The Influence of Hormonal Status and Features of the Metabolic Syndrome on Bone Density: A Population-Based Study of Swedish Women Aged 50 to 59 Years. The Women's Health in the Lund Area Study

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This study investigated whether there is an association between bone density and features of the metabolic syndrome in relation to hormonal status. All women aged 50 to 59 years living in a defined geographic area in Sweden were offered a health assessment program including blood glucose, lipid profile, blood pressure, and bone densitometry. Women were divided into 3 groups according to their hormonal status: premenopausal (PM), postmenopausal with hormone replacement therapy (PMT), and postmenopausal without hormone replacement therapy (PM0). Of the 6,886 women investigated, 7% were PM, 41% PMT, and 52% PM0. The overall prevalence of osteopenia and osteoporosis, according to the World Health Organization (WHO) definition, was 42.6% and 6.6%, respectively. T-score in the PM group was higher than in the PMT ($P < .05$) and PM0 groups ($P < .001$) and higher in the PMT group compared with the PM0 group ($P < .001$). Also, in the total cohort, the bone density was positively associated with body weight, body mass index (BMI), waist-to-hip ratio (WHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), serum triglycerides, and blood glucose ($P < .001$ for all) and negatively associated with serum levels of cholesterol ($P < .05$) and high-density lipoprotein (HDL) ($P < .001$). This was most evident among the PMO women, suggesting that the influence of metabolic factors on bone density increases when the levels of hormones decrease. This indicates that hormone replacement therapy maintains treated women in a premenopausal status concerning the metabolic factors.

OSTEOPOROSIS AND ITS clinical manifestation, the fragility fracture, is well recognized as a disease with major impact on quality of life of the individual, as well as on health care resources.[1-6] Hence, improving the identification of positive and negative factors for osteoporosis should be given high priority to initiate preventive measures where most appropriate.

In previous studies, several risk factors for osteoporosis, such as low body mass index (BMI), smoking, alcohol consumption, low physical activity, loss of ovarian function, and a family history of fractures have been identified.[7] It is well known that menopause accelerates bone loss.[1,8] A reduced risk of osteoporosis has been described in type 2 diabetic patients.[9,10] It may be hypothesized that females in the menopausal age with metabolic disorders connected to diabetes, such as the simultaneous presence of abnormal glucose tolerance, hypertension, central obesity, and dyslipidemia (the metabolic syndrome), may be sheltered against osteoporosis. With an average age of menopause at 51 years and an increasing average life span, women in the western world can expect to live more than 1 third of their lives in a postmenopausal estrogen-deficient state.[11] However, due to various symptoms of estrogen deficiency, many women choose to use hormone replacement therapy, which has been known to have favorable effects not only on general symptoms during the climacteric period, but also on glucose and insulin metabolism,[12] and on the lipid profile.[13,14]

The aim of the present study was to assess forearm bone density in women age 50 to 59 years with reference to their hormonal status and to outline possible associations between bone density and features of the metabolic syndrome.

SUBJECTS AND METHODS

Women living in the Lund area of southern Sweden by December 1, 1995 and who were born between December 2, 1935 and December 1, 1945 (N = 10,766) received an invitation to undergo a health screening program including bone densitometry. These women were located through a postal registration center, where all inhabitants are noted. Together with the invitation, all women obtained a questionnaire with questions on medical history, medications including hormone replacement therapy, menopausal status, and smoking habits.

Of the initially invited women, 6,917 agreed to participate in the study. Thirty-one women were excluded due to inability to establish hormonal status (n = 9) or missing bone density values (n = 22). The remaining 6,886 women (64%) form the basis for this report.

In conjunction with the densitometry, a specially trained midwife interviewed all women about their questionnaire, and potential problems were addressed. At the interview, 19% of the subjects made some corrections in their answers due to earlier misunderstandings when filling out the forms. Informed consent was obtained from participating subjects, and the ethics committee at Lund University approved the study.

