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Association between Site-specific Bone Mineral Density and Glucose Homeostasis and Anthropometric Traits in Healthy Men and Women

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Summary

Objective—Patients with type 2 diabetes mellitus have an increased risk of fracture despite normal or increased bone mineral density (BMD). Studies on the relationship of glucose homeostasis with BMD phenotypes have been inconclusive because distinguishing the roles of insulin resistance and hyperglycemia in bone remodeling is challenging. In this study, we sought to define the relationship of site-specific BMD with glucose homeostasis traits and anthropometric traits.

Design/Patients/Measurements—In a cross-sectional study, we examined 787 subjects from the Mexican-American Coronary Artery Disease (MACAD) cohort who had undergone euglycemic-hyperinsulinemic clamps, oral glucose tolerance testing, and dual x-ray absorptiometry. Glucose homeostasis traits included insulinogenic index (IGI30), insulin sensitivity (M value), insulin clearance (MCRI), fasting insulin, fasting glucose and 2-hr glucose. Univariate and multivariate analyses were performed to assess the association of glucose homeostasis and anthropometric traits with site-specific BMD.

Results—Two-hr glucose was negatively associated with arm BMD in women, which remained significant in multivariate analysis ($\beta=-0.15$, $p=0.0015$). Positive correlations between fasting insulin and BMD at weight-bearing sites, including pelvis ($\beta=0.22$, $p<0.0001$) and legs ($\beta=0.17$, $p=0.001$) in women and pelvis ($\beta=0.33$, $p<0.0001$) in men, lost significance after multivariate adjustment. Lean mass exhibited strong independent positive associations with BMD at multiple sites in both sexes.

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Conclusion—Our findings suggest that 1. Anabolic effects of insulin might work via mechanical loading from lean mass; 2. A direct negative effect of increasing glucose might be more prominent at cortical-bone-rich sites in women; 3. Lean mass is a strong positive predictor of bone mass.

Keywords

clinical study; osteoporosis; bone density; body composition; insulin resistance; hyperglycemia; diabetes complications

Introduction

Osteoporosis and type 2 diabetes (T2DM) are among the most common complex diseases in ageing societies. Diabetes not only causes vascular complications but also is strongly associated with musculoskeletal complications. Several large epidemiologic studies have observed significantly increased risk of fracture in patients with diabetes.[1] The Women's Health Initiative Observational Cohort study noted postmenopausal women with T2DM had a 20% increased risk of any fracture during 7 years of follow-up.[2] A meta-analysis including almost 840,000 men and women also found that patients with T2DM had a 70% increased risk of hip fracture.[3]

Despite the increased fracture risk, patients with T2DM have normal or even higher bone mineral density (BMD) at vertebral and femoral bones.[2] This counterintuitive phenomenon complicates assesment of skeletal health in patients with T2DM in current practice, which is heavily dependent on hip or vertebral BMD. This discrepancy raises the possibility that impairment in bone quality and not bone quantity increases the risk of fracture in T2DM.

Various factors may contribute to the pathophysiology of skeletal impairment in T2DM. Advanced glycation end-products (AGEs), by-products of unregulated glycation in the setting of hyperglycemia, were shown to disrupt crosslinking of collagen in bone.[4] Oral hypoglycemic agents such as thiazolidinediones[5] and sodium-glucose cotransporter 2 inhibitors[6] have also been directly or indirectly associated with reduced BMD and increased risk of fracture. Deleterious effects of hyperglycemia as well as glucose-lowering agents suggest a complex relationship between glucose and bone. In addition, patients with T2DM have been found to have a low bone turnover rate, and increased sclerostin levels, suggesting suppressed Wnt signaling pathways, and therefore suppressed bone formation.[7]

