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Association between bone mineral densities and serum lipid profiles of pre- and post-menopausal rural women in South Korea

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Abstract The objectives of this population-based study were to investigate the potential association between bone mineral density (BMD) and serum lipid profiles and to compare the effects of serum lipids on BMD at various skeletal sites in pre- and post-menopausal women. In July and August of 2004, BMD was measured at a variety of skeletal sites [lumbar spine (L_{1-4}), femoral neck, trochanter, Ward's triangle, shaft and proximal total hip] using the GE/Bravo Lunar DPX dual-energy X-ray absorptiometer in a South Korean population-based sample of 375 pre-menopausal and 355 post-menopausal rural women aged 19–80 years. The levels of serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were inversely associated with BMD in both pre- and post-menopausal women. In the pre-menopausal women, correlations were shown only for lumbar 1–4 (TC: $r = -0.12$, $P < 0.05$; LDL-C: $r = -0.12$, $P < 0.05$), whereas in the post-menopausal women, no correlation was evident for the lumbar sites. In the post-menopausal subjects, the TC levels showed significant correlations with the BMD values at the trochanter ($r = -0.15$, $P < 0.01$), shaft ($r = -0.16$, $P < 0.001$) and proximal total hip ($r = -0.15$, $P < 0.01$) sites, while the LDL-C levels showed significant correlations with the BMD values at the neck ($r = -0.13$, $P < 0.05$), trochanter ($r = -0.21$, $P < 0.001$), shaft ($r = -0.20$, $P < 0.001$) and proximal total hip ($r = -0.20$, $P < 0.001$) sites. The levels of triglyceride (TG) were shown to have a significant positive correlation with BMD values at the trochanter site ($r = 0.11$, $P = 0.05$) in the post-menopausal women; by contrast, subjects in a higher quartile of TG levels show lower lumbar BMD values in the pre-menopausal women. The levels of high-density lipoprotein cholesterol (HDL-C) were not associated with BMD values at any of the sites in the pre- and post-menopausal subjects. Our data indicate a relationship between BMD values and serum lipid levels and suggest differences between pre- and post-menopausal women in terms of the effects of serum lipids on BMD at various skeletal sites.

Keywords Bone mineral density · Serum lipids · Women

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Introduction

As the percentage of elderly people in the population increases, the number of osteoporosis and atherosclerosis cases has risen sharply, particularly in the case of post-menopausal women, who are more likely to suffer from estrogen-induced osteoporosis than men, and older women with low BMD have an increased risk of death from cardiovascular disease [1], which seriously affects their quality of life. Epidemiological data suggest that estrogen deficiency is a risk factor for cardiovascular diseases and osteoporosis. Estrogen receptors have been demonstrated to have effects on osteoblasts [2] and osteoclasts [3]. In the past decade, studies have suggested a link between atherosclerosis and osteoporosis [4, 5, 6, 7]. Lipids are widely recognized as a risk factor for atherosclerosis and cardiovascular disease, and bone mineral loss is a direct cause of osteoporosis. Considering that osteoporosis and atherosclerosis are often

found in the same person, and that some but not all clinical studies [8] support a role for lipids in osteoporosis, it is interesting to note that statins, which are used to treat hyperlipidemia, are associated with increased BMD and reduced risk for fractures [9, 10, 11, 12]. Conversely, estrogen therapy for post-menopausal osteoporosis [13] is known to reduce TC and LDL-C [14]. These studies imply that there are underlying possible etiological connections between bone metabolism and lipid metabolism. Thus, an increasing number of studies are investigating the relationship between BMD and serum lipids. However, published data on this topic are still scarce, and the reports that exist are inconsistent; some studies have found an association between BMD and serum lipids in post-menopausal women, whereas others have not [15]. The studies also differ in finding that individual lipid profiles are positively or negatively correlated with BMD. Orozco et al. found that early postmenopausal women with hypercholesterolemia (≥240 mg/dl), high LDL-C (≥160 mg/dl) or high lipoprotein (≥25 mg/dl) have a lower lumbar and femoral BMD than do those with a normal lipid profile [16]. By contrast, Adami et al. found that the LC, LDL-C and TG levels were positively related to the total body and hip BMD in women aged 68–75 [17]. However, the 34-year Framingham Osteoporosis Prospective Study by Samelson et al. found no strong correlation between the TC levels and BMD [15].

