0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(11):4161–4164

doi: 10.1210/jc.2007-0757

Bone Mineral Density in Adults with the Metabolic Syndrome: Analysis in a Population-Based U.S. Sample

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Background: The metabolic syndrome is associated with low-grade inflammation. It has been suggested that proinflammatory cytokines and low-grade systemic inflammation activate bone resorption and may lead to reduced bone mineral density (BMD), but no previous studies have evaluated the association between the metabolic syndrome and BMD. We examined this relationship in a representative U.S. population-based sample from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994).

Methods: We identified adult subjects enrolled in NHANES III with the metabolic syndrome as defined by the criteria of the Adult Treatment Panel III. We conducted a cross-sectional analysis of femoral neck BMD (FN-BMD) for subjects with and without the metabolic syndrome. Analyses were adjusted for relevant covariates and stratified by quintile of body mass index.

Results: Among 8197 persons at least 20 yr old who underwent FN-BMD measurement, 1773 (22%) had the metabolic syndrome. After multivariable adjustment, FN-BMD was higher among subjects with the metabolic syndrome (0.86 g/cm^2) than those without (0.80 g/cm^2; $P < 0.0001$). When stratified by body mass index, FN-BMD was similar between subjects with and without the metabolic syndrome. Adjusted FN-BMD increased with additional components of the metabolic syndrome ($P < 0.0001$ for trend), and there was a significant positive association with abdominal obesity ($P < 0.0001$). A subgroup of subjects with diabetes had higher FM-BMD than those without, independent of abdominal obesity.

Conclusions: In NHANES III, the metabolic syndrome was not associated with reduced FN-BMD. **(*J Clin Endocrinol Metab* 92: 4161–4164, 2007)**

THE METABOLIC SYNDROME is a cluster of conditions with detrimental effects on cardiovascular health and a known association with low-grade inflammation (1, 2). The metabolic syndrome includes obesity, dyslipidemia, impaired glucose tolerance, and hypertension (3). The proinflammatory state associated with the metabolic syndrome may lead to a reduction in bone mass (4). However, obesity or high body mass index (BMI) is known to have a protective effect against osteoporosis (5). A recent prospective study demonstrated that the metabolic syndrome reduced risks of nonvertebral fractures (6).

Osteoporosis is common in various inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis (7). Proinflammatory cytokines up-regulate receptor activator of nuclear factor-κB ligand, leading to increased bone resorption and osteoporosis (8–10). C-reactive protein (CRP) is a systemic inflammatory marker regulated by cytokines such as IL-1, IL-6, and TNF-α. Some have suggested that an elevated CRP is associated with osteoporosis and nontraumatic fracture (4, 11). The systemic inflammation related to the metabolic syndrome might activate bone resorption and lead to reduced bone mineral density (BMD).

First Published Online September 4, 2007

Abbreviations: BMD, Bone mineral density; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DXA, dual-energy x-ray absorptiometry; FG, fasting glucose; FN-BMD, femoral neck BMD; HDL, high-density lipoprotein; NHANES III, Third National Health and Nutrition Examination Survey.

Despite the association between the metabolic syndrome and obesity, the hypothesized underlying inflammatory state may lead to reduced BMD. However, no prior studies have directly evaluated the association with the metabolic syndrome and osteoporosis. Thus, we performed an analysis of the relationship between the metabolic syndrome and BMD in a representative U.S. sample from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994).

Subjects and Methods

Data source and subjects

NHANES III was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention between 1988 and 1994. The sample represents the civilian, noninstitutionalized population of the United States (12). We identified subjects aged 20 yr and older with the metabolic syndrome according to the criteria of the Adult Treatment Panel III using NHANES III (3). Subjects were considered to have the metabolic syndrome if they had three or more of the following abnormalities: abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women); hypertriglyceridemia ≥ 150 mg/dl; low high-density lipoprotein (HDL) cholesterol < 40 mg/dl; high blood pressure ≥ 130/85 mm Hg or use of antihypertensive medication; or high fasting glucose ≥ 110 mg/dl or use of antidiabetic medication (insulin or oral agents). Femoral neck BMD (FN-BMD) measured with dual-energy x-ray absorptiometry (DXA) was compared for the cohorts with and without the metabolic syndrome. Subjects without a DXA measurement were excluded from the analysis.

