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Osteoporosis and Cardiovascular Risk Among Premenopausal Women in Sri Lanka

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Abstract

We examined the association between bone mineral density (BMD) and cardiovascular risk in a group of premen- opausal women selected from the Southern province of Sri Lanka. One hundred six previously healthy premeno- pausal volunteers (aged 30e54 yr) were recruited by open invitations. Subjects with previous history of diabetes, hypertension, epilepsy, chronic renal or liver disease, hyperlipidemia, ischemic heart disease, endocrine diseases, or prolonged inflammatory conditions were excluded. Subjects who were taking medications that can affect bone density, blood sugar, serum lipids, or blood pressure (BP) were also excluded. Women with the history of previous fractures were not excluded. BMDs in the spine, hip, and total body (TB) were measured using a Hologic Discovery scanner (Hologic Inc, Bedford, MA). BP, fasting glucose, and fasting lipids were also measured. Independent of body mass index (BMI) and age, TB bone mineral content (BMC) and spine BMD showed inverse and significant correlations with total cholesterol (TC), low density cholesterol, and the ratio between TC and high density lipopro- tein cholesterol (r ranged from 0.24 to 0.27, p ! 0.05 for all). The highest mean lipid levels were seen among the women in the lowest third of spine BMD, whereas women in the upper third of spine BMD had the lowest lipid levels. The number of women with metabolic syndrome in the 3 tirtiles of spine BMD was not significantly

different. Fasting glucose or BP had no association with either BMD or BMC. In conclusion, our data demonstrates an asso- ciation, independent of age and BMI, between BMD and BMC or lipid levels among previously healthy, premen- opausal women. This may explain the high cardiovascular risk seen in women with osteoporosis in old age.

Key Words: Blood pressure; fasting glucose; lipids; osteoporosis; Sri Lanka.

Introduction

Epidemiological studies have shown a high occurrence of acute myocardial infarctions among patients with osteoporosis, suggesting a possible link between the 2 major noncommunica- ble diseases affecting women (1). An inverse association between bone mineral density (BMD) and calcification of aorta, which is a surrogate marker of cardiovascular disease,

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has also been documented (2,3). Among postmenopausal women, an association has been seen between BMD and serum lipids, in which, women with low BMD had a lipid profile that promotes atherosclerosis (4,5). This association, however, was not consistently seen in other studies (6,7). In 1999, Cappuccio et al, found an inverse association between femoral neck BMD and diastolic blood pressure (DBP) among postmenopausal women and this association was independent of age, body measurements, and other confounders (8).

The clinical consequences of low BMD and high lipids are well established. Although BMD shows a continuous associa- tion with the risk of osteoporosis-related fractures in postmen- opausal women (9), a similar relationship is observed between

cardiovascular disease and elevated total cholesterol (TC) or low density lipoprotein (LDL) cholesterol levels (10,11).

Most of the studies examining the association between bone health and cardiovascular health have used postmeno- pausal female populations who have a relatively higher risk for both osteoporosis and cardiovascular diseases when com- pared with premenopausal women. The association between osteoporosis and cardiovascular diseases among premeno- pausal women has not been well documented. Although data from older women would help clinicians to recognize the cardiovascular risk among women with

osteoporosis, and vice versa, data from younger patients would help to identify the origin of this association. Furthermore, most of the studies have been done in Caucasian populations and data from South Asian populations are limited.

The current study was performed in a group of previously healthy, middle-aged, premenopausal women selected from the Southern province of Sri Lanka to study the association between BMD and conventional cardiovascular risk factorsd serum lipids, fasting blood sugar, and BP.

Materials and Methods

Previously healthy, premenopausal women, aged 30 or more, were invited to participate in a research related to bone and cardiovascular health conducted by the Center for Metabolic Bone Diseases in Galle, Sri Lanka. Open invitations were sent to the nearby institutions and they included a govern- ment primary school, 2 hospitals, and a university. Posters were also displayed in public places, such as bus stops and religious places inviting middle-aged healthy female volunteers for the study. All volunteers who responded to our invitation (n 5 163) had a brief interview and a physical examination and women with the history of diabetes, hypertension, epilepsy, chronic renal or liver disease, hyperlipidemia, ischemic heart disease, endocrine diseases, or prolonged inflammatory condi- tions were excluded. Women who had taken drugs, such as systemic corticosteroids, heparin, vitamin D, antiresoptives, lipid-lowering therapy, hypoglycemic agents, antihyperten- sives, hormonal contraceptives, or pharmacological doses of calcium were also excluded (total number of exclusions 5 46). Although women younger than 30 yr (n 5 4) were excluded from the study, those who had previous traumatic fractures (n 5 8) were not excluded. Further, 7 subjects had no lipid reports and finally 106 women were selected for the study.