It seems likely that differences in BMD at various skeletal sites are related to serum lipids in pre- and post-menopausal women, as well as to the effects of onset and rate of bone loss and the effect of estrogen. Most studies have focused on this association in post-menopausal subjects; few studies, however, have specifically included both pre- and post-menopausal subjects. The objectives of this population-based study were to investigate the potential associations between BMD and serum lipid profiles, which are regarded as surrogate markers of osteoporosis and cardiovascular disease, respectively, and to evaluate differences in the effects of serum lipids on BMD of various sites in pre- and post-menopausal women.

Materials and methods

Subjects

The study included 867 women, aged 19–80 years, who participated in the Thyroid Disease Prevalence Study, which compared the prevalence rate of thyroid nodules and cancer for the rural population in different regions and investigated the risk factors for chronic disease, such as cardiovascular disease, osteoporosis and dementia. This study was carried out in the Yeonggwang and Muan Counties of Jeollanam-do Province, Korea, in July and August 2004. All the women underwent clinical examinations and answered a questionnaire regarding their time of menopause, medical history and life style.

Menopause was defined as at least 12 months of amenorrhoea resulting from the permanent cessation of ovarian function. The post-menopausal group included those subjects who had undergone a natural change of life. Therefore, we excluded 52 cases of surgical menopause, 22 cases of hormone replacement therapy, 26 and 3 women who reported menopause at <40 years and >60 years, respectively, 14 women with unconfirmed age of menopause and 18 women who had experienced less than 12 months of amenorrhea. One case with surgical menopause was also taking lipid-lowering medicine, and one other case was taking lipid-lowering medicine. Consequently, our study analyzed 730 women (375 pre-menopausal women with regular menstrual cycles and 355 post-menopausal women). All of the participants provided informed consent, and the study was conducted in accordance with the guidelines in the Declaration of Helsinki. The study was approved by the appropriate institutional research ethics committee.

Anthropometric measurements

Anthropometric measurements of subjects wearing light clothing and no shoes were conducted by experienced research staff. Height was measured to the nearest 0.1 cm, and weight was measured in the upright position to the nearest 0.1 kg. Weekly fitness activity was defined as more than three times weekly and for more than 30 min each time.

Measurements of bone mineral density

The BMD (g/cm^2) of the right hip and lumbar vertebra were carried out using the dual-energy X-ray absorptiometer (GE/Bravo Lunar DPX; Lunar, Madison, Wis.). BMD was measured in grams per square centimeter at the lumbar spine (L_{1-4}), right femoral neck, right trochanter, right shaft, right Ward's triangle and proximal total hip. Calibration was performed daily with a physical phantom. The within-day coefficients for duplicate measurements in 50 adults were 2.2, 1.9, 1.6, 2.3, 1.3 and 1.5%, for the femoral neck, trochanter, shaft, Ward's triangle, proximal total hip and L1–4 lumbar vertebra, respectively.

Lipid measurements

All the participants underwent at least 10 h of overnight fasting before blood samples were drawn from an antecubital vein. Serum was separated on-site and was stored at –70°C until it was analyzed (within 3–4 weeks). Serum TC and TG were analyzed enzymatically using Pureauto S TC-N (Daiichi Chemicals, Tokyo, Japan) and Determiner L TG (Kyowa Medics, Tokyo, Japan), respectively. HDL-C was determined using direct method and Determiner L HDL-C (Kyowa Medics, Tokyo, Japan). All samples were measured using an

automatic analyzer (AU5400, Olympus, Japan). LDL-C was estimated using the formula of Friedewald et al. [18]. The interassay coefficient of variation for determinations of TC, TG and HDL-C range were 3.0, 3.0 and 5.0% lower, respectively.

Statistical analysis

The descriptive data for the major characteristics and the BMD values of the two groups are expressed as mean ± standard deviation (SD). We used t-tests to determine statistical differences in the continuous variables and chi-square tests for the categorical variables. The coefficient of correlations was examined between the BMD at different skeletal sites and serum lipids using partial correlation after adjustment for the known effects on BMD of age, height, weight, age at menarche, menopause duration and weekly fitness activity.

The levels of serum lipid were divided into four quartiles. A general linear model was used to evaluate the linear relationship between adjusted BMD and serum lipids and to compare the adjusted BMD means according to the four quartiles of baseline serum lipid levels in the pre- and post-menopausal women. Bonferroni tests were applied to correct for multiple comparisons. The SPSS software version 11.0 (SPSS, Chicago, Ill.) was used.