Bone Density

Wrist bone mineral density was measured by means of dual energy x-ray absorptiometry (Osteometer DTX 200; Medi-Tech A/S, Rodovre, Denmark) and expressed as standard deviations from young healthy women (T-score). A phantom was used for the daily calibration of the instrument. The one and same investigator performed all measurements. The World Health Organization (WHO) standard was used to define patients with osteopenia and osteoporosis.[7,15]

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Clinical Investigation and Metabolic Variables

Body weight, height, minimal waist, and maximal hip circumference were measured. Blood pressure was measured twice after 15 minutes rest in the seated position using a mercury sphygmomanometer with the cuff size adjusted to the circumference of the arm. The average of the recordings was used as the blood pressure. Nonfasting blood samples were drawn for analysis of blood glucose, serum levels of triglycerides, cholesterol and high-density lipoprotein-cholesterol (HDL-C) using a Cholestech LDX-instrument (Cholestech Corp, Hayward, CA). Friedewald's formula was used when calculating low-density lipoprotein-cholesterol (LDL-C).

The population examined was divided in 2 separate ways. (1) Based on bone density data, women were divided into lowest and highest quartiles. (2) Based on hormonal status, the population was first divided into 3 groups, premenopausal (PM), postmenopausal with hormone replacement therapy (PMT), and postmenopausal without hormone replacement therapy (PM0), and, in each separate hormonal group, into lowest and highest quartiles of bone density.

Menopause was defined as a bleed-free interval of at least 12 months. The results of the clinical investigation of the subjects and the metabolic parameters were analyzed according to any relationship to bone density and with reference to hormonal status (PM, PMT, and PM0).

Statistics

Values are given as median (range). For the analysis of differences between groups regarding continuous variables, the Mann-Whitney U-test and the Kruskal-Wallis test were used. The χ^2 test was used to analyze differences between groups regarding categorical variables. To assess the association between risk factors and bone density expressed as T-score, partial correlation, controlling for age, was performed. *P* values less than .05 were considered significant.

RESULTS

Of the 6,886 participating women, 2,934 (42.6%) were osteopenic and 455 (6,6%) osteoporotic. According to hormonal status, 491 (7.1%) were PM, 2,808 (40.8%) PMT, and 3,587 (52.1%) PM0. Bone density was higher in the PM group than in the PMT ($P < .05$) and PM0 groups ($P < .001$) and higher in the PMT group compared with the PM0 group ($P < .001$) (Table 1). Among women in the PM0 group, 32.1% belonged to the lowest quartile of bone density. The corresponding values in the PMT and PM groups were 18.6% and 12.8%. The ratio between the number of subjects in lowest quartile and highest quartile was 1.5 in the PM0 group, 0.65 in the PMT group, and 0.39 in the PM group.

All Women

All measured variables were lower in the group with the lowest quartile of T-score compared with the group with the highest quartile ($P < .01$ to $< .001$). More women smoked in the lowest quartile compared with the highest quartile ($P < .01$) (Table 1).

In the whole cohort, the bone density was positively associated with body weight, BMI, waist-to-hip ratio (WHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), serum triglycerides, and blood glucose ($P < .001$ for all) and negatively associated with serum levels of cholesterol ($P < .05$), and HDL-C ($P < .001$). In both the lowest and highest quartiles, bone density was positively associated with body weight ($P < .001$), BMI ($P < .001$), WHR ($P < .01$), SBP ($P < .01$), and DBP ($P < .05$). In the highest quartile, bone density was also negatively associated with HDL-C ($P < .001$) (Table 2). Smokers had lower bone density than nonsmokers in the whole cohort (-1.00 and -0.90, respectively; $P < .001$).

