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Associations between the Metabolic Syndrome and Bone Health in Older Men and Women: The Rancho Bernardo Study

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Abstract

The metabolic syndrome (MS) is a cluster of risk factors, including abdominal obesity, high glucose, triglycerides, hypertension and low HDL levels, associated with cardiovascular disease morbidity. The association between components of the MS and bone mineral density (BMD) has been reported, but results are contradictory. We used multivariate regression models to examine the cross-sectional associations of MS defined by NCEP-ATP III criteria with BMD and osteoporosis, and the longitudinal association of MS with fractures in 417 men and 671 women from the Rancho Bernardo Study. Prevalence of MS at baseline was 23.5% in men and 18.2 % in women. In age-adjusted analyses, men and women with MS had higher BMD at total hip when compared to those without MS ($p<0.001$ and $p=0.01$, respectively). Men but not women with MS also had higher BMD at femoral neck ($p=0.05$). After adjusting for BMI, these associations were reversed, such that MS was associated with lower and not higher BMD. Incidence of clinical non-vertebral fractures was higher in participants with MS. MS may be another risk factor for osteoporotic fractures. The association of MS with higher BMD was explained by the higher BMI in those with MS.

Key words men women, BMI

Introduction

Metabolic syndrome is defined as a cluster of risk factors that are associated with diabetes, central obesity, and increased risk of cardiovascular disease (1). The 2001 National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) (2) definition requires the presence of at least 3 of 5 of the following categorically defined risk factors: abdominal obesity (waist circumference greater than 102 cm in men or greater than 88 cm in women), high triglycerides (150mg/dl or greater), low HDL cholesterol (less than 40mg/dL in men or less than 50mg/dL in women), hypertension (130/85 mmHg or greater), and hyperglycemia (110mg/dL or greater). The association between each of these risk factors and osteoporosis, a major cause of morbidity and mortality in old age (3), has been extensively studied, but results are inconsistent and sometimes contradictory (4-11). Moreover, the combined effect of the metabolic syndrome risk factors on bone health has not yet been reported.

Overweight and obesity protect against excessive bone loss in aging. A recent meta-analysis that included 60,000 men and women from 12 cohorts (12) showed that low BMI is associated with an increased fracture risk, but osteopenia or osteoporosis has been associated with central adiposity (4, 5). Although hyperglycemia is a predictor of bone loss and osteoporotic fractures, the association between high glucose levels or insulin resistance with bone mineral density (BMD) is inconclusive (6). In a previous study from the Rancho Bernardo cohort, hyperinsulinemia was positively associated with BMD in women, but not men, suggesting sex differences (13). The evidence for associations between high triglycerides or low HDL levels with BMD is contradictory, with studies claiming strong evidence for either positive or negative associations (7, 8). In cross-sectional studies hypertension has been associated with both increased (10) or decreased BMD (9, 14); one longitudinal study reported bone loss associated with hypertension (15).

Based on these inconsistent results, and the high prevalence of osteoporosis and heart disease risk factors in the aging U.S. population, we conducted a cross-sectional and prospective study to examine the association between metabolic syndrome and BMD, osteoporosis, and fractures among community-dwelling ambulatory older men and women. Our specific aims were: 1) to determine whether metabolic syndrome is associated with BMD, osteoporosis, and prevalent non-vertebral osteoporotic fractures in both sexes; 2) to determine whether metabolic syndrome predicts incident non-vertebral osteoporotic fractures; and 3) to determine whether any observed associations were independent of age, body mass index (BMI), lifestyle, medication use, and the presence or absence of type 2 diabetes.

Methods

Population Studied

Between 1997 and 1999 all surviving participants from the Rancho Bernardo Study, an all Caucasian cohort in southern California, were invited to participate in a study of osteoporosis. A total of 420 men and 676 women, approximately 60% of the surviving cohort, participated. Main reasons for non-participation among survivors included having moved away, being too sick or too busy, or being institutionalized. Three men and 5 women were excluded because they were either unable to lie prone for the BMD measurement or did not have adequate blood samples for measurement of lipids and glucose. This analysis includes the remaining 417 men and 671 postmenopausal women aged 38 to 97 years. Between 2000 and 2002 surviving participants (316 men and 491 women) returned for a follow-up visit (mean interval 2 years, range 1-4), when they were queried about interim fractures. All were ambulatory and gave written informed consent. The study was approved by the Institutional Review Board of the University of California, San Diego.