Results

Table 1 shows the main characteristics of the two groups of women. There were significant differences between the groups in terms of age, height, weekly fitness activity, age at menarche, BMD and serum lipids. For the serum lipids, with the exception of HDL-C, which was higher in pre-menopausal women, the levels of serum TG, TC and LDL-C were significantly lower in the pre-menopausal women than they were in the post-menopausal women. The values for the BMDs at all sites, height and weekly fitness activity were significantly higher in premenopausal than post-menopausal subjects, while age at menarche was significantly lower for the pre-menopausal subjects. No body-weight differences were noted between the two groups. The mean ages of the pre- and post-menopausal groups were 38.5 ± 8.6 years and 63.5 ± 6.5 years, respectively. The mean of menopause duration was 14.4 ± 8.4 years.

The partial correlations between the BMD values and serum lipid levels are presented in Table 2. We adjusted for the variables age, height, weight, age at menarche, menopause duration and weekly fitness activity, which are known to affect BMD. The associations between BMD and serum lipids were different in pre- and post-menopausal women. The serum levels of TC and LDL-C were inversely correlated with BMD value at lumbar 1–4 in the pre-menopausal group (TC: $r = -0.12$, $P < 0.05$ and LDL-C: $r = -0.12$, $P < 0.05$), but not in the post-menopausal group. In the post-menopausal subjects, the TC levels showed significant correlation with the BMD values at the trochanter ($r = -0.15$, $P < 0.01$), shaft ($r = -0.16$, $P < 0.001$) and proximal total hip ($r = -0.15$, $P < 0.01$) sites, while the LDL-C levels correlated with the BMD values at the neck ($r = -0.13$, $P < 0.05$), trochanter ($r = -0.21$, $P < 0.001$), shaft ($r = -0.20$, $P < 0.001$) and proximal total hip ($r = -0.20$, $P < 0.001$) sites, but not in the pre-menopausal. The TG levels showed a significant positive correlation only with BMD value at the trochanter site ($r = 0.11$, $P = 0.05$) in the post-menopausal group. The HDL-C levels were not associated with BMD value at any site in the pre- and

Table 1 Characteristics of the subjects by status of menopause

Characteristics	Pre-menopausal ($n = 375$)	Post-menopausal ($n = 355$)	P^*
Age (years)	38.5 ± 8.6	63.5 ± 6.5	0.00
Height (cm)	157.5 ± 5.1	151.7 ± 5.0	0.00
Body weight (kg)	58.1 ± 8.5	57.4 ± 7.9	0.20
Weekly fitness activity (%)	41.4	18.7	0.00
Menopause duration (years)	-	14.4 ± 8.4	
Age at menarche (years)	15.8 ± 8.4	17.9 ± 4.7	0.00
Bone mineral density (g/cm^2)			
Lumbar (1–4)	1.18 ± 0.13	0.94 ± 0.14	0.00
Femoral neck	0.96 ± 0.11	0.82 ± 0.12	0.00
Ward's triangle	0.83 ± 0.14	0.60 ± 0.13	0.00
Trochanter	0.78 ± 0.10	0.68 ± 0.11	0.00
Shaft	1.16 ± 0.14	1.01 ± 0.15	0.00
Proximal total hip	0.99 ± 0.11	0.86 ± 0.12	0.00
TG (mg/dl)	78.6 ± 52.1	119.7 ± 71	0.00
TC (mg/dl)	158.2 ± 29.7	185.5 ± 36.0	0.00
HDL-C (mg/dl)	48.9 ± 11.5	46.4 ± 11.8	0.00
LDL-C (mg/dl)	93.6 ± 26.0	115.2 ± 30.9	0.00

Unless otherwise indicated, the data are shown as mean ± standard deviation. TG: triglycerides; TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol. $^*P$ value, as determined by the t-test or chi-square test as appropriate

Table 2 Partial correlation between BMD at various sites and lipid content in pre- and post-menopausal women

	Lumbar (1–4)	Femoral neck	Ward's triangle	Trochanter	Shaft	Proximal total hip
Pre-menopausal						
TG	−0.09	−0.02	−0.02	0.03	0.01	0.01
TC	−0.12[c]	−0.01	−0.01	0.00	−0.05	−0.03
HDL-C	0.03	0.02	0.02	−0.01	−0.01	0.00
LDL-C	−0.12[c]	−0.02	−0.01	−0.01	−0.05	−0.04
Post-menopausal						
TG	0.07	0.08	0.05	0.11[c]	0.07	0.09
TC	0.02	−0.10	−0.05	−0.15[b]	−0.16[a]	−0.15[b]
HDL-C	0.01	−0.05	0.04	−0.04	−0.03	−0.04
LDL-C	−0.01	−0.13[c]	−0.10	−0.21[a]	−0.20[a]	−0.20[a]

TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol. Adjusted for age, height, weight, age at menarche and weekly fitness activity in pre-menopausal women; adjusted for age, height, weight, age at menarche, weekly fitness activity and menopause duration in post-menopausal women. [a] $P < 0.001$; [b] $P < 0.01$; [c] $P < 0.05$

post-menopausal women. As the result of general linear model analysis, and only in the post-menopausal group, a significant linear relationship was observed between the adjusted mean BMD values at the proximal total hip site and the quartiles of the LDL-C and TC levels (Table 3, Table 4), but not at the lumbar site, with linear trend P values of 0.001 and 0.01, respectively, while in the pre-menopausal group, this linear correlation was not observed. The adjusted mean BMD values at the proximal total hip site in the highest quartile of the LDL-C levels were significantly lower than that in the lowest (0.84 ± 0.01 vs. 0.89 ± 0.02) and second (0.84 ± 0.01 vs. 0.88 ± 0.01) quartiles in the post-menopausal women (Table 3). There was no significant difference between the adjusted mean BMD values at the proximal total hip site in each quartile of the TC levels in the post-menopausal women (Table 4). There was no significant difference between the adjustment mean BMD values at lumbar and proximal total hip site in each quartile of serum TG levels (Table 5). However, in the pre-menopausal women, there was a significant difference between the adjusted mean BMD values at the lumbar site in each quartile of serum TG levels, but not at the proximal hip site (Table 5), even if the partial correlation was not observed between BMD values at the lumber site and serum TG levels.

Discussion

This study was conducted to explore the associations between the serum lipid levels and BMD values of rural Korean women. Our results indicate that there are skeletal site-specific differences between pre- and post-menopausal women in terms of the association of BMD with serum lipids

Our results show that the levels of LDL-C are inversely correlated with the hip BMD values in post-menopausal women and the lumbar BMD values in pre-menopausal women. Yamaguchi et al. [19] found an inverse association between the BMDs at two (lumbar spine and radius) of the four sites measured (lumbar spine, femoral neck, radius and total body) and serum LDL-C levels. Poli et al. [20] found that the BMD of only the measured lumbar spine (2–4) site showed a negative association with serum LDL-C levels in post-menopausal women. Although these two reports, which indicate an inverse relationship between LDL-C and BMD, are similar to our findings, they differ from our results with respect to the sites of BMD. These differences can be explained by different study populations (i.e., pre-menopausal women were not included in two studies), age distribution and differences in the methods

Table 3 Adjusted mean BMD values at lumbar and proximal total hip sites by quartiles of LDL-C in pre- and post-menopausal women

Quartile of LDL-C	Lumbar(1–4)		Proximal total hip	
	Pre-menopausal	Post-menopausal	Pre-menopausal	Post-menopausal
1 (<84 mg/dl)	1.19 ± 0.01	0.95 ± 0.02	0.99 ± 0.01	0.89 ± 0.02
2 (85–102 mg/dl)	1.18 ± 0.01	0.95 ± 0.02	0.99 ± 0.01	$0.88 \pm 0.01^{*}$
3 (103–124 mg/dl)	1.19 ± 0.01	0.94 ± 0.01	1.00 ± 0.01	$0.85 \pm 0.01^{\dagger}$
4 (>124 mg/dl)	1.15 ± 0.02	0.94 ± 0.01	0.97 ± 0.01	$0.84 \pm 0.01^{\ddagger}$
Between group (P value)	0.24	0.97	0.52	0.01
Linear trend (P value)	0.18	0.85	0.87	0.00

Adjusted for age, height, weight, age at menarche, weekly fitness activity, and menopause duration in post-menopausal women; adjusted for age, height, weight, age at menarche, and weekly fitness activity in pre-menopausal women. $^{*}P < 0.05$: group 2 compared with group 4 (Bonferroni adjustment for multiple comparisons). $^{\dagger}P < 0.05$: group 1 compared with group 3 (Bonferroni adjustment for multiple comparisons). $^{\ddagger}P < 0.01$: group 4 compared with group 1 (Bonferroni adjustment for multiple comparisons)

Table 4 Adjusted mean BMD values at lumbar and proximal total hip sites by quartiles of TC in pre- and post-menopausal women