The effects of insulin resistance and hyperglycemia, hallmarks of T2DM, on bone are not clearly understood, and the studies that examined the relationships among glucose homeostasis and BMD phenotypes have been inconclusive. Observational studies relating BMD to glucose homeostasis have used traits derived from fasting metabolic panels, oral or intravenous glucose tolerance tests. Insulin resistance measured by the homeostasis model assessment of insulin resistance (HOMA-IR) index had positive,[8,9] negative,[10,11] or no[12] relationship with vertebral or femoral BMD. Abrahamsen et al. reported an inverse relationship between femoral and whole body BMD and insulin sensitivity measured using intravenous glucose tolerance testing in 55 non-diabetic patients with ischemic heart disease.[13] Lastly, a study from Hungary performed euglycemic-hyperinsulinemic clamps in 20 healthy and 51 glucose intolerant female subjects, and reported a negative relationship of

total body glucose utilization with lumbar and femoral BMD in the healthy group but not in subjects with impaired glucose tolerance.[14]

Challenges to interpreting this literature arise from heterogenous cohorts with secondary factors affecting skeletal health, small numbers of subjects, and use of diverse measurements such as fasting glucose, fasting insulin, HOMA-IR, or calculated insulin sensitivity, which are not the best assessments of glucose homeostasis.[15]

The primary aim of our study was to clearly define the relationship of site-specific BMD with anthropometric traits and glucose homeostasis traits measured by both euglycemic-hyperinsulinemic clamps and a multi-timepoint oral glucose tolerance test.

Materials and Methods

Subjects

Metabolic and BMD phenotypes were assessed in the Mexican-American Coronary Artery Disease (MACAD) cohort, a study of Mexican-American families from Los Angeles.[16] To be classified as Mexican and qualify for the study, subjects had to report at least three grandparents of Mexican origin. In the present study, 787 subjects from 203 families (339 male and 448 female) with BMD values were included, comprising adult offspring (age 18 or older) of probands with coronary artery disease, and the spouses of those offspring (if available). By design, detailed phenotyping was performed only in the offspring and spouses, who were free of overt diabetes or cardiovascular disease, thus avoiding secondary changes in phenotype caused by overt disease. Patients were free of major medical illness and none were taking glucocorticoids or antihyperglycemic agents that could affect glucose homeostasis. Phenotyping procedures revealed 41 subjects (5.2% of the cohort) to have previously undiagnosed diabetes; these subjects were not excluded because their diabetes was mild and they were not taking antidiabetic medications. All studies were approved by Human Subjects Protection Institutional Review Boards at UCLA, Cedars-Sinai Medical Center, and Harbor-UCLA. All subjects gave informed consent before participation.

Phenotyping

Subjects underwent a three-day phenotyping protocol. On one day, fasting blood was obtained, followed by a 75-g oral glucose tolerance test (OGTT). On a separate day, a dual x-ray absorptiometry (DXA) scan was performed, and on a further day, a euglycemic-hyperinsulinemic clamp was performed.

The primary goal of the DXA scan was to assess body fat distribution (fat mass and lean mass). The regions of interest (ROIs) of these whole-body scans were those frequently used for body composition assessment, yet also provide accurate information on BMD.[17] In the current study, we focused on arm ROIs that included the entire left and right arms (including hands), leg ROIs that included the entire left and right legs (feet included), pelvis ROI defined superiorly by a horizontal line (pelvis line) across the upper boundaries of the iliac crests and inferiorly by two angled lines passing through the femoral necks, and lumbar spine ROI defined by vertical lines lateral to the vertebral bones, a line at the T12-L1 disc space, and the pelvis line. We focused on these regions to examine BMD at these sites as

they would be of highest interest clinically. Regional BMD from whole body DXA scans has been found to correlate well with sites typically measured by site-specific DXA, with high correlation between lumbar spine region and AP spine BMD (r^2=0.92), arm region and total wrist BMD (r^2=0.83), arm region and mid-radius BMD (r^2=0.75) and more modest correlation at the femoral neck (r^2=0.69 with leg regional BMD and r^2=0.6–0.7 with pelvis region BMD).[18,19] In appendicular bone, an average of right and left arm or leg BMD was calculated and used for assessment.