At the research clinic visit, participants completed standardized questionnaires about medical history including health behaviors (cigarette smoking, alcohol consumption, physical activity). Current medication use was verified by examination of pills and prescriptions brought to the clinic for that purpose. Postmenopausal hormone

therapy was defined as current estrogen or estrogen plus progestin use at the time of the baseline visit. Height and weight were measured in participants wearing light clothing and no shoes. Body mass index was calculated as body weight (in kilograms) divided by height (in meters) squared. Waist was measured in centimeters at the bending point using a flexible tape measure, with the participant wearing single-thickness clothing and standing in an erect position with feet together.

Laboratory measurements

At the baseline visit, morning blood samples were obtained after a requested 12-hour fast. Plasma glucose levels were measured using a glucose oxidase assay. Lipid and lipoprotein levels were measured in a Center for Disease Control-certified Lipid Research Clinic (LRC) laboratory. Total cholesterol (TC) and triglycerides (TG) levels were measured by enzymatic techniques using an ABA-200 biochromatic analyzer (Abbott Laboratories, Irving, TX). High-density-lipoprotein (HDL) cholesterol was measured by precipitating the other lipoproteins with heparin and manganese chloride according to the standard LRC protocol (LRC Manual) (13). Low-density-lipoprotein (LDL) cholesterol was estimated using the Friedewald formula (14): LDL = TC – HDL – (TG/5). Serum creatinine was measured in a commercial laboratory using a variation of the Jaffe enzymatic method on a Hitachi 911 analyzer (Roche Diagnostics Corp., Indianapolis, IN). Creatinine clearance was calculated by the Cockcroft-Gault equation (16).

Bone mineral density and fractures

Bone mineral density (BMD) was defined as total bone mineral content (gm) divided by the area (cm^2). BMD was measured at the baseline visit using dual energy x-ray absorptiometry measured by a Hologic QDR 1000 scanner (Hologic Inc., Bedford, MA), calibrated daily using a standard phantom provided by the manufacturer. Measurements were maintained within the manufacturers' precision standards of ≤ 1.5%. Total hip BMD included the greater trochanter, femoral neck, and intertrochanter area. Lumbar spine BMD was the mean of lumbar vertebrae 1-4. The BMD measurements were compared as T scores expressed in standard deviations using the peak bone mass from the manufacturer's reference population. Osteoporosis was defined in accordance

with the WHO, as BMD at any site greater than 2.5 standard deviations (SD) below the young adult mean, and osteopenia as BMD 1 to 2.5 SD below the young adult mean. Incident osteoporotic fractures were clinical fractures at the hip, femur, forearm or wrist occurring after the baseline visit and not related to major trauma (auto accident or fall from height). Ninety-five percent of all self-reported fractures were confirmed by examination of medical records or radiology reports.

Metabolic Syndrome

The prevalence of metabolic syndrome and its components were defined by NCEP-ATP III criteria (2). Participants were classified as having the metabolic syndrome if any three of the following were present: abdominal obesity (waist circumference greater than 102 cm in men or greater than 88 cm in women), triglycerides of 150 mg/dL (1.7 mmol/L) or greater, HDL cholesterol levels less than 40mg/dL (1.04 mmol/L) in men or less than 50 mg/dL (1.29 mmol/L) in women, fasting glucose of 110 mg/dL (6.1mmol/L) or greater, or blood pressure of 130/85mmHg or greater. Participants with documented use of antihypertensive medication were categorized as meeting the blood pressure criteria. Diabetes was defined by the American Diabetes Association 1998 guidelines (fasting plasma glucose equal or greater than 126mg/dL or 2-h plasma glucose in 75g oral glucose tolerance test equal or greater than 200mg/dL) (11).