Premenopausal Women

Premenopausal women were younger than women in the PMT and the PM0 groups ($P < .001$ for both) and had lower

Table 1. Subject Characteristics of the Total Population and in Groups Divided According to Hormonal Status

Variable	All (n = 6,886)	Lowest Quartile of T-Score (n = 1,705)	Highest Quartile of T-Score (n = 1,727)	PM (n = 491)	PMT (n = 2,808)	PM0 (n = 3,587)
Age (yr)	56.1 (50.1, 64.1)	57.5 (50.1, 63.8)*	55.5 (50.1, 64.1)	53.1 (50.1, 60.6)*	56.0 (50.1, 63.9)*	56.8 (50.1, 64.1)*
Body weight (kg)	67.5 (28.8, 141.0)	63.9 (28.8, 109.8)*	73.0 (34.0, 141.0)	66.4 (43.0, 135.0)	67.0 (34.0, 120.0)*	68.1 (28.8, 141.0)‡
BMI (kg/m^2)	24.9 (13.7, 52.4)	23.8 (13.7, 43.3)*	26.7 (17.0, 52.4)	24.3 (16.4, 48.0)	24.3 (15.0, 48.4)*	25.2 (13.7, 52.4)*
WHR	0.78 (0.53, 1.11)	0.76 (0.60, 1.00)*	0.79 (0.60, 1.11)	0.77 (0.53, 1.06)	0.77 (0.53, 1.11)*	0.78 (0.60, 1.09)*
Systolic BP (mm Hg)	130 (80, 230)	130 (80, 230)†	130 (94, 196)	130 (95, 185)	130 (87, 212)	130 (80, 230)†
Diastolic BP (mm Hg)	85 (30, 143)	85 (30, 143)†	85 (55, 132)	85 (60, 114)	85 (30, 125)†	85 (50, 143)‡
S-triglycerides (mmol/L)	1.47 (0.51, 7.34)	1.40 (0.51, 7.30)*	1.58 (0.60, 7.34)	1.29 (0.60, 7.30)†	1.41 (0.51, 7.34)*	1.55 (0.52, 7.34)*
S-cholesterol (mmol/L)	5.90 (0.62, 12.90)	6.00 (0.62, 12.90)*	5.84 (2.90, 9.61)	5.68 (3.04, 11.10)	5.60 (0.62, 12.90)*	6.13 (2.59, 12.90)*
S-HDL (mmol/L)	1.71 (0.39, 4.23)	1.76 (0.42, 2.59)*	1.63 (0.46, 2.59)	1.75 (0.60, 2.59)‡	1.68 (0.39, 2.90)†	1.72 (0.41, 4.23)
S-LDL (mmol/L)	3.41 (0.10, 8.33)	3.50 (0.59, 7.16)†	3.37 (0.49, 7.43)	3.26 (0.35, 7.27)	3.18 (0.10, 7.00)*	3.58 (0.83, 8.33)*
B-glucose (mmol/L)	5.87 (2.78, 23.40)	5.83 (2.78, 19.30)†	5.92 (2.78, 20.00)	5.79 (3.49, 22.40)	5.84 (2.78, 23.40)†	5.91 (3.08, 20.30)‡
T-score (SD)	−0.90 (−6.20, 3.90)	−2.10 (−6.20, −1.61)	0.30 (−0.20, 3.90)	−0.70 (−3.40, 2.60)‡	−0.80 (−6.20, 3.50)*	−1.10 (−4.80, 3.90)*
Smoking (n/%)	1404/20.4	392/23.0†	316/18.3	91/18.5	500/17.8*	813/22.7‡

NOTE. Values are expressed as median (range).

Abbreviations: PM, premenopausal; PMT, postmenopausal with hormone replacement therapy; PM0, postmenopausal without hormone replacement therapy.

*$P < .001$, †$P < .01$, ‡$P < .05$, lowest quartile of T-score compared with highest quartile, PM compared with PMT, PMT with PM0, and PM0 with PM.

