechanical loading effects from weight and FFM. We found that most of the studied OB indices were positively associated with BMD at three skeletal sites, but after the adjustment with weight, some of their associations were still significant but reverse, and after adjusted with FFM, their associations were still positive and significant but their regression coefficients have been changed smaller, compared to the unadjusted associations.

As we mentioned earlier, previous studies have showed both positive and negative effects of OB on bone. One straightforward and important positive effect is that greater FM imposes a greater mechanical stress on bone, and in response, bone mass increases to accommodate the greater loading[5,6]. From physiological point, the biologically active factors which expressed and secreted by adipose tissues (e.g., estrogen, resistin, leptin, adiponectin, and interleukin-6), have two-way effects (positive and negative) on bone[14-16,35-37]. When we analyzed the relation between OB parameters and OP with body weight as a covariate to adjust, the effects of mechanical loading due to fat mass tissue have been eliminated at the meanwhile, and the effects of the above-mentioned physiological factors secreted by adipose tissues were left. Previous study[34] and this study have consistently shown that after adjustment of weight the associations between OB and OP were negative. It seems that the physiological factors secreted by adipose tissues have both positive and negative effects on bone, but taken together the integrative physiological effects are negative in direction.

Since the adjustment of weight would eliminate the static mechanical loading effect due to FM, this study first proposed the correction of FFM to evaluate the combined relation of OB to OP. Weight includes FM, LM and bone mass, i.e., FFM= LM + bone mass. The adjustment of FFM has evaluated the combined effects of OB due to the physiological factors secreted from adipose tissues and the static mechanical loading from FM. The results from our study showed that the combined relation of OB to OP is positive in direction. The physiological factors secreted by adipose tissues have integrative negative effects on bone, but their relation has been changed into positive effects after combined with the effect of static mechanical loading due to FM. Of course, the mechanical loading effects are not only from the gravity of body mass (static) but also from muscle contraction (dynamic). Since there are no available muscle contraction data in evaluating the mechanical loading effects, the mechanical loading effect in this study refers to the static loading effect.

An important advantage of this study is that it includes comprehensive OB indices. A variety of OB related indices have been developed and applied in clinical diagnosis and evaluation, but no extremely perfect index was detected. Each index has its own advantage and disadvantage. For example, BMI is widely used as an index of the degree of obesity, primarily because it is easy to measure, but it is not a perfect parameter to evaluate the distribution of adipose tissue in the body[38]. WC can evaluate the distribution of adipose tissue, but cannot distinguish between subcutaneous and visceral adipose tissues. In addition, few studies have reported the correlations between central OB distribution indices (e.g., WC, WHR and trunk-PFM) and OP[19,31,32], and no study on the lower limb OB indices. As we expected these indices have generally similar association patterns with OP under three adjustment conditions. An additional advantage was that we adopted corresponding indices in trunk and lower limb (T-weight, L-weight, T-FFM and L-FFM) to adjust the loading when we analyzed the associations of central and lower limb adiposity and OP to eliminate excessive correction, instead of the whole body indices[32].

Gender difference is a very important observation in this study. Except for WHR and BMI, the studied parameters, including BMD and three types of OB indices, were different between males and females. Specifically, males have higher BMD, as well as heaver weight and lean mass than females, but females have higher PFM and heaver FM. Although the detected associations in sex-stratified groups were similar to those in sex-stratified groups, the regression coefficients in males was slightly higher than that of females. More interestingly, although FM and PFM of the whole body, trunk and lower limbs were lower in males than in females, VFR was higher in males than in females. This suggests that the fat mass was more probably accumulated in viscera in males than in females. Such accumulation is linked to many cardiovascular health problems.

Apparently, individuals cannot be guided to strengthen bones by increasing body adipose in clinical guidance. Excessive fat accumulation in OB patients imposes a greater mechanical stress on bone, and in response, bone mass increases to accommodate the greater loading. However, OB is linked to many cardiovascular health problems and increased production of adipokines which affects many functions, such as energy intake and expenditure, inflammation, immunity, insulin sensitivity, vascular homeostasis, blood pressure as well as hemostasis[39-43].