Data analyses

SPSS (SPSS Inc., SPSS Base 13.0 for Windows User's Guide) and SAS (SAS Institute SAS User's Guide, Version 9.0) were used for analysis. Results were expressed as mean ± 95% confidence interval (CI) or percentages, and were compared using the Student t test, one-way analyses of variance (ANOVA), or Chi-square tests, as appropriate. The cross-sectional analyses used data collected at the 1997-1999 visit. Analysis of covariance (ANCOVA) was used to compare the BMD levels of those with and without metabolic syndrome at the lumbar spine, femoral neck and total hip after adjusting for known BMD covariates including age, body mass index, exercise, alcohol use, current smoking, calcium supplements and estrogen use in women. Univariate and multivariate regression models were used to examine the association of metabolic

syndrome components and metabolic syndrome with BMD. Incident non-vertebral osteoporotic fractures were assessed at a subsequent 1999-2002 visit. In the prospective study, logistic regression analyses were used to examine the association between metabolic syndrome and incident osteoporotic fractures. All analyses were repeated after exclusion of participants with creatinine clearance ≤ 30ml/min, diabetes mellitus or current estrogen use. All statistical tests were two-tailed, and statistical significance was defined as $p< 0.05$.

Results

The mean age of the 417 men and 671 women was 74.2 (SD=9.7) and 74.4 years (SD=10.9), and the mean BMI was 26.5 (SD= 3.5) and 24.9 (SD= 4.2), respectively. The prevalence of metabolic syndrome was 23.5% in men and 18.2% in women. Compared to men, women had higher levels of total cholesterol and HDL (214 ± 35 mg/dl vs. 193 ± 33 mg/dl and 67 ± 19 mg/dl vs. 50 ± 13 mg/dl, $p<0.001$ for both comparisons), but similar levels of LDL and triglycerides (119 ± 31mg/dl vs. 123 ± 33mg/dl and 125 ± 98mg/dl vs. 125 ± 65 mg/dl, respectively). Men had higher waist circumference (94.9 ± 10cm vs. 79.9 ± 12cm, $p<0.001$), and reported more alcohol intake (85 ± 93 g/week vs. 48 ± 65 gm/week, $p<0.001$) than women. Men also had higher BMD at all measured sites (0.954 ± 0.148 vs. 0.795 ± 0.144 for total hip, 0.762 ± 0.134 vs. 0.657 ± 0.121 for femoral neck, and 1.112 ± 0.213 vs. 0.940 ± 0.192 for lumbar spine, all p's < 0.001), and an increased prevalence of diabetes (13.1% vs. 7.2% p=0.001) when compared to women. Waist circumference was highly correlated with BMI in both sexes ($r=0.86$ for men and $r=0.83$ for women, both p's <0.001). Four and a half percent reported current medication for osteoporosis, all but 3 of whom were women. Forty eight percent of women reported current postmenopausal estrogen therapy.

Age and age-adjusted baseline characteristics and risk-factor distribution by sex and metabolic syndrome status are shown in Table 1. Men and women with metabolic syndrome had higher levels of BMI, waist circumference, systolic blood pressure, triglycerides, and fasting plasma glucose (all p's < 0.01). Total cholesterol levels were

not associated with metabolic syndrome; LDL levels were higher in women with metabolic syndrome ($p<0.001$), but not in men. More than 70% of men and women had hypertension, and close to 20% of men and women had low HDL, hypertriglyceridemia, and/or abdominal obesity. Men had a significantly higher prevalence of fasting hyperglycemia than the women (30.5% versus 12.1%, $p<0.001$). In both sexes, participants with metabolic syndrome had a lower prevalence of osteoporosis than participants without metabolic syndrome, with statistically significant results for men at the lumbar spine (1.1% versus 7.7%, $p=0.03$). Figure 1 shows the number of metabolic syndrome components by sex.