Quartile of TC	Lumbar (1–4)		Proximal total hip	
	Pre-menopausal	Post-menopausal	Pre-menopausal	Post-menopausal
1 (< 147 mg/dl)	1.19 ± 0.01	0.93 ± 0.02	0.99 ± 0.01	0.89 ± 0.02
2 (148–169 mg/dl)	1.19 ± 0.01	0.93 ± 0.02	1.00 ± 0.01	0.87 ± 0.01
3 (170–196 mg/dl)	1.16 ± 0.01	0.95 ± 0.01	0.98 ± 0.01	0.85 ± 0.01
4 (> 197 mg/dl)	1.16 ± 0.02	0.95 ± 0.01	0.98 ± 0.02	0.84 ± 0.01
Between group (P value)	0.16	0.74	0.39	0.07
Linear trend (P value)	0.06	0.40	0.32	0.01

Adjusted for age, height, weight, age at menarche, weekly fitness activity, and menopause duration in post-menopausal women; adjusted for age, height, weight, age at menarche, and weekly fitness activity in pre-menopausal women

used (the skeletal site of BMD measurement). In addition, previous studies have shown differences in age-related BMDs at various skeletal sites in different races [21]. Therefore, it is possible that BMD values at different sites produce different outcomes. Orozco et al. found that early postmenopausal women with high LDL-C ($\geq$160 mg/dl) have lower lumbar and femoral BMD than those with normal lipid profile [16]. However, Adami et al. reported a significant positive association of serum LDL-C levels with total body BMD and hip BMD in female subjects aged 68–75 years [17].

Previous studies on the association between BMD and serum TC also show several inconsistencies. Three previous studies have shown no significant correlation between serum TC and BMD [15, 22, 23, 24], which suggests that serum TC plays no significant role in bone cell activity. However, associations between serum TC and BMD have come not only from animal studies, but also from clinical trials. Cholesterol-fed rabbits show trabecular bone loss in the hip [25]. Cholesterol and its metabolites influence the functional activities of osteoblasts both in vitro and in vivo [26, 27]. The cholesterol biosynthetic pathway is important in osteoblast differentiation [28]. Broulik and Kapitola [29] have demonstrated that women with osteoporosis have higher cholesterol levels than control subjects. Our findings that serum TC levels are negatively correlated with lumbar BMD in pre-menopausal women and with hip BMD in post-menopausal women support this observation.

Our results indicate that serum TG levels show a significant positive correlation with hip BMD in the post-menopausal group, which is similar to Adami et al.'s [17]. In contrast, subjects in the higher quartile of serum TG levels show lower lumbar BMD values in the pre-menopausal group. These findings suggest that there is a difference in the effect of TG levels on BMDs at various skeletal sites in pre- and post-menopausal women. However, it is difficult to illustrate the role of serum TG on the BMD through a cross-sectional study, such as the present study. Moreover, the reference in the effect of serum TG on BMD is scarce.

Notably, several studies have reported that BMD is associated with the levels of HDL-C [19, 30], although theses results are not in accordance. Yamaguchi et al. [19] reported a positive relationship, while D'Amelio et al. [30] reported a negative relationship between these two parameters. However, to the best of our knowledge, Poli et al. [20] did not find an association between BMD and serum HDL-C levels in post-menopausal women. Similar to their findings, our study did not find any significant association between the BMDs at the lumbar and hip sites and the serum HDL-C levels in pre- and post-menopausal women.

There are several possible explanations for skeletal site-specificity differences between pre- and post-menopausal women. First, lumbar spines measurement in elderly persons are difficult owing to aortic calcifications, osteophytes and other degenerative changes; these age-related artifacts probably induce lumbar BMD changes that have no association with the serum lipid levels in post-menopausal women. Second, the initiation and speed of loss of bone mass are not the same for bone

Table 5 Adjusted mean BMD values at lumbar and proximal total hip sites by quartiles of TG in pre- and post-menopausal women

Quartile of TG	Lumbar (1–4)		Proximal total hip	
	Pre-menopausal	Post-menopausal	Pre-menopausal	Post-menopausal
1 (< 57 mg/dl)	1.20 ± 0.01	0.96 ± 0.02	1.00 ± 0.01	0.86 ± 0.01
2 (58–83 mg/dl)	1.17 ± 0.01	0.93 ± 0.01	0.97 ± 0.01	0.86 ± 0.01
3 (84–123 mg/dl)	1.16 ± 0.02	0.93 ± 0.01	0.99 ± 0.01	0.85 ± 0.01
4 (> 124 mg/dl)	1.15 ± 0.02	0.95 ± 0.01	0.99 ± 0.02	0.86 ± 0.01
Between group (P value)	0.04	0.31	0.18	0.81
Linear trend (P value)	0.01	0.71	0.63	0.95