In conclusion, this study is the first effort in evaluating the mediation effect of FFM on the relation of OB to OP. These findings suggested that the adjustment of mechanical effects due to body weight or the components (e.g., FM and FFM) is an important issue that should be carefully considered when investigating the relation of OB to OP. Based on previous results and current evidence, the choice of adjustment is depended on the study purpose.

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Authors' Contribution

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References

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. The American journal of medicine 1993;94:646-50.
2. Liu ZH, Zhao YL, Ding GZ, Zhou Y. Epidemiology of primary osteoporosis in China. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 1997;7 Suppl 3:S84-7.
3. Chen P, Li Z, Hu Y. Prevalence of osteoporosis in China: a meta-analysis and systematic review. BMC public health 2016;16:1039.
4. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377-96.
5. Lanyon LE. Analysis of surface bone strain in the calcaneus of sheep during normal locomotion. Strain analysis of the calcaneus. Journal of biomechanics 1973;6:41-9.
6. Lanyon LE. Control of bone architecture by functional load bearing. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research 1992;7 Suppl 2:S369-75.
7. Skerry TM, Bitensky L, Chayen J, Lanyon LE. Early strain-related changes in enzyme activity in osteocytes following bone loading *in vivo*. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 1989;4:783-8.
8. Wozniak M, Fausto A, Carron CP, Meyer DM, Hruska KA. Mechanically strained cells of the osteoblast lineage organize their extracellular matrix through unique sites of alphavbeta3-integrin expression. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2000;15:1731-45.
9. Norvell SM, Ponik SM, Bowen DK, Gerard R, Pavalko FM. Fluid shear stress induction of COX-2 protein and prostaglandin release in cultured MC3T3-E1 osteoblasts does not require intact microfilaments or microtubules. Journal of applied physiology 2004;96:957-66.
10. Pavalko FM, Chen NX, Turner CH, et al. Fluid shear-induced mechanical signaling in MC3T3-E1 osteoblasts requires cytoskeleton-integrin interactions. The American journal of physiology 1998;275:C1591-601.
11. Guignandon A, Boutahar N, Rattner A, Vico L, Lafage-Proust MH. Cyclic strain promotes shuttling of PYK2/Hic-5 complex from focal contacts in osteoblast-like cells. Biochemical and biophysical research communications 2006;343:407-14.
12. Guignandon A, Akhouayri O, Usson Y, et al. Focal contact clustering in osteoblastic cells under mechanical stresses: microgravity and cyclic deformation. Cell communication & adhesion 2003;10:69-83.
13. Li J, Duncan RL, Burr DB, Turner CH. L-type calcium channels mediate mechanically induced bone formation *in vivo*. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2002;17:1795-800.
14. Zou L, Zhang G, Liu L, Chen C, Cao X, Cai J. Caveolin-1 is critical in the proliferative effect of leptin on osteoblasts through the activation of Akt. Molecular medicine reports 2016;14:1915-22.
15. Elefteriou F, Ahn JD, Takeda S, et al. Leptin regulation of bone resorption by the sympathetic nervous system and CART. Nature 2005;434:514-20.
16. Luo XH, Guo LJ, Xie H, et al. Adiponectin stimulates RANKL and inhibits OPG expression in human osteoblasts through the MAPK signaling pathway. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2006;21:1648-56.
17. Kelly OJ, Gilman JC, Boschiero D, Ilich JZ. Osteosarcopenic Obesity: Current Knowledge, Revised Identification Criteria and Treatment Principles. Nutrients 2019;11.
18. Wang J, Yan D, Hou X, et al. Association of adiposity