During the euglycemic-hyperinsulinemic clamp,[20] a priming dose of human insulin (Novolin; Novo Nordisk, Clayton, NC) was given and followed by infusion for 120 min at a constant rate (60 mU $\cdot$ m^{-2} $\cdot$ min^{-1}) to achieve a plasma insulin concentration of ≥ 600 pmol/L. Blood was sampled every 5 min, and the rate of 20% dextrose coinfused was adjusted to maintain plasma glucose concentrations at 5.3–5.6 mmol/L. The glucose infusion rate (M value) during the last 30 minutes of steady-state glucose and insulin levels reflects glucose uptake by all tissues of the body (mainly insulin-mediated glucose uptake in muscle) and is directly correlated with tissue insulin sensitivity. Often, an insulin sensitivity index (M/I) is calculated as M divided by the steady state plasma insulin level (I). In this study, to clearly distinguish between insulin sensitivity and insulin clearance in multivariate analyses, we relied on M as the measure of insulin sensitivity in our primary analyses because the calculations of M/I and insulin clearance both use steady-state insulin in the denominator. The metabolic clearance rate of insulin (MCRI) was calculated as the insulin infusion rate divided by the steady state insulin level of the euglycemic clamp, as previously described.[20,21]

Insulinogenic index at 30 minutes (IGI30), a commonly used index of acute insulin secretion, was calculated from the OGTT data as the change in insulin (0 to 30 min) divided by change in glucose (0 to 30 min).

We examined anthropometric indices including BMI and waist-to-hip ratio (WHR) and total lean mass and total fat mass derived from the DXA scans.

Statistical Analysis

Log-transformed (BMI, IGI30, fasting insulin, 2-hr glucose values) or square-root transformed (total fat mass, M value, MCRI) trait values were used to normalize the distribution for statistical analysis. Categorical traits (sex, diabetes, and current smoking status) were coded as 0 and 1 prior to inclusion in analyses. T-tests for quantitative traits and chi square tests for categorical traits were used to compare traits between men and women.

All of the following regression analyses were performed separately for male and female subjects, considering the significant gender differences in body composition and skeletal size.[22] Generalized estimating equations (GEE) were used to assess the effects of single traits (univariate analyses) or joint effects of multiple traits (multivariate analyses) on BMD, adjusting for familial relationships. The weighted GEE1[23] was computed assuming an exchangeable correlation structure and using the sandwich estimator of the variance to account for familial correlation present in family data. GEE was used to derive standardized regression coefficients, which in any one regression equation are measured on the same

scale, with a mean of zero and a standard deviation of one. They are then directly comparable to one another, with the largest coefficient indicating which independent variable has the greatest association with the dependent variable.

Using GEE to adjust for familial relationships, we computed univariate correlation coefficients between each regional BMD (pelvic, lumbar spine (LS), arm and leg) and glucose homeostasis indices and body composition variables. At each BMD site, the variables with statistical significance in univariate analyses were selected for subsequent multivariate analysis. Multiple regression analyses were performed to identify the variables independently associated with each regional BMD. Given that 13 variables were tested in the univariate analyses, only variables meeting a multiple testing corrected P value cutoff of 0.004 (0.05/13) were advanced to multivariate analyses. In the multivariate analyses, P values of <0.05 were considered significant.

To assess for multicollinearity within the regression models, variance inflation factors (VIF) were calculated. VIF less than 5 are acceptable while VIF above 10 indicate poorly estimated regression coefficients due to multicollinearity.

Results

The clinical characteristics of the 787 subjects are shown in Table 1. Subjects were young, with median age of 34 years, and 57% were women. Body composition was significantly different in men and women, with women having higher fat mass. Men had significantly higher lean mass and bone density at the pelvis, arms and legs. The metabolic profiles were also different by sex. Men tended to have higher insulin sensitivity (M value); however, insulinogenic index (IGI30) was significantly higher in women. Previously unknown diabetes was revealed by oral glucose tolerance testing in 5.0% of men and 5.4% of women. Given that they had mild diabetes and were not taking antidiabetic agents when phenotyped, these subjects were included in the analyses herein.