All women included in the study signed an informed con- sent form, filled a health-related questionnaire, and underwent a detailed physical examination during which 2 mL of venous whole blood was collected with a minimum of 12 h overnight fasting. Weight was measured while wearing light cloths and after emptying the urinary bladder. Height was measured without footware using a stadiometer (Nagata, Tainan, Tai- wan). All body measurements were taken by one technician, adhering to the standard protocols of defining these measure- ments. After 15 min of resting, systolic BP (SBP) and DBP were measured, twice, with 15-min interval between the mea- surements and average BPs were considered for the analysis.

Serum TC, high density lipoprotein (HDL), triglyceride (TG), and plasma glucose concentrations were measured using Humalyzer 2000 (Wiesbaden Human, Germany). Con- centration of LDL was calculated using the Friedewald for- mula. None of the subjects had TG level that would make the application of this formula invalid.

All subjects had total body (TB) dual-energy X-ray absorptiometry (DXA) performed

using Hologic Discovery scanner (Hologic Inc, Bedford, MA) to measure TBBMD and TB bone mineral content (TBBMC). DXA was also per- formed over the lumber spine and left proximal femur to mea- sure total spine BMD (TSBMD) from L1 to L4 in the anteroposterior projection, total hip BMD (THBMD), and femoral neck BMD (FNBMD). All scans were performed and analyzed by one technician. Precision errors of BMD estimations in the same machine were checked by measuring 30 postmenopausal women, twice on the same day, with repo- sitioning between scans and found to be 0.008, 0.001, and 0.002 g/cm^2 for the TS, FN, and TH, respectively (12). Ethi- cal approval for the study was obtained from the local Ethics Review Committee of the Faculty of Medicine, Galle.

Statistical Analyses

The characteristics of the 106 women included in the analysis are given as mean and standard deviation (SD) (Table 1). Corre- lations between age, body mass index (BMI), BMDs, lipid levels, BPs, and plasma glucose level were examined first and

Table 1

Descriptive Data of 106 Premenopausal Women Included in the Analysis

Measure
Age (yr) Weight (kg) Height (m) BMI (kg/m^2) Waist circumference (cm) Hip circumference (cm) Waist hip ratio
TC (mg/dL) LDL cholesterol (mg/dL) HDL cholesterol (mg/dL) TG (mg/dL) TG/HDL ratio TBBMD (g/cm^2) TBBMC (g) TSBMD (g/cm^2) THBMD (g/cm^2) FNBMD (g/cm^2)
Mean (SD)
42.0 (6.0) 57.6 (8.9) 1.54 (0.06) 24.4 (3.6) 84.9 (9.2) 96.9 (7.5) 0.87 (0.06)
201.7 (32.9) 129.2 (31.5) 44.7 (6.4) 137.9 (33.8)
4.5 (0.94) 1.065 (0.086) 1782.63 (226.9) 0.923 (0.136) 0.922 (0.099) 0.764 (0.097)

Abbr: SD, standard deviation; BMI, body mass index; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipo- protein; TG, triglyceride; TBBMD, total body bone mineral density; BMC, bone mineral content; TBBMC, total body bone mineral con- tent; TSBMD, total spine bone mineral density; THBMD, total hip bone mineral density; FNBMD, femoral neck bone mineral density.

partial correlations between the TBBMC, BMDs, lipids, BPs, and fasting glucose were examined after adjusting for age and BMI. Using analysis of variance (ANOVA), mean levels of lipids, blood sugar, and BPs in the thirds of the TSBMD were estimated and compared, initially unadjusted and then adjusted for age and BMI. Homogeneity of variance of the model was checked using Levene test and interactions between BMD, BMC, and indices of cardiovascular risk were also checked. TSBMD was selected for the above analysis as it showed the highest correlation with lipid levels. Women were diagnosed to have metabolic syndrome if they had waist circumference 80 cm or more and 2 other abnormalitiesdHDL cholesterol less than 50 mg/dL, TG more than 150 mg/dL, fasting glucose more than 100 mg/dL, or BP greater than 130/85 mm Hg. The mean TBBMC, TBBMD, and regional BMDs in women with and without metabolic syndrome were estimated and compared, using unpaired Student's t-test, initially unadjusted and then ad- justed for age. Statistical Package For the Social Sciences (SPSS Inc., Chicago) for Windows version 10 was used for all analyses and 2-tailed p less than 0.05 was taken as the level of statistical significance.