Adjusted for age, height, weight, age at menarche, weekly fitness activity, and menopause duration in post-menopausal women; adjusted for age, height, weight, age at menarche, and weekly fitness activity in pre-menopausal women

tissues at different sites [31]. Spinal bone loss diminishes by age 60 and may even stabilize, while femoral bone loss continues and may even accelerate [32, 33, 34]. Therefore, it is important in the assessment of the effects of lipids on bone to evaluate different skeletal sites and the influence of ageing.

Previous studies have suggested a link between atherosclerosis and osteoporosis [4, 5, 6, 7]. Tanko and Bagger recently reported that low BMD of the hip and atherosclerosis in post-menopausal women were linked by common risk factors and pathomechanisms [35]. The co-existence factors of osteoporosis and age-independent atherosclerotic calcification include oxidized lipids, leptin and osteoprotegerin [36]. Bone matrix proteins such as osteopontin [7], osteocalcin [6] and bone morphogenetic protein [37] have been found in atherosclerotic plaques. Regulators of bone resorption, such as vitamin D(38) and osteoprotegerin [39], are associated with vascular calcifications. Several clinical studies have shown that statin use is associated with increased BMD and reduced risk for fracture [9, 10, 11, 12]. More recently, LDL-receptor-related protein 5 has been found to be a key regulator of osteoblast proliferation and bone formation [40, 41]. The loss of function of LRP5 in both humans and mice led to decreased bone formation [42, 43]. These findings suggest that the processes of atherosclerosis and osteoporosis are related.

The mechanism governing the relationship between lipids and BMD is unclear. The following hypothesis has been proposed. Increased serum lipids and lipoproteins may lead to the progressive accumulation in the artery walls and the subendothelial matrix of bone vessels, where they undergo oxidation. Oxidized lipids not only promote inflammatory responses by artery wall cells that initiate the atherosclerotic lesion formation [44], but also inhibit the differentiation and mineralization of bone cells [27]. Although our study did not evaluate the levels of oxidized lipids directly, this mechanism may explain our finding that serum lipid levels, such as TC and LDL-C, are inversely related to BMD. The association showed skeletal site-specific differences in pre- and post-menopausal women. Consequently, our results also indirectly support an association between osteoporosis and atheroclerosis.

Our study is population-based and includes a relatively large sample size. Most previous studies dealing with the relationship between BMD and serum lipid content focused only on post-menopausal subjects, while relatively few studies have focused on comparing post-menopausal women with pre-menopausal women. However, in this type of cross-sectional study, it is difficult to determine directly differences in the effects of lipid levels on BMDs between pre- and post-menopausal women.

In conclusion, our data indicate an association between BMD and serum lipid levels. This relationship suggests skeletal site-specificity differences between pre- and post-menopausal women in terms of the effects of serum lipids on BMDs at various skeletal sites.