Age-adjusted linear regression analyses between each metabolic syndrome component and BMD are provided in Table 2. As shown, only waist circumference was consistently and positively associated with BMD at all three sites, both in men and women. Triglycerides were positively associated with total hip and lumbar spine BMD in women only, HDL was positively associated with total hip in men only, and fasting plasma glucose (FPG) was positively associated with lumbar spine in women and negatively associated with lumbar spine in men. Table 3 shows results from analyses of covariance with adjusted mean BMD at each bone site in men and women with and without metabolic syndrome. In age-adjusted analyses, the total hip and lumbar spine were significantly higher in participants with metabolic syndrome when compared to participants without metabolic syndrome (p's < 0.04); BMD at the femoral neck was also higher in men and women with metabolic syndrome when compared to men and women without metabolic syndrome ($p=0.05$ for men and $p=0.06$ for women). Inclusion of BMI reversed this pattern for all categories, such that BMD was lower in those with MS, with statistically significant results for the femoral neck in men ($p = 0.02$). The inclusion of other covariates (alcohol intake, smoking, exercise, calcium supplements, and estrogen or osteoporosis medication use in women) did not change the magnitude or direction of these associations.

Fourteen percent of men and 16.3% of women had at least one prevalent non-vertebral fracture; incident fractures occurred in 2.9% of men and 4.5% of women. There

was no association between metabolic syndrome and prevalent osteoporotic fractures in the cross-sectional analyses. However, after an average follow up of 2 years (range 1-4 years), incident clinical fractures were 2.6 (95% CI 1.2 -5.4, p=0.01) times more likely to occur in participants with metabolic syndrome as compared to participants without metabolic syndrome. Sex-specific logistic regression models adjusted for age, BMI, estrogen use, exercise, calcium supplements, and alcohol intake showed that metabolic syndrome significantly increased the odds of incident fractures in women (OR=3.76, 95%CI 1.27-11.13, p=0.02); a smaller, non-significant association was seen in men (OR= 2.48, 0.49-12.60, p=0.27). Further adjustment for smoking status, baseline BMD, prevalent osteoportic fractures or osteoporosis medication in women did not change the results (Table 4).

Table 5 shows that in age-adjusted linear regression analyses, the number of metabolic syndrome components was positively associated with BMD at each site (p's< 0.03) in both sexes. However, after further adjustment for BMI, the increasing number of components was associated with a decrease in BMD at the neck and total hip; differences were significant in men, but not in women. No significant association was seen between number of components and BMD at the spine. Further adjustments for lifestyle variables or medication use did not change these results.

In order to determine if the metabolic syndrome-bone association was explained by diabetes we repeated the analysis stratified by diabetes status. Fifty five (13.1%) men and 49 (7.2%) women had diabetes, the majority of whom also had metabolic syndrome (74.5 % of men and 62 % of women). Conversely, 42% of the men and 24% of the women with metabolic syndrome had diabetes. Excluding participants with diabetes did not materially change any of the results. Because impaired renal function may be a component of the metabolic syndrome, and is associated with BMD, we repeated the analysis excluding the 5 men (1.2%) and 43 women (6.4%) who had creatinine clearance < 30 ml/min. This exclusion did not change any of the results. Given the effect of estrogen use on triglycerides and HDL levels we also conducted analyses stratified by estrogen use, The association between MS and osteoporotic fractures was increased

among the women not using estrogen (OR=10.00, 95%CI= 2.66;37.55, p=0.001) but there were too few incident fractures among women using estrogen for meaningful analyses. Women currently using estrogen were less likely to have MS than women not using estrogen (35% versus 65%), and only 8 women in that group had non-vertebral fractures.

Discussion

The prevalence of metabolic syndrome in adult Caucasians in the United States is between 20 to 25% (1). In Rancho Bernardo, more men (23.5%) than women (18.2%) met the NCEP-ATP III criteria for MS, similar to the trend reported in other large U.S. population-based studies with older adults, including the Framingham Offspring Study (MS prevalence of 30.3% in men and 24.7% in women) (17), the San Antonio Heart Study (29.3 % in men, 26.3% in women in the first cohort; 20.4% in men and 16.3% in women in the second cohort) (18), and results based on NHANES III data (38% in men, 24% in women) (19). The average BMD for men and women in our study is similar to the levels reported for the U.S. adult population reported by Looker and colleagues (20) using NHANES III data. In the present study we found a lower prevalence of osteoporosis in participants with metabolic syndrome, but the reversal of this association when analyses were adjusted for BMI. Moreover, incidence of osteoporotic fractures was higher in participants with metabolic syndrome when compared to participants without it, before and after adjustments for BMI, with significant results in women.