indices with bone density and bone turnover in the Chinese population. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2017; 28:2645-52.
19. Dytfeld J, Ignaszak-Szczepaniak M, Gowin E, Michalak M, Horst-Sikorska W. Influence of lean and fat mass on bone mineral density (BMD) in postmenopausal women with osteoporosis. Archives of gerontology and geriatrics 2011;53:e237-42.
20. Bilic-Curcic I, Makarovic S, Mihaljevic I, Franceschi M, Jukic T. Bone Mineral Density in Relation to Metabolic Syndrome Components in Postmenopausal Women With Diabetes Mellitus Type 2. Acta clinica Croatica 2017;56:58-63.
21. Hawamdeh ZM, Sheikh-Ali RF, Alsharif A, et al. The influence of aging on the association between adiposity and bone mineral density in Jordanian postmenopausal women. Journal of clinical densitometry: the official journal of the International Society for Clinical Densitometry 2014;17:143-9.
22. Andreoli A, Bazzocchi A, Celi M, et al. Relationship between body composition, body mass index and bone mineral density in a large population of normal, osteopenic and osteoporotic women. La Radiologia medica 2011;116:1115-23.
23. El Hage R, Jacob C, Moussa E, Baddoura R. Relative importance of lean mass and fat mass on bone mineral density in a group of Lebanese postmenopausal women. Journal of clinical densitometry: the official journal of the International Society for Clinical Densitometry 2011;14:326-31.
24. Sotunde OF, Kruger HS, Wright HH, et al. Lean Mass Appears to Be More Strongly Associated with Bone Health than Fat Mass in Urban Black South African Women. The journal of nutrition, health & aging 2015;19:628-36.
25. Lacombe J, Cairns BJ, Green J, et al. The Effects of Age, Adiposity, and Physical Activity on the Risk of Seven Site-Specific Fractures in Postmenopausal Women. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research 2016;31:1559-68.
26. Xia MF, Lin HD, Yan HM, et al. The association of liver fat content and serum alanine aminotransferase with bone mineral density in middle-aged and elderly Chinese men and postmenopausal women. Journal of translational medicine 2016;14:11.
27. Nunez NP, Carpenter CL, Perkins SN, et al. Extreme obesity reduces bone mineral density: complementary evidence from mice and women. Obesity 2007;15:1980-7.
28. Casale M, von Hurst PR, Beck KL, et al. Lean Mass and Body Fat Percentage Are Contradictory Predictors of Bone Mineral Density in Pre-Menopausal Pacific Island Women. Nutrients 2016;8.
29. Halade GV, Rahman MM, Williams PJ, Fernandes G. High fat diet-induced animal model of age-associated obesity and osteoporosis. The Journal of nutritional biochemistry 2010;21:1162-9.
30. Dolan E, Swinton PA, Sale C, Healy A, O'Reilly J. Influence of adipose tissue mass on bone mass in an overweight or obese population: systematic review and meta-analysis. Nutrition reviews 2017;75:858-70.
31. Hind K, Pearce M, Birrell F. Total and Visceral Adiposity Are Associated With Prevalent Vertebral Fracture in Women but Not Men at Age 62 Years: The Newcastle Thousand Families Study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2017;32:1109-15.
32. Bhupathiraju SN, Dawson-Hughes B, Hannan MT, Lichtenstein AH, Tucker KL. Centrally located body fat is associated with lower bone mineral density in older Puerto Rican adults. The American journal of clinical nutrition 2011;94:1063-70.
33. Hsu YH, Venners SA, Terwedow HA, et al. Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. The American journal of clinical nutrition 2006;83:146-54.
34. Zhao LJ, Liu YJ, Liu PY, Hamilton J, Recker RR, Deng HW. Relationship of obesity with osteoporosis. The Journal of clinical endocrinology and metabolism 2007;92:1640-6.
35. Kameda T, Mano H, Yuasa T, et al. Estrogen inhibits bone resorption by directly inducing apoptosis of the bone-resorbing osteoclasts. The Journal of experimental medicine 1997;186:489-95.
36. Bradford PG, Gerace KV, Roland RL, Chrzan BG. Estrogen regulation of apoptosis in osteoblasts. Physiology & behavior 2010;99:181-5.
37. Lecke SB, Morsch DM, Spritzer PM. Leptin and adiponectin in the female life course. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas 2011;44:381-7.
38. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. International journal of obesity 2008;32:959-66.
39. Chaldakov GN, Stankulov IS, Hristova M, Ghenev PI. Adipobiology of disease: adipokines and adipokine-targeted pharmacology. Current pharmaceutical design 2003;9:1023-31.
40. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998;395:763-70.
41. Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 1998;22:1145-58.
42. Spiegelman BM, Flier JS. Adipogenesis and obesity: rounding out the big picture. Cell 1996;87:377-89.
43. Yki-Jarvinen H. Ectopic fat accumulation: an important cause of insulin resistance in humans. Journal of the Royal Society of Medicine 2002;95 Suppl 42:39-45.