Table 2. Partial Correlation Analysis Between Risk Factors and Bone Density (T-score) in the Total Population and in Groups Divided According to Hormonal Status

	T-Score in the Total Population			T-Score in the PM Group			T-Score in the PMT Group			T-Score in the PM0 Group		
Risk Factor	Lowest Quartile *r*	Highest Quartile *r*	All *r*	Lowest Quartile *r*	Highest Quartile *r*	All *r*	Lowest Quartile *r*	Highest Quartile *r*	All *r*	Lowest Quartile *r*	Highest Quartile *r*	All *r*
Body weight	.21*	.26*	.35*	NS	.46*	.44*	.13†	.24*	.31*	.24*	.24*	.39*
BMI	.21*	.27*	.35*	NS	.47*	.42*	.14†	.28*	.33*	.26*	.22*	.39*
WHR	.08†	.08†	.17*	NS	.18‡	.25*	NS	.11†	.18*	.10†	NS	.18*
SBP	.06†	.09†	.09*	NS	NS	.15†	NS	NS	.07*	.07‡	.15*	.09*
DBP	.06‡	.06‡	.06*	NS	.21‡	.16†	NS	NS	NS	.07‡	.09‡	.08*
S-triglycerides	NS	NS	.09*	NS	NS	NS	NS	NS	.10*	NS	NS	.12*
S-cholesterol	NS	NS	−.03‡	NS	NS	NS	NS	NS	NS	NS	NS	NS
S-HDL-C	NS	−.09*	−.12*	NS	−.20‡	−.16†	NS	−.11†	−.10*	NS	NS	−.12*
S-LDL-C	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
B-glucose	NS	NS	.05*	NS	NS	NS	NS	NS	.05‡	NS	NS	.06†

Abbreviations: NS, nonsignificant; PM, premenopausal; PMT, postmenopausal with hormone replacement therapy; PM0, postmenopausal without hormone replacement therapy.

*$P < .001$, †$P < .01$, ‡$P < .05$.

body weight ($P < .05$), BMI, WHR, serum triglycerides, serum cholesterol, serum LDL-C ($P < .001$ for all 5), and blood glucose ($P < .05$) compared with the PM0 group. Fewer women smoked in the PM group than in the PM0 group ($P < .05$) (Table 1). There were no differences in bone density between smokers and nonsmokers.

In the whole PM group, bone density was positively associated with body weight, BMI, WHR ($P < .001$ for all), SBP and DBP ($P < .01$ for both), and negatively associated with serum HDL-C ($P < .01$). No associations were found in the lowest quartile, but in the highest quartile, body weight, BMI ($P < .001$ for both), WHR, DBP, and HDL ($P < .05$ for all 3) were associated with bone density (Table 2).

Postmenopausal Women With Hormone Replacement

Postmenopausal women with hormone replacement had lower age, body weight, BMI, WHR, serum triglycerides, serum cholesterol, serum LDL-C ($P < .001$ for all), serum HDL-C ($P < .01$), and blood glucose ($P < .01$) compared with women in the PM0 group. There were fewer women smoking in the PMT group than in the PM0 group ($P < .001$) (Table 1). Smokers had the same bone density as nonsmokers.

In the PMT group, bone density was positively associated with body weight, BMI, WHR, SBP, serum triglycerides ($P < .001$ for all), and blood glucose ($P < .05$) and negatively associated with serum HDL-C ($P < .001$). In the lowest quartile, bone density was positively associated with body weight and BMI ($P < .01$ for both). In the highest quartile, bone density correlated with body weight, BMI ($P < .001$ for both), WHR ($P < .01$), and HDL-C ($P < .01$) (Table 2).

Postmenopausal Women Without Hormone Replacement

In the PM0 group, bone density was associated with body weight, BMI, WHR, SBP, DBP, serum triglycerides, HDL-C (negative correlation) ($P < .001$ for all), and blood glucose ($P < .01$). In the lowest quartile, bone density was associated with body weight, BMI ($P < .001$ for both), WHR ($P < .01$), SBP, and DBP ($P < .05$ for both). In the highest quartile, bone was associated with body weight, BMI, SBP ($P < .01$ for all), and DBP ($P < .05$) (Table 2). Smokers had lower bone density than nonsmokers ($P < .01$).