Covariates

Demographic and medical risk factors predictive of reduced BMD were considered potential confounders. In addition to gender, age, and race, other important covariates included: BMI (kilograms per square meter), smoking (current *vs.* former or never), alcohol intake (number of drinks in the previous month), physical activity (metabolic equivalents/

TABLE 1. Baseline characteristics of subjects by presence of the metabolic syndrome (n = 8197)

Variables	Metabolic syndrome (n = 1773)	No metabolic syndrome (n = 6424)
Age (yr)	56.7 (±16.7)[a]	44.2 (±8.7)
Female	995 (56.1)[a]	3176 (49.4)
White	851 (48.0)[a]	2552 (39.7)
BMI (kg/m^2)	31.1 (±5.3)[a]	25.9 (±5.0)
Current smoker	369 (20.8)[a]	1807 (28.1)
Alcohol (drinks/month)	10.2 (±33.0)	16.5 (±40.5)
Physical activity (METs/month)	65.5 (±96.0)[a]	91.5 (±120.9)
Fracture of hip or wrist	139 (7.8)	515 (8.0)
Poor health, self-reported	123 (6.9)[a]	200 (3.1)
Menopause	686 (70.1)[a]	1138 (36.3)
Serum 25-hydroxy vitamin D (ng/ml)	24.4 (±9.9)[a]	26.1 (±11.2)
Total calcium intake (mg/d)	711.8 (±488.0)	790.3 (±559.5)
Oral glucocorticoid use	39 (2.2)[a]	79 (1.2)
Thiazide use	285 (16.0)[a]	212 (3.3)
Hormone replacement therapy use	57 (3.2)[a]	124 (1.9)
Statin use	38 (2.1)[a]	40 (0.6)
β-Blocker use	214 (12.1)[a]	194 (3.0)
CRP (mg/dl)	0.53 (±0.97)[a]	0.26 (±0.75)
Congestive heart failure	107 (6.0)[a]	142 (2.2)
Cerebral vascular accident	90 (5.1)[a]	116 (1.8)
COPD	245 (13.8)[a]	672 (10.5)
Nonskin cancer	91 (5.1)[a]	205 (3.2)

Values are shown as n (%) or mean (±SD).

[a] $P \leq 0.01$, compared with subjects without the metabolic syndrome.

month), history of hip or wrist fracture, poor self-reported health, and menopause status. Relevant chronic medical conditions included congestive heart failure, cerebrovascular accidents, chronic obstructive pulmonary disease (COPD), and nonskin cancer. We also examined serum levels of 25-hydroxyvitamin D (nanograms per milliliter), and serum CRP (milligrams per deciliter) as confounders (13). BMI was not included in the analysis because it generally parallels abdominal obesity for definition of the metabolic syndrome. However, secondary analyses were stratified by BMI.

We considered use of potentially relevant medications such as oral glucocorticoids, thiazide diuretics, hormone replacement therapy, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), and β-blockers. Users of osteoporosis therapy such as calcitonin, bisphosphonate, or selective estrogen receptor modulators were sparse, so we could not control for these medications. Total calcium intake (milligrams per day) was calculated by summing the average dietary intake plus the supplements. Medication use was ascertained by asking, "Have you taken or used any medicines for which a doctor's or dentist's prescription is needed in the past month?" and each medication container was checked by the interviewer. Participants reported the duration of use for each medication.

BMD

All analyses considered FN-BMD as the primary outcome and were cross-sectional comparisons. DXA (QDR 1000; Hologic, Waltham, MA) was used with appropriate quality control measures (13). The BMDs of other anatomic sites were not available in NHANES III.

Statistical analysis

Baseline characteristics of subjects with the metabolic syndrome and controls were compared by Student's *t* test for continuous variables and Pearson's χ^2 test for categorical variables. We used a multivariable linear regression model to assess the relationship between the metabolic syndrome and FN-BMD. The FN-BMD was also examined for each specific component of the metabolic syndrome and by the number of components present. We repeated our analyses using more parsimonious models, excluding a history of fractures and CRP levels. $P < 0.05$ (two sided) was considered statistically significant.