To our knowledge, this is the first study to examine the association between MS and bone health measured by BMD and incidence of osteoporotic fractures. The associations between individual components of the MS and low bone mineral density or osteoporotic fractures have been extensively studied, but results are inconclusive. BMI is recognized as one of the strongest predictors for BMD in both men and women (34), but the evidence regarding the association between central adiposity and BMD and is mixed. In a study of 272 healthy Polish men aged 20-60 years, central obesity was significantly associated with low bone mass at the ultra distal radius (4). In another study of men and

women with primary osteoporosis (55 cases versus 125 age matched controls), those with osteoporosis had a lower BMI but a higher waist to hip ratio than in the controls (5). These 2 studies support the hypotheses that osteopenia and/or osteoporosis is related to waist girth, a key component of the metabolic syndrome. However, another case-control study in obese women (60 cases, 35 controls) reported that central obesity was associated with higher BMD at the ultra distal and proximal radius BMD, independent of BMI (35). In a previous publication from the Rancho Bernardo Study, all measures of body size, including waist to hip ratio, were positively associated with BMD in both sexes. These results are similar to those in the present report, where waist circumference was highly correlated with BMI ($r=0.86$ for men and $r=0.83$ for women, p's < 0.001), and was consistently and positively associated with higher BMD levels at all sites in both sexes (36).

Yamaguchi and colleagues (7) reported a positive and independent association between HDL-cholesterol and BMD at the lumbar spine, femoral neck, and total body in 214 Japanese postmenopausal women aged 47-86 years. In that study, plasma triglycerides levels were significantly lower in women with vertebral fractures than in those without fractures. Our results are more in accord with those reported by Adami and colleagues (8) who studied 746 community-dwelling healthy Italian men and women aged 68-75 years (mean = 72.7 years for both sexes). In that study hip BMD was positively associated with triglycerides and negatively associated with HDL-cholesterol in both sexes, before and after adjusting for body weight, height, or fat mass. In the Rancho Bernardo cohort there was a positive association between triglycerides levels and BMD at the total hip and lumbar spine in women, but not in men, and HDL levels were negatively associated with total hip BMD in men, but not in women.

There is also contradictory information about the association between high blood pressure and bone. Hanley and colleagues (10) studied 5566 women and 2187 men aged 50 years and older from the Canadian Multicentre Study of Osteoporosis, and found an independent association of hypertension with higher BMD for both sexes, with more pronounced differences at the lumbar spine and femoral neck in women, and at the lumbar spine in men. However, in the Study of Osteoporotic Fractures, systolic (SBP)

and diastolic (DBP) blood pressure were linearly associated with the rate of bone loss measured at the femoral neck in 3676 white women aged 65 years and older who were followed up for a mean of 4 years (15). The authors speculated that the findings might reflect excess urinary calcium loss, a feature of hypertension, leading to an increase in parathyroid hormone and subsequent increase in bone resorption. The Rancho Bernardo results are in accord with the NHANES I data (22), which found no significant association between SBP or DBP and BMD at any bone site in a large sample of postmenopausal women.

Type 1 diabetes is associated with decreased adult bone mass and increased risk for osteoporosis, and it is generally accepted that poor metabolic control negatively influences bone acquisition (23-25). However, the association of type 2 diabetes or insulin resistance with bone health is less consistent. Some investigators found higher BMD in the presence of type 2 diabetes (24, 26), whereas others reported an inverse association (27). In previous publications from the Rancho Bernardo Study, hyperinsulinemia was positively associated with higher BMD in women, but not men (13), and women with type 2 diabetes or hyperglycemia had higher BMD than women with normal glucose tolerance independent of body weight and other risk factors: bone density did not differ by glycemic status in men (28). Similarly, in Rancho Bernardo we found a positive association between lumbar spine BMD and FPG in women, but an inverse association in men.