Univariate analyses demonstrated positive correlations between fasting insulin and BMD at the pelvis and legs in women, and at the pelvis in men (Table 2). In women, insulinogenic index (IGI30) was also positively associated with pelvis and leg BMD. There was no significant correlation of IGI30 or MCRI with BMD at any site in men. Insulin sensitivity (M value), however, was negatively correlated with BMD at the pelvis in men. In addition, 2-hr glucose was inversely associated with arm BMD in women. Male subjects did not show any significant relationship between 2-hr glucose and BMD. In terms of body composition, total lean mass was positively correlated with BMD at all sites in both sexes, only missing statistical significance at LS in men. Total fat mass also showed positive association but only at weight-bearing sites such as pelvis and legs in women and pelvis in men.

BMD traits that were correlated with more than one glucose homeostasis or anthropometric trait were subjected to multivariate analyses. In multivariate analyses, the positive association of fasting insulin and BMD at weight-bearing sites disappeared after adjustment for body composition and other significant glucose homeostasis indices (Tables 3 and 4). The negative association of 2-hr glucose with arm BMD in women remained significant.

Other glucose homeostasis indices such as IGI30, M value, MCRI, or fasting glucose did not demonstrate any significant relationship in multivariate analysis. In addition, total lean mass persistently showed positive correlation with BMD at all sites, but total fat mass was not significant after adjustment for total lean mass.

All of the above analyses were repeated with exclusion of the subjects with diabetes, which yielded essentially the same results (data not shown).

Discussion

Our study included the largest number of subjects with euglycemic-hyperinsulinemic clamps used to examine the relationship between glucose homeostasis and bone mineral density at different sites. From these data, the direction of causality between bone and glucose homeostasis remains to be determined.

Recent studies have suggested bone is an endocrine organ that plays a role in metabolism as osteocytes release undercarboxylated osteocalcin, which enhances insulin secretion from beta-cells and increases insulin sensitivity.[24] In the so-called “bone-pancreas loop,” insulin works as an anabolic hormone on bone remodeling, stimulating osteoblast differentiation and proliferation as well as osteoclastogenesis through receptor activator of nuclear factor kappa-B ligand expression to maintain bone turnover.[25] However, the anabolic effect of insulin does not seem to be absolutely required in bone remodeling, given the observation of normal bone density in bone-specific insulin receptor (IR) knock-out mice, which may be explained by increased insulin-like growth factor-1 signaling.[26]

In our study, we observed positive correlation between fasting insulin and BMD in both sexes. Interestingly, the positive association was only noted at the weight-bearing sites such as pelvis and legs in women, and pelvis in men. This positive association from univariate analysis, however, disappeared after the adjustment for other significant variables including body composition, and only lean mass remained significant in multivariate analysis. We can postulate that insulin might exert anabolic effects on bone remodeling but through mechanical stimuli generated by lean mass. Furthermore, insulin might sensitize the response to mechanical loading in bone, which needs to be further studied.

In addition, we found a significant negative association between 2-hr glucose and arm BMD in univariate analysis. This association was only noted in women and persisted after adjusting for other glucose homeostasis indices and body composition in multivariate analysis. Without any significant association with insulin sensitivity (M value), a direct harmful effect of increasing glucose levels on bone mass can be postulated.