Results

Among 17,872 participants 20 yr old or older, we identified 8,197 eligible people who underwent DXA measurement. A total of 1773 (22%) subjects had the metabolic syndrome and 6424 did not. The baseline characteristics of subjects with and without the metabolic syndrome were different (Table 1). Compared with controls, subjects with the metabolic syndrome were older; were more female and white; less frequently used tobacco; reported less physical activity, had worse health; were more frequently menopausal; had lower serum 25-hydroxyvitamin D and higher CRP levels; and were more likely to have congestive heart failure, cerebrovascular disease, COPD, and cancer. In addition, those with the metabolic syndrome more frequently used oral glucocorticoids, thiazides, hormone replacement therapy, statins, and

TABLE 2. Femoral neck BMD for persons with and without the metabolic syndrome by quintile of BMI[a]

	n	Group	Metabolic syndrome (n = 1773)	No metabolic syndrome (n = 6421)	*P* value
All subjects	8149	Unadjusted	0.83 (0.82, 0.84)	0.84 (0.84, 0.85)	0.0020
		Age and gender adjusted	0.89 (0.88, 0.89)	0.83 (0.83, 0.83)	<0.0001
		Fully adjusted[b]	0.86 (0.85, 0.86)	0.80 (0.80, 0.80)	<0.0001
BMI by quintile (kg/m^2)					
<25.0	3251	Unadjusted	0.69 (0.67, 0.72)	0.80 (0.80, 0.81)	<0.0001
		Age and gender adjusted	0.82 (0.80, 0.84)	0.80 (0.79, 0.80)	0.045
		Fully adjusted[b]	0.78 (0.76 0.80)	0.77 (0.77, 0.78)	0.7
25.0–29.9	2900	Unadjusted	0.78 (0.77, 0.80)	0.87 (0.86, 0.87)	<0.0001
		Age and gender adjusted	0.85 (0.84, 0.86)	0.85 (0.84, 0.86)	0.9
		Fully adjusted[b]	0.81 (0.80, 0.82)	0.82 (0.82, 0.83)	0.3
30.0–34.9	1321	Unadjusted	0.86 (0.85, 0.87)	0.90 (0.89, 0.91)	<0.0001
		Age and gender adjusted	0.89 (0.88, 0.90)	0.88 (0.87, 0.89)	0.3
		Fully adjusted[b]	0.92 (0.90, 0.93)	0.86 (0.85, 0.87)	0.003
≥35	722	Unadjusted	0.92 (0.91, 0.94)	0.95 (0.93, 0.97)	0.0045
		Age and gender adjusted	0.94 (0.93, 0.96)	0.94 (0.92, 0.95)	0.6
		Fully adjusted[b]	0.92 (0.90, 0.94)	0.90 (0.88, 0.92)	0.6

[a] Least square mean (95% confidence interval) (g/cm^2).

[b] Age, gender, race, smoking, alcohol, physical activity (METs/month), self-reported health, menopause, serum 25-hydroxyvitamin D, total calcium intake, glucocorticoids, thiazide, hormone replacement therapy, statin, β -blocker use, CRP level, and comorbidity (congestive heart failure, cerebral vascular accident, COPD, and cancer).

TABLE 3. Femoral neck BMD for persons with different number of components of the metabolic syndrome[a]

No. of components	0 (n = 2472)	1 (n = 2262)	2 (n = 1690)	3 (n = 1113)	4 (n = 517)	5 (n = 143)	*P* value[b]
Unadjusted	0.85 (0.85, 0.86)	0.84 (0.83, 0.85)	0.84 (0.83, 0.85)	0.84 (0.83, 0.85)	0.81 (0.80, 0.83)	0.82 (0.79, 0.85)	<0.0001
Age and gender adjusted	0.80 (0.80, 0.81)	0.83 (0.83, 0.84)	0.86 (0.85, 0.87)	0.89 (0.88, 0.89)	0.89 (0.88, 0.90)	0.92 (0.90, 0.94)	<0.0001
Fully adjusted[c]	0.78 (0.77, 0.78)	0.80 (0.79, 0.81)	0.83 (0.82, 0.84)	0.86 (0.85, 0.87)	0.86 (0.85, 0.87)	0.90 (0.88, 0.91)	<0.0001