In a recent publication, Ahmed and colleagues (21) examined the effect of some components of the metabolic syndrome (BMI, HDL, Triglycerides and hypertension) and risk of non-vertebral fractures in 12,780 men and 14,211 women aged 25-98 years (mean= 47 years for both sexes) from the Tromso study, and concluded that increasing burden of metabolic syndrome components protects against non-vertebral fractures. However, this study is not comparable to ours because they did not measure waist circumference, and levels of plasma glucose and lipids were measured in non-fasting samples. Also, their population spanned a wide age range, and fractures were not limited to low trauma osteoporotic fractures. Traumatic fractures are more likely to occur in

younger participants, and may have a different pathophysiology than osteoporotic fractures.

Previous studies have reported an association of non-vertebral fractures with type 2 diabetes (29-31). Older women with type 2 diabetes have an increased risk for non spine fractures, in particular hip fracture, but the higher risk of falling associated with diabetes may explain this increased risk (32). In the large Rotterdam Study (33), men and women aged 55 year and older with type 2 diabetes had higher BMD levels than those without, but they also had an increased risk of non-vertebral fracture risk after an average **7** year follow-up, independent of age and BMI. The authors speculated that the increased fracture risk could be caused by complications of diabetes such as vascular disease or peripheral neuropathy, or by a detrimental effect of hyperglycemia on bone strength.

Limitations to the present study should be noted. The Rancho Bernardo cohort is nearly all Caucasian , middle-to upper-middle class and relatively well educated; results may not generalize to other populations. Due to old age, recall bias regarding OP fractures cannot be excluded. However, OP fractures in the elderly are a major health event, and less likely to be forgotten. Survival bias, whereby participants with MS/diabetes were more likely to have died, or participants with hip fractures were not able to attend the clinic visit are also possible, but this would have attenuated the association we found between MS and fracture.

In conclusion, in the cross-sectional study we found that older Caucasian men and women with the metabolic syndrome had higher BMD at the hip and spine, suggesting a protective effect of metabolic syndrome on bone. However, this higher BMD was explained by the higher BMI in persons with metabolic syndrome, indicating that this protection was confounded by the increased body weight associated with metabolic syndrome. In the longitudinal study, the increased risk of incident non-vertebral fractures associated with metabolic syndrome suggests that metabolic syndrome might be another risk factor for non-vertebral osteoporotic fractures.

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Table 1. Age and age adjusted characteristics and risk factors distribution by metabolic syndrome status

	Men			Women		
Metabolic Syndrome	**YES (n=98) Mean ± SE**	**NO (n=319) Mean ± SE**	**P value**	**YES (n=122) Mean ± SE**	**NO (n=549) Mean ± SE**	**P Value**
Age	72.9 ± 0.9	74.6 ± 0.6	0.15	75.9 ± 0.9	74.0 ± 0.5	0.08
BMI	29.4 ± 0.3	25.6 ± 0.2	<0.001	28.7 ± 0.3	24.1 ± 0.2	<0.001
Alcohol (g/w)[a]	89.7 ± 9.4	83.8 ± 5.2	0.59	37.8 ± 5.9	50.5 ± 2.8	0.05
Cholesterol (mg/dl)	192.3 ± 3.3	192.9 ± 1.9	0.86	217.2 ± 3.2	213.7 ± 1.5	0.32
Triglycerides[a] (mg/dl)	203.3 ± 8.9	100.7 ± 4.9	<0.001	181.9 ± 5.4	112.8 ± 2.5	<0.001
HDL (mg/dl)	41.0 ± 1.2	52.9 ± 0.7	<0.001	49.4 ± 1.5	70.5 ± 0.7	<0.001
LDL (mg/dl)	114.0 ± 3.1	119.9 ± 1.7	0.10	132.6 ± 3.0	120.6 ± 1.4	<0.001
Waist (cm)	103.6 ± 0.9	92.2 ± 0.5	<0.001	92.1 ± 0.9	77.2 ± 0.4	<0.001
SBP (mmHg)	140.4 ± 1.9	133.1 ± 1.1	0.001	140.8 ± 1.7	135.6 ± 0.8	0.008
DBP (mmHg)	75.3 ± 0.9	75.4 ± 0.5	0.91	73.6 ± 0.9	72.6 ± 0.4	0.32
FPG (mg/dl)	124.2 ± 1.5	100.7 ± 0.8	<0.001	114.3 ± 1.7	95.3 ± 0.8	<0.001
	%	**%**		**%**	**%**	
Alcohol >3/week	56.2	58.0	0.76	28.9	45.0	0.001
Exercise 3/week	68.3	80.6	0.001	52.7	73.0	<0.001
Smoking	2.8	4.8	0.39	3.6	4.9	0.53
Calcium suppl.	*16.3*	*22.6*	*0.18*	*54.9*	*56.7*	*0.72*
BP medication	64.8	35.0	<0.001	59.1	35.5	<0.001
Blood sugar med.	17.4	1.6	<0.001	10.5	1.9	<0.001
Diabetes	42.1	4.3	<0.001	23.6	3.3	<0.001
Current Estrogen	-	-	-	37.0	50.5	0.005
Osteoporosis[b]						
Total hip	3.4	7.9	0.13	16.6	19.6	0.43
Femoral neck	28.0	38.0	0.07	42.3	48.9	0.18
Lumbar spine	1.1	7.0	0.03	14.0	20.4	0.10