Two mechanisms whereby chronic hyperglycemia leads to microvascular complications are the polyol pathway (aldose reductase converts glucose to sorbitol, which damages tissues) and accumulation of advanced glycation end-products (AGEs). Studies have implicated both of these as having adverse effects on bone. Galactose-fed rats exhibited suppressed osteocalcin and bone loss, which was prevented by treating with an aldose reductase inhibitor, suggesting the polyol pathway plays a negative role in bone metabolism.[27] In a diabetic mouse model with induced periodontitis, blockade of receptors for AGEs decreased

alveloar bone loss and inflammatory markers including tissue-destructive matrix metalloproteinases.[28]

The sex- and site-specific associations in our study are not fully understood. Sex hormones play a critical role in bone remodeling, contributing significantly to sexual dimorphism in bone phenotypes as they interact with the growth hormone axis and mechanical stimuli.[29] In addition, estrogen enhances glucose uptake and modulates glucose metabolism in muscle and fat.[30] We can speculate that sex hormones also affect glucose metabolism in bone; estrogen may facilitate glucose uptake in bone tissue, augmenting the negative effect of increasing glucose in women.

In terms of site-specific associations with glucose homeostasis, T2DM increases the risk of fracture in cortical-bone-rich appendicular bone.[31] A study in women found that diabetes was associated with unfavorable cortical bone microarchitecture; higher glucose was associated with lower cortical volumetric BMD.[12] In line with these findings, we observed negative association between 2-hr glucose and BMD only at cortical-bone-rich appendicular bone such as the arms. Our findings suggest that cortical and trabecular microarchitectural compartments might respond differently to increasing glucose levels.

We also examined the relationship of lean and fat mass with BMD at each site. Lean body mass demonstrated positive correlations with BMD at all sites, just missing statistical significance at LS in men; these associations remained significant in multivariate analyses. Our finding is consistent with large epidemiologic studies. A meta-analyses including 20,226 men and women reported lean mass was correlated positively with femoral neck BMD,[32] and subsequent cohort studies demonstrated that decreased lean mass is an independent risk factor for osteoporosis and fracture.[33] The underlying mechanism of the positive effect of lean mass on bone is likely mechanical in nature. The skeleton responds to mechanical loading with building, maintaining or removing bone. Osteocytes in lacunar-canaliculi networks play an important role as mechano-sensing cells to translate mechanical stimuli to biochemical response.[34] More recent studies suggest that muscle might directly affect bone, for example, by releasing peptides such as irisin.[35]

Fat mass was positively correlated with BMD, especially at weight-bearing sites such as the pelvis and legs in women, and pelvis in men in univariate analysis, which became insignificant after adjustment for lean mass. Our results are consistent with early studies suggesting fat mass may be beneficial to bone mass as a source of passive mechanical loading.[36] However, recent studies with adjustment for body weight or lean mass suggested that fat might be harmful to bone.[37] Studies using magnetic resonance spectroscopy found bone marrow fat to be an independent negative determinant of BMD.[38] In the current study, we could not discern different fat depots, especially bone marrow fat, and fat may exert endocrine or paracrine effects by releasing adipokines, which needs to be further studied.

Our study has several strengths. We measured glucose homeostasis indices in over 750 patients using euglycemic-hyperinsulinemic clamps. In addtion, subjects did not have confounding co-morbidities affecting skeletal phenotypes, which enabled us to assess properly the relationship of glucose metabolism with bone mineral density. A limitation of

our study is that it was cross-sectional and thus could not establish causal relationships between glucose impairment and skeletal health. Also, the findings might not be generalizable to other ethnicities since the subjects were solely Mexican-American. Unfortunately, our cohort lacks measurements of sex hormones, which might have a critical role in the relationship of glucose homeostasis to bone remodeling. Given the relatively young average age of the cohort, there were too few older women to allow analyses stratifying by menopausal status. Markers of bone turnover and BMD measurements at the total hip or femoral neck were not available.

In conclusion, our findings suggest that insulin might exert its anabolic effect through mechanical stimuli from lean mass. We observed a direct negative effect of 2-hr glucose that was more pronounced at cortical-bone-dominant sites in women, which needs to be further studied. Lastly, we confirm that lean mass is a strong predictor of bone mass, highlighting the clinical importance of sarcopenia in assessing skeletal health and risk of fracture.