Results

Age of the women ranged from 30 to 54 with mean (SD) of 42.0 (6.0) yr. None of the subjects had ever smoked, whereas only 5 (4.7%) women had taken alcohol previously. Ninety- three (87.7%) of them were married and the median (Inter- quartile range) number of children was 2 (2,3). Eight (7.5%) women had suffered traumatic fractures but none had suffered fragility fractures.

Age showed no significant correlations with BMI, BMD, or lipid levels, whereas BMI showed significant correlations with spine and hip BMDs (r 5 0.31e0.41, p ! 0.05) but not with lipids. When adjusted for age and BMI, the TC, LDL choles- terol and the ratio between TC and HDL (TC/HDL) showed negative correlations with the TBBMC and all BMD values. Of these correlations, only the correlations seen with the TBBMC and TSBMD were statistically significant. Although not statistically significant, TG showed negative associations with BMDs and TBBMC. HDL cholesterol showed positive correlations with BMDs and TBBMC but these associations too were not statistically

significant (Table 2).

When adjusted for age and BMI, fasting glucose, DBP, and SBP showed no statistically significant correlations with the TBBMC or BMDs measured at various sites.

The highest mean TC, LDL cholesterol, and TC/HDL ratio were seen among women in the lower third of TSBMD, whereas the lowest mean lipid levels were seen among women in the upper third of spinal BMD. These differences were statistically significant and were independent of age and BMI. Mean values of HDL cholesterol, TG, fasting glucose, SBP, or DBP were not statistically different in the tirtiles of the TSBMD (Tables 3 and 4).

Fifty-seven (53.8%) women in the study sample had waist circumference either equal or greater than 80 cm and 47 (44.3%) of them had 2 other criteria of metabolic syndro-medHDL less than 50 mg/dL, TG greater than 150 mg/dL, fasting glucose greater than 100 mg/dL or BP more than 130/85, and they were diagnosed to have metabolic syn-drome. Independent of age, women with metabolic syndrome had lower BMC and BMD, but only the difference in the TH

Table 2

Age and BMI Adjusted Partial Correlations Between BMD, BMC, and Lipids

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Variable

TBBMD TBBMC TSBMD THBMD FNBMD

TC

LDL cholesterol

TGs

0.01 (0.20 to p50.95 0.12 (0.31 to p50.30 0.05 (0.24 to p50.64 0.03 (0.16 to p50.78 0.06 (0.25 to p50.57

HDL cholesterol

0.05 (0.14 to 0.24) p50.64 0.08 (0.11 to 0.27) p50.49 0.13 (0.06 to 0.31) p50.25 0.12 (0.07 to 0.31) p50.28 0.14 (0.05 to 0.32) p50.21

TC/HDL ratio

0.15 (0.33 to 0.04) p50.19 0.26 (0.43 to 0.06) p50.02 0.27 (0.44 to 0.08)

p50.02 0.10 (0.29 to 0.09) p50.34 0.23 (0.41 to 0.04) p50.05

0.13 (0.31 to 0.06) p50.25 0.25 (0.43 to 0.06) p50.03 p50.03 0.26 0.26

0.18)

0.07)

0.14)

0.22)

0.13)

(0.43 to 0.06) p50.03 0.04 (0.23 to 0.15) p50.74

0.18 (0.37 to 0.01) p50.11

(0.43 to 0.06) p50.018 0.07 (0.26 to 0.12) p50.54

0.21 (0.39 to 0.02) p50.06

0.14 (0.31 to 0.05) p50.19 0.25 (0.43 to 0.06)

Abbr: BMI, body mass index; BMD, bone mineral density; BMC, bone mineral content; TC, total cholesterol; LDL, low density lipopro- tein; TGs, triglycerides; HDL, high density lipoprotein; TBBMD, total body BMD; TBBMC, total body BMC; TSBMD, total spine BMD; THBMD, total hip BMD; FNBMD, femoral neck BMD.