[a] Distribution is skewed, but results were similar with log transformed variables. [b] By WHO definition (T score < 2.5 SD below mean). SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HDL = high density lipoprotein, LDL = low density lipoprotein

Figure 1. Prevalence of Metabolic Syndrome and Number of Components

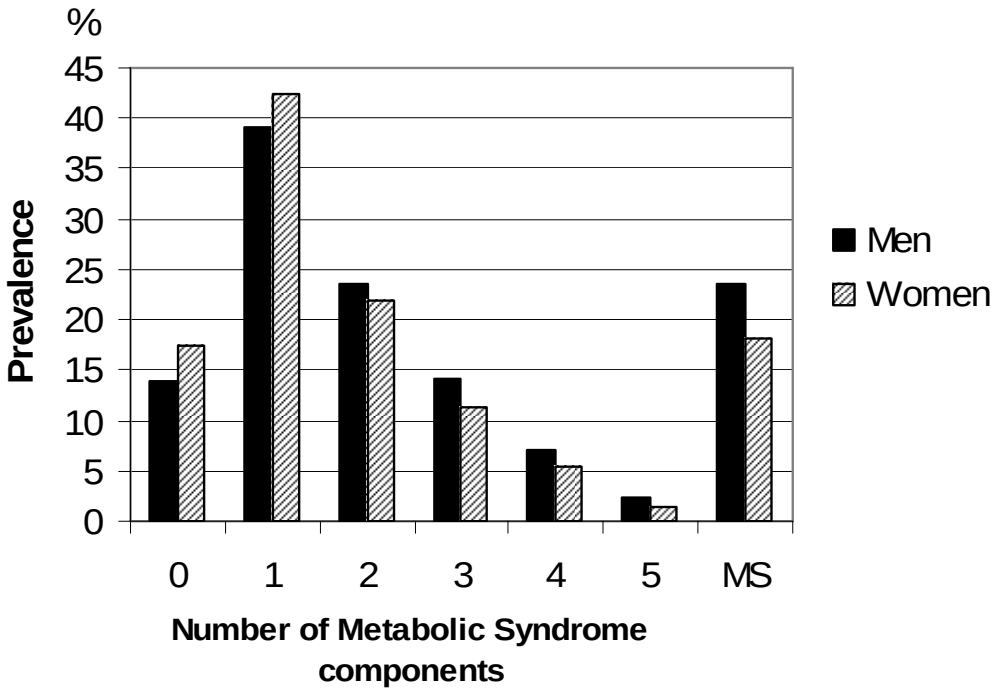

Table 2. Age-adjusted linear regression between BMD and each specific component for metabolic syndrome