DISCUSSION

Osteoporosis is common in the western World, and northern Europe has the highest incidence of hip fractures.[16-19] In US women aged 50 to 65 years, the prevalence of osteoporosis increases from 1% to 13% and osteopenia from 33% to 40% according to National Health and Nutrition Examination Survey (NHANES) data.[20,21] In a study from Malmö, Sweden of women aged 50 to 59 years, 7% were found osteoporotic and 42% osteopenic.[5] These findings are in line with this material of 6,886 women, in which 6.6% were osteoporotic and 42.6% osteopenic.

In the present study, the bone density was lowest in the PM0 group and also lower in the PMT group compared with the PM group. The PM and PMT women were more frequently represented in the highest quartile of bone density and less in the lowest, while the opposite was found for the PM0 women. In line with earlier findings, this indicates that even if the incidence and prevalence of osteoporosis and osteopenia increases with age, hormonal status is a more important predictor of bone mineral density than age alone, at least in the immediate postmenopausal situation, as in the present study.[1,22] Hormones may, according to these results, delay the age-dependent deterioration of bone mineral density.

Diabetes mellitus has been shown to be associated with reduced risk of osteoporosis.[9,10] Hyperinsulinemia, associated with the metabolic syndrome, has also been shown to stimulate growth through increased levels of circulating free insulin-like growth factor -1 (IGF-1) and a reduction of IGF-binding protein-3 (IGFBP-3), which may contribute to the increased bone density seen in those subjects.[23,24] As in some previous reports,[7,25] bone density in the present study was positively correlated with body weight, BMI, and WHR. Positive correlations were also found between bone density and blood glucose, SBP, DBP, and serum triglycerides and a negative cor-

relation with serum HDL-C. These findings indicate an association between high bone density and features of the metabolic syndrome, such as the simultaneous presence of abnormal glucose tolerance, hypertension, central obesity, and dyslipidemia.

Overall, fewer correlations with perceived metabolic risk factors were found in the PM and PMT groups. As long as the hormone levels are high, the other risk factors are of less importance. However, when hormones decrease, the influence of the metabolic factors on bone density increases. This indicates that hormone replacement therapy maintain treated women in a premenopausal status concerning the metabolic factors.

The associations between metabolic risk factors and bone density in this study were most evident among women in the highest quartile of bone density, while few correlations were found in the lowest quartile. This difference in risk factor correlations between lowest and highest quartiles seems to be enhanced by endogenous and exogenous hormones. Previously published data on relations between bone density and other conceivable risk factors used regression analysis comparing all measurements available in each study. Any distinction between lowest and highest bone density measurements has not been performed. This seems to be of importance, as fewer associations were found in the lowest quartile in the present study, which may offer an explanation as to why the predictive value for future fracture incidence in other studies was lower than expected.[26]

Smoking has been recognised as a risk factor for osteoporosis, mediated by a negative effect on estrogen metabolism.[7] In this study, women who smoked had a lower bone density than nonsmoking women in the whole cohort and in the PM0 group. In the PM and PMT groups, however, there were no differences in bone density between smokers and nonsmokers. This could mean that endogenous and exogenous hormones eliminate the negative influence of smoking on bone density. Findings supporting this fact have recently been presented in a study from Denmark, in which exogenous estradiol seemed to reduce the negative impact by smoking.[27]

In conclusion, this study on 6,886 middle-aged women contributes to the understanding of age-related bone loss, mainly due to the number of participants, but also due to the supplemental focus on blood glucose and insulin metabolism and on lipids. Although the data are associative, they demonstrate the relatively profound effect of hormone replacement therapy compared with all other risk factors.

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