Given in cells are r, 95% confidence intervals (within brackets) and p values examined by partial correlation, adjusted for age and BMI. Journal of Clinical Densitometry: Assessment of Skeletal Health Volume 12, 2009

Table 3

Mean (SEM) Lipids, Fasting Blood Glucose, and BPs in the Thirds of the TSBMD of 106 Premenopausal Women

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Variable

TC Crude

Age and BMI LDL cholesterol

Crude

Age and BMI HDL cholesterol

Crude

Age and BMI TG

Crude

Age and BMI TC/HDL

Crude

Age and BMI Fasting glucose

Crude

Age and BMI SBP

Crude

Age and BMI DBP

Crude Age and BMI

adjusted adjusted adjusted adjusted adjusted adjusted adjusted

adjusted

Lower third of spinal BMD

210.8 (6.0) 210.9 (6.1)

138.4 (5.8) 138.8 (5.9)

44.5 (1.2) 44.2 (1.2)

139.9 (6.5) 140.9 (6.3)

4.8 (0.18) 4.8 (0.18)

83.5 (2.6) 82.9 (2.7)

109.3 (2.0) 109.1 (1.8)

72.3 (1.4) 72.2 (1.3)

Middle third of spinal BMD

207.8 (6.2) 208.1 (6.3)

136.1 (6.0) 135.6 (6.1)

43.4 (1.2) 43.6 (1.2)

140.4 (6.7) 143.3 (6.5)

4.8 (0.18) 4.8 (0.18)

84.8 (2.7) 84.9 (2.8)

111.3 (2.0) 112.7 (1.9)

71.9 (1.5) 72.8 (1.4)

Upper third of spinal BMD

188.4 (6.3) 187.9 (6.6)

115.1 (6.1) 115.3 (6.3)

46.0 (1.2) 46.2 (1.3)

135.6 (6.8) 131.4 (6.7)

4.1 (0.19) 4.1 (0.19)

83.1 (2.8) 83.6 (2.9)

112.5 (2.1) 111.3 (2.0)

75.0 (1.5) 74.2 (1.4)

p Value*

0.026 0.029

0.013 0.021

0.32 0.33

0.86 0.42

0.021 0.017

0.90 0.88

0.53 0.39

0.29 0.60

Abbr: SEM, the standard error of the mean; BPs, blood pressures; BMD, bone mineral density; TSBMD, total spine BMD; TC, total cho- lesterol; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*p Value contrasts differences in mean values in 3 columns and calculated using post-hoc analysis of variance with Bonferroni correction.

was statistically significant. Further, the percentages of women with metabolic syndrome in the lower, middle, and upper thirds of the TSBMD were 40.7%, 50%, and 38.5%, respectively, and this difference was not statically significant (p50.67).

Discussion

Osteoporosis-related fractures and cardiovascular diseases are 2 major noncommunicable diseases seen among postmen- opausal women. Moreover, there is substantial mortality, mor- bidity, and loss of productivity associated with these diseases. Early detection and treatment are the main measures adopted by current health care systems to reduce the burden of these 2 diseases.

Results of the current study demonstrate an association between measures of bone health and lipid levels among these previously healthy, middle-aged, premenopausal females. In this analysis, TC, LDL cholesterol and TC/HDL ratio inversely and significantly correlated with the TBBMC and TSBMD. In contrast to women with high TSBMD, women

with low TSBMD had high TC, LDL cholesterol, and TC/ HDL ratio. Furthermore, women with metabolic syndrome had lower BMD and BMC, but only the difference observed in the TH was significantly different. Although there was an inverse correlation between TG and BMD among our sub- jects, the association was not statistically significant and not in keeping with previous reports (13). In general, results of the current study indicate a coexistence of low bone mass and dyslipidemia in these middle-aged women.

In previous studies, women with low bone mass had high cardiovascular mortality (1), calcification of aorta (2,3) and lipid abnormalities that would promote atherosclerosis (4,5). In contrast, Adami et al and Brownbill et al, found a positive association between BMD and lipids levels where women with higher BMD had elevated lipid levels (5,7). An association between BMD and BP has been observed among postmeno- pausal women. In one study, the group of women with low BMD and high BP had high urinary calcium excretion, suggest- ing a possible mechanism of this association (8). We did not find an association between BP and BMD or BMC and our results are consistent with a large epidemiological study conducted

Table 4

Mean (SEM) BMC and BMD Values Among Women With and Without Metabolic Syndrome

increasing BMD (19). This indicates the existence of shared metabolic pathway in bone and lipid metabolism.

The exact mechanism involving regulation of bone mass and cardiovascular risk in humans is not known. Some obser- vational studies have indicated that atherosclerosis could lead to local bone loss. Finding of low BMD and aortic calcifica- tion among women with intermittent claudication of legs would support this hypothesis (2). Also obstructing atheromas were found in the small and large arteries supplying the hip region in women with osteoporotic hip fractures (20,21).