[a] Least square mean (95% confidence interval) (g/cm^2).
[b] *P* value for trend.
[c] Age, gender, race, smoking, alcohol, physical activity (METs/month), self-reported health, menopause, serum 25-hydroxyvitamin D, total calcium intake, glucocorticoids, thiazide, hormone replacement therapy, statin, β-blocker use, CRP level, and comorbidity (congestive heart failure, cerebral vascular accident, COPD, and cancer).

β-blockers (all $P < 0.01$). The distributions of other variables were similar.

Unadjusted FN-BMD was reduced ($P < 0.005$) among persons with the metabolic syndrome, but after adjustment for age and gender and other covariates, it was higher in subjects with the metabolic syndrome than in controls ($P < 0.001$). In analyses stratified by BMI, adjusted BMD in subjects with the metabolic syndrome was similar to controls (Table 2). With the presence of increasing components of the metabolic syndrome, there was a significant trend toward higher FN-BMD ($P < 0.001$ for trend) (Table 3). The adjusted CRP level increased with more components: CRP = 0.17 mg/dl for no component, 0.25 mg/dl for one component, 0.35 mg/dl for two components, 0.49 mg/dl for three components, 0.53 mg/dl for four components, and 0.27 mg/dl for five components ($P < 0.001$ for trend). We examined multivariable linear regression models for each component of the metabolic syndrome separately and found significantly higher FN-BMDs in subgroups of people with abdominal obesity ($P < 0.001$) and diabetes ($P < 0.001$). To better assess the role of obesity in the relationship between the metabolic syndrome and FN-BMD, we conducted analyses stratified by abdominal obesity. The associations between the metabolic syndrome components and FN-BMD remained the same (Table 4).

We performed an analysis stratified on abdominal obesity examining the potential relationship between low-grade inflammation and BMD. Among male subjects with abdominal obesity present, we found lower BMD for those with CRP 1 or greater (0.80 g/cm^2) *vs.* CRP less than 1 (0.88 g/cm^2, $P = 0.052$). None of the other patient subgroups (men without abdominal obesity or women) exhibited a similar relationship. When CRP was removed from the primary model, the adjusted BMD stratified by BMI was unchanged from the results presented in Table 2.

We examined FN-BMD in light of the relationship between the metabolic syndrome and insulin resistance and found a trend toward higher BMD as fasting glucose (FG) level increases ($P = 0.0012$ for trend): 0.81 g/cm^2 (FG < 125 mg/dl); 0.86 g/cm^2 (FG 125–199 mg/dl); 0.88 g/cm^2 (FG 200–249 mg/dl); 0.83 g/cm^2 (FG 250–299 mg/dl); 0.80 g/cm^2 (FG 300–349 mg/dl); and 1.02 g/cm^2 (FG ≥ 350 mg/dl).

Discussion

In this study of a representative the U.S. adult population, subjects with the metabolic syndrome had an increased FN-BMD, compared with controls without the metabolic syndrome. This association was mainly driven by abdominal obesity, and stratified analysis by BMI showed similar BMD between subjects with and without the metabolic syndrome. We also found a higher BMD as the number of the metabolic syndrome components increased. We observed that higher BMD in the metabolic syndrome is largely determined by abdominal obesity. The protective effect of fat mass may be multifactorial: not only does mechanical loading increase BMD, but high circulating insulin levels as well as factors that are cosecreted with insulin (*e.g.* amylin and preptin arising from pancreatic β-cells) may promote bone formation (15).