References

1. Von der Recke P, Hansen MA, Hassager C (1999) The association between low bone mass at the menopause and cardiovascular mortality. Am J Med 106:273–278
2. Eriksen EF, Colvard DS, Berg NJ, Graham ML, Mann KG, Spelsberg TC, Riggs BL (1988) Evidence of estrogen receptors in normal human osteoblast-like cells. Science 241:84–86
3. Oursler MJ, Pederson L, Fitzpatrick L, Riggs BL, Spelsberg T (1994) Human giant cell tumors of the bone (osteoclastomas) are estrogen target cells. Proc Natl Acad Sci USA 91:5227–5231
4. Kiel DP, Kauppila LI, Cupples LA, Hannan MT, O'Donnell CJ, Wilson PW (2001) Bone loss and the progression of abdominal aortic calcification over a 25-year period: the Framingham Heart Study. Calcif Tissue Int 68:271–276
5. Hak AE, Pols HA, van Hemert AM, Hofman A, Witteman JC (2000) Progression of aortic calcification is associated with metacarpal bone loss during menopause: a population-based longitudinal study. Arterioscler Thromb Vasc Biol 20:1926–1931
6. Fleet JC, Hock JM (1994) Identification of osteocalcin mRNA in nonosteoid tissue of rats and humans by reverse transcription-polymerase chain reaction. J Bone Miner Res 9:1565–1573
7. Giachelli CM, Liaw L, Murry CE, Schwartz SM, Almeida M (1995) Osteopontin expression in cardiovascular diseases. Ann N Y Acad Sci 760:109–126
8. Reid IR, Hague W, Emberson J, Baker J, Tonkin A, Hunt D, MacMahon S, Sharpe N (2001) Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. Long-term intervention with pravastatin in ischaemic disease. Lancet 357:509–512
9. Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, Boyce B, Zhao M, Gutierrez G (1999) Stimulation of bone formation in vitro and in rodents by statins. Science 286:1946–1949
10. Edwards CJ, Hart DJ, Spector TD (2000) Oral statins and increased bone-mineral density in postmenopausal women. Lancet 355:2218–2219
11. Wang PS, Solomon DH, Mogun H, Avorn J (2000) HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. JAMA 283:3211–3216
12. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H (2000) HMG-CoA reductase inhibitors and the risk of fractures. JAMA 283:3205–3210
13. Torgerson DJ, Bell-Syer SE (2001) Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. JAMA 285:2891–2897
14. Davidson MH, Maki KC, Marx P, Maki AC, Cyrowski MS, Nanavati N, Arce JC (2000) Effects of continuous estrogen and estrogen-progestin replacement regimens on cardiovascular risk markers in postmenopausal women. Arch Intern Med 160:3315–3325
15. Samelson EJ, Cupples LA, Hannan MT, Wilson PW, Williams SA, Vaccarino V, Zhang Y, Kiel DP (2004) Long-term effects of serum cholesterol on bone mineral density in women and men: the Framingham Osteoporosis Study. Bone 34:557–561
16. Orozco P (2004) Atherogenic lipid profile and elevated lipoprotein (a) are associated with lower bone mineral density in early postmenopausal overweight women. Eur J Epidemiol 19:1105–1112
17. Adami S, Braga V, Zamboni M, Gatti D, Rossini M, Bakri J, Battaglia E (2004) Relationship between lipids and bone mass in two cohorts of healthy women and men. Calcif Tissue Int 74:136–142
18. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499–502
19. Yamaguchi T, Sugimoto T, Yano S, Yamauchi M, Sowa H, Chen Q, Chihara K (2002) Plasma lipids and osteoporosis in postmenopausal women. Endocr J 49:211–217

20. Poli A, Bruschi F, Cesana B, Rossi M, Paoletti R, Crosignani PG (2003) Plasma low-density lipoprotein cholesterol and bone mass densitometry in postmenopausal women. Obstet Gynecol 102:922–926

21. Wu XP, Liao EY, Huang G, Dai RC, Zhang H (2003) A comparison study of the reference curves of bone mineral density at different skeletal sites in native Chinese, Japanese, and American Caucasian women. Calcif Tissue Int 73:122–132

22. Perez-Castrillon JL, De Luis D, Martin-Escudero JC, Asensio T, del Amo R, Izaola O (2004) Non-insulin-dependent diabetes, bone mineral density, and cardiovascular risk factors. J Diabetes Complications 18:317–321

23. Tanko LB, Bagger YZ, Nielsen SB, Christiansen C (2003) Does serum cholesterol contribute to vertebral bone loss in postmenopausal women? Bone 32:8–14

24. Wu LY, Yang TC, Kuo SW, Hsiao CF, Hung YJ, Hsieh CH, Tseng HC, Hsieh AT, Chen TW, Chang JB, Pei D (2003) Correlation between bone mineral density and plasma lipids in Taiwan. Endocr Res 29:317–325

25. Bartels T, Beitz J, Hein W, Schumann M, Laag L, Beitz A, Szymanski C, Mest HJ (1990) [Changes in the spongiosa density in the femoral head of rabbits in atherosclerosis]. Beitr Orthop Traumatol 37:291–297

26. Parhami F, Garfinkel A, Demer LL (2000) Role of lipids in osteoporosis. Arterioscler Thromb Vasc Biol 20:2346–2348

27. Parhami F, Morrow AD, Balucan J, Leitinger N, Watson AD, Tintut Y, Berliner JA, Demer LL (1997) Lipid oxidation products have opposite effects on calcifying vascular cell and bone cell differentiation. A possible explanation for the paradox of arterial calcification in osteoporotic patients. Arterioscler Thromb Vasc Biol 17:680–687

28. Parhami F, Mody N, Gharavi N, Ballard AJ, Tintut Y, Demer LL (2002) Role of the cholesterol biosynthetic pathway in osteoblastic differentiation of marrow stromal cells. J Bone Miner Res 17:1997–2003