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Table 1

Clinical characteristics

Trait	Men	Women	p-value
Number (%)	339 (43%)	448 (57%)	n/a
Anthropometry			
Age (yr)	34 (14)	34 (13)	0.98
Current smoking (%)	24.8	10.9	<0.0001
Height (cm)	169.5 (7.5)	157.2 (7.0)	<0.0001
Weight (kg)	83.3 (17.4)	72.2 (17.5)	<0.0001
BMI (kg/m^2)	28.53 (5.39)	28.23 (6.78)	0.79
Waist-hip ratio	0.94 (0.07)	0.85 (0.09)	<0.0001
Lean body mass (kg)	61.93 (9.64)	43.35 (8.60)	<0.0001
Fat body mass (kg)	20.99 (8.70)	26.83 (11.34)	<0.0001
Glucose homeostasis indices			
Fasting glucose (mmol/L)	5.27 (0.72)	5.02 (0.70)	<0.0001
2 hrs glucose (mmol/L)	5.88 (2.67)	6.36 (2.36)	0.0009
Fasting insulin (pmol/L)	67.7 (45.9)	72.3 (45.1)	0.97
IGI30 ($pmol \cdot L^{-1} \cdot mmol^{-1} \cdot L$)	116.7 (118.9)	154.6 (160.0)	0.0005
M value ($\mu mol \cdot min^{-1} \cdot m^{-2}$)	1429.7 (884.1)	1187.6 (742.3)	0.0051
MCRI ($mL \cdot m^{-2} \cdot min^{-1}$)	473.69 (151.21)	471.20 (142.80)	0.86
T2DM (OGTT) (%)	5.0	5.4	0.87
BMD (g/cm^2)			
Arm	0.86 (0.07)	0.72 (0.06)	<0.0001
Leg	1.29 (0.13)	1.12 (0.11)	<0.0001
Lumbar spine	0.99 (0.15)	1.01 (0.16)	0.039
Pelvis	1.28 (0.20)	1.24 (0.18)	<0.0001

Quantitative traits are presented as median (interquartile range (IQR)). Categorical traits (current smoking, diabetes) are presented as percent.

Table 2

Association of site-specific BMD with anthropometric and glucose homeostasis traits

	Female				Male			
BMD	**Arm**	**Leg**	**Pelvis**	**LS**	**Arm**	**Leg**	**Pelvis**	**LS**
Age	−0.142 (0.014)	−0.115 (0.035)	−0.084 (0.169)	−0.172 (0.005)	−0.022 (0.720)	**−0.154 (0.003)**	−0.007 (0.916)	−0.059 (0.441)
Current Smoking	0.273 (0.064)	0.228 (0.233)	0.111 (0.522)	−0.072 (0.621)	0.177 (0.144)	0.032 (0.806)	0.004 (0.974)	−0.057 (0.684)
BMI	0.037 (0.439)	**0.285 (<0.0001)**	**0.309 (<0.0001)**	0.056 (0.214)	0.150 (0.008)	**0.257 (<0.0001)**	**0.451 (<0.0001)**	0.064 (0.223)
Waist-Hip ratio	−0.031 (0.573)	0.042 (0.421)	0.094 (0.096)	−0.095 (0.095)	0.022 (0.698)	0.008 (0.894)	**0.232 (0.0002)**	−0.047 (0.526)
Lean body mass	**0.292 (<0.0001)**	**0.504 (<0.0001)**	**0.412 (<0.0001)**	**0.183 (<0.0001)**	**0.351 (<0.0001)**	**0.442 (<0.0001)**	**0.493 (<0.0001)**	0.146 (0.005)
Fat body mass	−0.010 (0.853)	**0.257 (<0.0001)**	**0.301 (<0.0001)**	0.076 (0.094)	0.004 (0.954)	0.147 (0.015)	**0.360 (<0.0001)**	0.013 (0.811)
Fasting glucose	−0.027 (0.601)	−0.001 (0.979)	0.069 (0.096)	−0.035 (0.434)	0.062 (0.285)	0.079 (0.154)	**0.194 (0.0019)**	0.085 (0.125)
2 hrs glucose	**−0.167 (0.0007)**	−0.115 (0.017)	−0.056 (0.201)	−0.134 (0.006)	−0.135 (0.015)	−0.064 (0.200)	0.065 (0.232)	−0.078 (0.134)
Fasting plasma insulin	−0.007 (0.887)	**0.167 (0.001)**	**0.223 (<0.0001)**	0.051 (0.254)	−0.008 (0.876)	0.109 (0.097)	**0.331 (<0.0001)**	−0.016 (0.776)
IGI30	0.142 (0.007)	**0.194 (<0.0001)**	**0.164 (0.001)**	0.109 (0.019)	−0.033 (0.611)	0.008 (0.903)	0.042 (0.513)	0.020 (0.724)
M value	0.097 (0.032)	−0.023 (0.574)	−0.123 (0.005)	−0.002 (0.967)	0.102 (0.092)	0.025 (0.676)	**−0.254 (<0.0001)**	0.021 (0.728)
MCRI	−0.020 (0.726)	−0.145 (0.008)	−0.121 (0.036)	0.002 (0.968)	0.085 (0.122)	−0.012 (0.864)	−0.110 (0.079)	0.047 (0.379)
T2DM (OGTT)	−0.438 (0.051)	−0.007 (0.974)	0.059 (0.793)	−0.299 (0.233)	−0.195 (0.545)	−0.246 (0.158)	−0.154 (0.420)	−0.210 (0.387)