Our results are similar to those of previous cross-sectional studies in that patients with diabetes had higher BMD (16, 17). A recent study reported that the metabolic syndrome protects against nonvertebral fractures (16). Insulin resistance is a cardinal feature of the metabolic syndrome, and prior studies demonstrated that circulating insulin levels and/or indices of insulin resistance are associated with bone density (18–20). Although type 1 diabetes may be related to bone mass reduction (21), longitudinal population-based study revealed that women with type 2 diabetes had a higher hip BMD at baseline but rapid bone loss over time (17).

TABLE 4. Adjusted femoral neck BMD by component of the metabolic syndrome stratified by abdominal obesity[a,b]

		Abdominal obesity present 0.86 (0.85, 0.86)				Abdominal obesity absent 0.78 (0.78, 0.79)				$P < 0.0001$
All subjects	n	(+)	n	(−)	*P*	n	(+)	n	(−)	*P*
HTN	1078	0.83 (0.82, 0.84)	2289	0.81 (0.80, 0.81)	0.13	686	0.82 (0.80, 0,83)	4144	0.81 (0.80, 0.82)	0.3
Diabetes	811	0.86 (0.85, 0.87)	2556	0.80 (0.80, 0.81)	<0.0001	443	0.85 (0.84,0.86)	4387	0.81 (0.81, 0.82)	0.0072
TG	1382	0.81 (0.80, 0.81)	1985	0.82 (0.81, 0.82)	0.12	988	0.80 (0.79, 0.81)	3842	0.82 (0.81, 0.82)	0.2
Low HDL	1648	0.83 (0.82, 0.83)	1719	0.81 (0.80, 0.83)	0.085	1365	0.82 (0.81, 0.83)	3465	0.81 (0.81, 0.82)	0.6

HTN, Hypertension; TG, triglyceride.
[a] Least square mean (95% confidence interval) (g/cm^2).
[b] All BMD values are adjusted for age, gender, race, smoking, alcohol, physical activity (METs/month), self-reported health, menopause, serum 25-hydroxy vitamin D, total calcium intake, glucocorticoids, thiazide, hormone replacement therapy, statin, β-blocker use, CRP level, comorbidity (congestive heart failure, cerebral vascular accident, COPD, and cancer), and each component of the metabolic syndrome.

Hyperinsulinemia is associated with bone formation in type 2 diabetes (21). We also observed increased BMD with higher fasting glucose levels, a marker of insulin resistance. Because subjects with high insulin resistance showed more inflammation than subjects with a low insulin resistance state (22, 23), elevated inflammation in diabetes may eventually result in reduced BMD.

A central question raised by this study is whether inflammation associated with the metabolic syndrome offsets the protective effect of adiposity or diabetes on bone mass. The metabolic syndrome is a complex set of conditions that includes obesity, a factor associated with enhanced BMD, and inflammation, a factor thought to reduce BMD. In the primary analytic models, we controlled for CRP but removed it from the parsimonious models. The different sets of models gave the same results. Whereas previous work suggests that osteoporosis is linked to inflammation, it is not yet clear whether higher CRP levels are associated with bone loss (4, 24). In the metabolic syndrome, we found a trend toward reduced BMD with higher CRP levels in obese men, but there was no association between inflammation and BMD in other subjects. The low-grade inflammation in the metabolic syndrome could affect BMD, but the protective effect of adiposity or diabetes may counteract the negative influence of inflammation on bone mass.

Our study has several limitations. Because our data are cross-sectional, we have limited ability to assess the temporal relationship between the metabolic syndrome and FN-BMD. Also, we did not have DXA measurements on nonfemoral bone. It is possible that the effects of the metabolic syndrome on BMD vary by anatomic site.

In conclusion, we found higher BMD among subjects with the metabolic syndrome, in which obesity appeared to be the main component increasing FN-BMD. Whereas adjusted FN-BMD stratified by BMI was similar between those subjects with and without the metabolic syndrome, an increase in the number of the metabolic syndrome components and diabetes were associated with a higher BMD. Longitudinal studies that include more information regarding inflammation will be helpful in better characterizing this relationship.

Acknowledgments

Received April 5, 2007. Accepted August 23, 2007.

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This work was supported in part by National Institutes of Health Grant R21 AG 027066 (to D.H.S.).

Disclosure Statement: The authors have nothing to disclose.

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