29. Broulik PD, Kapitola J (1993) Interrelations between body weight, cigarette smoking and spine mineral density in osteoporotic Czech women. Endocr Regul 27:57–60

30. D'Amelio P, Pescarmona GP, Gariboldi A, Isaia GC (2001) High density lipoproteins (HDL) in women with postmenopausal osteoporosis: a preliminary study. Menopause 8:429–432

31. Morita R, Yamamoto I, Takada M, Yuu I, Ohta T, Matsushita R, Hamanaka Y (1998) [Recent development and clinical application of bone mineral measurements]. Nippon Rinsho 56:1458–1463

32. Arlot ME, Sornay-Rendu E, Garnero P, Vey-Marty B, Delmas PD (1997) Apparent pre- and postmenopausal bone loss evaluated by DXA at different skeletal sites in women: the OFELY cohort. J Bone Miner Res 12:683–690

33. Ensrud KE, Palermo L, Black DM, Cauley J, Jergas M, Orwoll ES, Nevitt MC, Fox KM, Cummings SR (1995) Hip and calcaneal bone loss increase with advancing age: longitudinal results from the study of osteoporotic fractures. J Bone Miner Res 10:1778–1787

34. Jones G, Nguyen T, Sambrook P, Kelly PJ, Eisman JA (1994) Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. Bmj 309:691–695

35. Tanko LB, Bagger YZ, Christiansen C (2003) Low bone mineral density in the hip as a marker of advanced atherosclerosis in elderly women. Calcif Tissue Int 73:15–20

36. Tintut Y, Demer LL (2001) Recent advances in multifactorial regulation of vascular calcification. Curr Opin Lipidol 12:555–560

37. Bostrom K (2001) Insights into the mechanism of vascular calcification. Am J Cardiol 88:20E–22E

38. Price PA, June HH, Buckley JR, Williamson MK (2001) Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. Arterioscler Thromb Vasc Biol 21:1610–1616

39. Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, Capparelli C, Scully S, Tan HL, Xu W, Lacey DL, Boyle WJ, Simonet WS (1998) Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev 12:1260–1268

40. Bollerslev J, Wilson SG, Dick IM, Islam FM, Ueland T, Palmer L, Devine A, Prince RL (2005) LRP5 gene polymorphisms predict bone mass and incident fractures in elderly Australian women. Bone 36:599–606

41. Koay MA, Woon PY, Zhang Y, Miles LJ, Duncan EL, Ralston SH, Compston JE, Cooper C, Keen R, Langdahl BL, MacLelland A, O'Riordan J, Pols HA, Reid DM, Uitterlinden AG, Wass JA, Brown MA (2004) Influence of LRP5 polymorphisms on normal variation in BMD. J Bone Miner Res 19:1619–1627

42. Gong Y, Slee RB, Fukai N, Rawadi G, Roman-Roman S, Reginato AM, Wang H, Cundy T, Glorieux FH, Lev D, Zacharin M, Oexle K, Marcelino J, Suwairi W, Heeger S, Sabatakos G, Apte S, Adkins WN, Allgrove J, Arslan-Kirchner M, Batch JA, Beighton P, Black GC, Boles RG, Boon LM, Borrone C, Brunner HG, Carle GF, Dallapiccola B, De Paepe A, Floege B, Halfhide ML, Hall B, Hennekam RC, Hirose T, Jans A, Juppner H, Kim CA, Keppler-Noreuil K, Kohlschuetter A, LaCombe D, Lambert M, Lemyre E, Letteboer T, Peltonen L, Ramesar RS, Romanengo M, Somer H, Steichen-Gersdorf E, Steinmann B, Sullivan B, Superti-Furga A, Swoboda W, van den Boogaard MJ, Van Hul W, Vikkula M, Votruba M, Zabel B, Garcia T, Baron R, Olsen BR, Warman ML (2001) LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. Cell 107:513–523

43. Kato M, Patel MS, Levasseur R, Lobov I, Chang BH, Glass DA 2nd, Hartmann C, Li L, Hwang TH, Brayton CF, Lang RA, Karsenty G, Chan L (2002) Cbfa1-independent decrease in osteoblast proliferation, osteopenia, and persistent embryonic eye vascularization in mice deficient in Lrp5, a Wnt coreceptor. J Cell Biol 157:303–314

44. Witztum JL, Berliner JA (1998) Oxidized phospholipids and isoprostanes in atherosclerosis. Curr Opin Lipidol 9:441–448