Data are correlation coefficients (p-value), with significance (bolded) as p <0.004 (see Methods).

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Table 3

Multivariate analyses in women

Domain/Trait	Standardized coefficient	Standard error	95% confidence interval		P-value
Arm					
Lean body mass	0.186	0.045	0.097	0.275	<0.0001
2-hr glucose	−0.148	0.046	−0.238	−0.056	0.0015
Leg					
BMI	−0.024	0.102	−0.223	0.175	0.814
Lean body mass	0.659	0.072	0.518	0.801	<0.0001
Fat body mass	−0.167	0.110	−0.382	0.048	0.129
Fasting insulin	−0.073	0.055	−0.182	0.035	0.186
IGI30	0.089	0.048	−0.005	0.184	0.064
Pelvis					
BMI	0.148	0.133	−0.113	0.409	0.267
Lean body mass	0.360	0.071	0.220	0.499	<0.0001
Fat body mass	−0.057	0.128	−0.309	0.195	0.658
Fasting insulin	−0.011	0.057	−0.123	0.101	0.844
IGI30	0.072	0.045	−0.016	0.160	0.110

For each BMD site, results for all independent variables included in the multiple regression model are displayed. Variance inflation factors were 1.00 for both variables for arm; ranged from 1.07 to 5.43 for leg; and 1.07 to 5.43 for pelvis.

Table 4

Multivariate analyses in men

Domain/Trait	Standardized coefficient	Standard error	95% confidence interval		P-value
Arm					
Lean body mass[a]	0.351	0.051	0.251	0.452	<0.0001
Leg					
Age	−0.157	0.047	−0.248	−0.065	0.0008
BMI	−0.122	0.076	−0.270	0.026	0.107
Lean body mass	0.534	0.074	0.389	0.679	<0.0001
Pelvis					
BMI	0.266	0.119	0.033	0.499	0.025
Waist-hip ratio	0.029	0.067	−0.101	0.159	0.662
Lean body mass	0.338	0.078	0.185	0.490	<0.0001
Fat body mass	−0.155	0.099	−0.348	0.039	0.117
Fasting glucose	0.045	0.061	−0.075	0.165	0.462
Fasting insulin	0.063	0.066	−0.066	0.193	0.337
M value	−0.029	0.068	−0.162	0.104	0.668

For each BMD site, results for all independent variables included in the multiple regression model are displayed. Variance inflation factors ranged from 1.02 to 2.21 for leg; and 1.13 to 5.67 for pelvis.

[a]The univariate result for arm is presented for completeness.