	Men		Women	
Total hip	Beta (stand)	P value	Beta (stand)	P value
FPG	.093	0.05	.056	0.12
Triglycerides	.083	0.09	**.104**	**0.004**
HDL	**-.138**	**0.004**	-.019	0.60
Waist*	**.368**	**<0.001**	**.293**	**<0.001**
SBP	.028	0.57	.076	0.06
Neck				
FPG	-.010	0.84	.050	0.16
Triglycerides	.077	0.11	.062	0.09
HDL	-.077	0.11	.020	0.58
Waist *	**.287**	**<0.001**	**.225**	**<0.001**
SBP	.040	0.42	.077	0.06
Spine				
FPG	**-.136**	**0.006**	**.093**	**0.01**
Triglycerides	.074	0.14	**.107**	**0.006**
HDL	-.068	0.17	-.029	0.45
Waist	**.347**	**<0.001**	**.267**	**<0.001**
SBP	.074	0.15	.056	0.19

SBP/DBP = systolic/diastolic blood pressure (mmHg), FPG = fasting plasma glucose (mg/dl), HDL = high density lipoproteins (mg/dl), LDL = low density lipoprotein (mg/dl), waist (cm)

Table 3. Mean (SE) bone mineral density by metabolic syndrome status

	Men			**Women**		
	YES (n= 98)	**NO (n=319)**	**P value**	**YES (n=122)**	**NO (n=549)**	**P Value**
	Mean (SE)	**Mean (SE)**		**Mean (SE)**	**Mean (SE)**	
Total Hip						
Age adjusted	.997 (.014)	.942 (.008)	0.001	.822 (.012)	.788 (.006)	0.01
Age + BMI	.936 (.014)	.960 (.007)	0.14	.788 (.012)	.798 (.005)	0.14
All covariates	.937 (.014)	.960 (.007)	0.16	.788 (.012)	.797 (.005)	0.51
Femoral Neck						
Age adjusted	**.784 (.013)**	**.755 (.007)**	**0.05**	.673 (.010)	.652 (.005)	0.06
Age + BMI	**.735 (.013)**	**.770 (.007)**	**0.025**	.644 (.011)	.659 (.005)	0.21
All covariates	**.737 (.013)**	**.769 (.007)**	**0.038**	.653 (.011)	.658 (.005)	0.65
Lumbar spine						
Age adjusted	1.179 (.021)	1.092 (.012)	<0.001	.973 (.017)	.931 (.008)	0.030
Age + BMI	1.104 (.022)	1.115 (.011)	0.67	.925 (.018)	.942 (.006)	0.42
All covariates	1.104 (.022)	1.115 (.011)	0.67	.939 (018)	.943 (.008)	0.86

All covariates: age, BMI, alcohol, exercise, smoking status, *calcium supplements*, and current estrogen use at baseline in women

Table 4. Metabolic syndrome (MS) as a predictor of osteoporotic fractures* – results of logistic regression

	MEN			WOMEN		
	OR (95% CI)		**P value**	**OR (95% CI)**		**P value**
Age (years)	1.01	(0.94;1.10)	0.73	1.01	(0.96;1.06)	0.73
BMI (units)	0.90	(0.71;1.13)	0.35	0.94	(0.83;1.06)	0.33
Estrogen (yes)	-	-	-	0.68	(0.26;1.78)	0.43
Calcium (yes)	*0.44*	*(0.05:3.64)*	*0.45*	*0.53*	*(0.21;1.29)*	*0.53*
Exercise (yes)	0.87	(0.17;4.50)	0.87	0.86	(0.33;2.24)	0.76
Alcohol use (yes)	0.84	(0.22;3.23)	0.79	1.04	(0.42;2.57)	0.93
MS (yes)	2.48	(0.49;12.60)	0.27	3.76	(1.27;11.13)	0.017

* After a mean of 2 years (range 1-4); follow-up for survivors (316 men and 491 women)

Table 5. Linear regression between number of metabolic syndrome components and BMD

	Men		Women	
	Beta*	P value	Beta*	P value
Total hip				
Age adjusted	.023	<0.001	.020	<0.001
Age + BMI	-.010	0.095	-.003	0.52
Neck				
Age adjusted	.014	0.008	.013	0.001
Age + BMI	-.012	0.031	-.002	0.66
Spine				
Age adjusted	.033	<0.001	.031	<0.001
Age + BMI	-.008	0.41	.010	0.17

* Unstandardized Beta

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