The role of lipids, especially in oxidized form, in the cau- sation of atherosclerosis and mineralization of vascular wall and bone tissue has been discussed. In 1999, a study involving mice, showed that minimally-oxidized LDL (MM-LDL) is capable of promoting adipogenic differentiation of marrow stromal cells while inhibiting their osteoblastic differentiation (22). Parhami et al in 1997 reported that MM-LDL and other oxidized lipoproteins could promote mineralization of vascu- lar cells while inhibiting mineralization of bone cells (23). Brodeur et al (2008) demonstrated the influence of oxidized LDL in reducing the viability of osteoblasts, mediated through lysosomal membrane damage (24). Bagger et al examining the role of lipids in the link between bone and car- diovascular heath were unable to find a significant association between lipids and bone health. In this observational study the presence of apolipoprotein E 34

allele had significant impact on lipid profile but not on BMD measurements (25). Osteoprotegerin, receptor activator of nuclear factor kB (RANK), and RANK-ligand, the well-established cytokinin network in bone metabolism, has been linked to cardiovascular disease. Studies have established links between this pathway and vascular calcification, advanced atherosclerosis, plaque destabilization, and heart failure indicating its role in the pathophysiology of cardiovascular disease (26).

The current study has many limitations. Women participated in this study were volunteers who responded to our open invita- tion. As they were not selected on random basis, selection bias would have occurred. Thirty-five of them were used in seden- tary type of jobs and others were mainly housewives. Although these subjects would not be representative of the normal mid- dle-aged female population of the country, we were able to draw a sample, which had employment ratio roughly equal to the normal population of the country. Small sample size prob- ably contributed to inconclusive results in many analyses. Although uniform patterns were seen in TG and HDL cholesterol, the differences were not statistically significant, probably, because of small sample size. It can be argued that BMD decline associated with estrogen deficiency may have already begun in perimenopausal women included in this study and this may have contributed to the results. We examined the cor- relations between age, BMI, BMDs, and lipids among women older than 50 yr (n 5 7) and then women older than 45 yr (n 5 35) and found no association between these variables. Hence this is an unlikely possibility.

In summary this study, involving a selected group of pre- menopausal healthy women, showed an inverse association, independent of age and BMI, between BMD and BMC or TC,

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Variable

TBBMD Crude

Age and BMI adjusted

TBBMC Crude

Age and BMI adjusted

TSBMD Crude

Age and BMI adjusted

THBMD Crude

Age and BMI adjusted

FNBMD Crude

Age and BMI adjusted

With metabolic syndrome (n 5 45)

1.061 (0.013) 1.061 (0.013)

1782 (33) 1783 (33)

0.931 (0.017) 0.931 (0.017)

0.905 (0.014) 0.906 (0.014)

0.757 (0.013) 0.758 (0.013)

Without metabolic syndrome (n 5 34)

p

Value*

1.080 (0.015) 0.33 1.078 (0.015) 0.39

1823 (38) 0.41 1820 (38) 0.47

0.950 (0.020) 0.90 0.935 (0.020) 0.87

0.950 (0.016) 0.036 0.948 (0.016) 0.046

0.785 (0.015) 0.18 0.784 (0.015) 0.21

Abbr: SEM, the standard error of the mean; BMC, bone mineral content; BMD, bone mineral density; TBBMD, total body BMD; BMI, body mass index; TBBMC, total body BMC; TSBMD, total spine BMD; THBMD, total hip BMD; FNBMD, femoral neck BMD.

*p Value contrasts differences in mean values in 2 columns and calculated using Student's t-test (unpaired) with Bonferroni correction.

using 2738 nationally representing group of women where no association between BMD and hypertension was found (14). Similarly there was no significant association between blood sugar and BMD or BMC among our women and this is keeping with the data seen previously (15).

Coexistence of osteoporosis and dyslipidemia has not been proven yet. Hence, current

practice guidelines do not recom- mend routine testing of lipids in women with osteoporosis. If further studies confirm this coexistence, it can have several clinical implications. Once a woman is detected to have one abnormality, clinician will be required to search for the other and then attempt to reverse both conditions. Non-pharmaco- logical measures such as enhanced physical activity and limit- ing the intake of alcohol can reverse dyslipidemia while influencing BMD positively (16). Furthermore, cessation of smoking would help both conditions. Therapy with selective estrogen receptor modulators (17) or bisphosphonates (18) in postmenopausal women led to reversal of dyslipidemia. Therapy with statins in women with high lipids resulted in

LDL cholesterol, or TC/HDL ratio. Fasting sugar, TG, HDL cholesterol, and BP were not found to have significant associa- tions with BMD or BMC. Finding this association in premeno- pausal age would support the idea that association between lipids and bone health is established early in life, predisposing them to long-term complications in old age. If further studies generate similar associations, clinicians will be required to adopt a holistic approach in evaluating patients with abnormal lipids or low BMD to assess overall mortality and morbidity.

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