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Plasma Lipids and Osteoporosis in Postmenopausal Women

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Abstract. Many clinical studies have shown that osteoporosis is associated with atherosclerosis and cardiovascular death. Although both high plasma levels of low density lipoprotein cholesterol (LDL-C) and low plasma levels of high density lipoprotein cholesterol (HDL-C) are known to be risk factors for atherosclerosis, it is unclear whether such lipid derangements are also associated with the pathogenesis of osteoporosis. In this study, we evaluated the relationships between plasma levels of total C, LDL-C, HDL-C, or triglyceride (TG) versus bone mineral density (BMD) at the lumbar spine, femoral neck, radius, or total body as well as the presence of vertebral fractures in 214 Japanese postmenopausal women (age range, 47–86 years, mean 62.7). Multiple regression analysis was performed between BMD at each skeletal site versus each lipid level adjusted for age, years after menopause, body mass index (BMI), and %fat. Plasma LDL-C levels were significantly and inversely correlated with the absolute values of both one-third radial (1/3R) and distal radial (UDR) BMD ($p<0.01$), and tended to be inversely correlated with the absolute values of L-BMD ($p=0.051$). In contrast, plasma HDL-C levels were significantly and positively correlated with the absolute values of L, 1/3R and UDR BMD ($p<0.05$). On the other hand, plasma TG levels were significantly lower in women with vertebral fractures than in those without fractures (97.0±36.5 vs. 126.4±65.8 mg/dl, mean±SD, $p<0.05$). When multivariate logistic regression analysis was performed with the presence of vertebral fractures as a dependent variable and each lipid level adjusted for age, years after menopause, BMI, and %fat as independent variables, TG alone was selected as an index affecting the presence of vertebral fractures (odds ratio: 0.51, 95% confidential interval: 0.29–0.89 per SD increase, $p<0.05$). Our study showed that plasma LDL-C and HDL-C levels were inversely and positively correlated with both R- and L-BMD values, respectively, while low plasma TG levels were associated with the presence of vertebral fractures in postmenopausal women. Thus, plasma lipids might be related to bone mass and bone fragility, and might be the common factor underlying both osteoporosis and atherosclerosis.

Key words: Plasma lipid, Osteoporosis, Bone mineral density, Vertebral fracture, Postmenopausal women

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MANY clinical studies have shown that osteoporosis is associated with atherosclerosis or cardiovascular disease. An epidemiological study indicated that aortic calcification was more prevalent in communities where osteoporosis was more prevalent [1]. Other studies showed that after age-adjustment, calcified aortic plaques were inversely related to bone mineral density (BMD) of the lumbar spine [2] or distal and proximal radius [3]. A study using aortic pulse wave velocity as a surrogate measure of aortic calcification showed that calcification was inversely correlated with radial BMD even after correction for age and body weight [4]. Uyama *et al.* [5] also reported that the plaque score assessed by ultrasonography of the carotid artery wall was significantly correlated with low total BMD and total cholesterol level after adjustment for age by multiple linear regression analysis. Barengolts *et al.* [6] compared coronary calcium scores measured by electron beam computed tomography in asymptomatic, postmenopausal women with normal and low BMD, who were

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similar in age and body mass index (BMI), and found that the score was significantly higher in the osteoporosis group than in the control group. Moreover, low radial BMD was associated with increased risks of stroke [7] and cardiovascular death [8], after adjustments for age and several other potential confounders.

It is well established that the incidence of atherosclerotic cardiovascular disease is positively related to plasma levels of low density lipoprotein cholesterol (LDL-C) and is inversely related to those of high density lipoprotein cholesterol (HDL-C) [9]. Many *in vivo* and *in vitro* experiments show that LDL oxidation products play important roles in atherosclerotic lesion formation by accumulating in the vessel wall [10, 11], while HDLs may protect against excess lipid accumulation by inhibiting the oxidation of LDLs and facilitating cholesterol transport from the vessel wall to the liver [12]. On the other hand, Parhami and Demer [13] and Parhami *et al.* [14] showed that minimally oxidized LDL also inhibited osteoblastic differentiation of the MC3T3-E1 preosteoblastic cells as well as M2-10B4 stromal cells and promoted adipogenic differentiation of the latter cells as well as 3T3-L1 preadipocytes, suggesting that LDL oxidation products could also promote osteoporotic loss of bone by inhibiting differentiation of osteoblasts and by directing progenitor marrow stromal cells to undergo adipogenic instead of osteogenic differentiation. Thus, it is possible that LDL oxidation products may be the common factors underlying the pathogenesis of both atherosclerosis and osteoporosis.

However, few clinical studies have statistically investigated the linkage of plasma lipids to osteoporosis-related factors such as BMD and fractures. In this study, we examined the relationships between plasma levels of total C, LDL-C, HDL-C, or triglyceride (TG) versus BMD values at the lumbar spine, femoral neck, radius, whole body as well as the presence of vertebral fractures in 214 Japanese postmenopausal women to determine whether plasma lipids were associated with osteoporosis.

Subjects and Methods

Subjects

Two hundred and fourteen women (age range, 47–86 years, mean 62.7), who had been postmenopausal for at least 12 months and who had been referred for the first time to our hospital for the evaluation of osteoporosis, were recruited into this study. Of these 214 women, 35 had vertebral fractures. Ethics approval for this study was granted by the Institutional Review Board of our institution. The subjects gave informed consent for monitoring biochemical parameters and BMD values. None of the subjects had diabetes mellitus, thyroid disorder or metabolic bone diseases, or were taking drugs or hormones that influence bone metabolism or plasma lipids.

Biochemical measurements

Each patient came to the hospital after an overnight fast and provided a fasting heparinized blood samples and urine specimen for analysis of biochemical parameters. Concentrations of total C, HDL-C, TG, calcium (Ca), phosphorus (P), alkaline phosphate (ALP), albumin (Alb), blood urea nitrogen (BUN), and creatinine (Cr) were measured by automated techniques at the central laboratory of our hospital (normal range: total C 146–233 mg/dl, HDL-C 43–65 mg/dl, TG 28–147 mg/dl, Ca 8.5–9.9 mg/dl, P 2.4–4.5 mg/dl, ALP 100–303 IU/l, Alb 4.1–5.0 mg/dl, BUN 9–22 mg/dl, and Cr 0.5–1.3 mg/dl). LDL-C was calculated using Friedewald's formula (LDL-C = total C − HDL-C − TG/5) [15] (normal range: <130 mg/dl). Midregion parathyroid hormone (mPTH) was measured by a radioimmunoassay (Yamasa hypersensitive PTH-RIA kit, Yamasa Shoyu Co., Ltd., Japan, normal range: 160–520 pg /ml) [16].

BMD and body composition measurements

BMD values were measured by dual energy X-ray absorptiometry (DXA) using QDR-2000 (Hologic Inc., Waltham, MA) at the lumbar spine, femoral neck, radius, and whole body as previously described [17]. BMD was automatically calculated from the bone area (cm^2) and bone mineral content (BMC) (g) and expressed absolutely in g/cm^2. Values except that at the whole body were also expressed relatively as the standard deviation (SD) of age- and sex-matched normal Japanese mean values provided by the manufacturer (Z score). Accurate Z scores of

whole body BMD values were not available in Japan because of a lack of sufficient data on a normal Japanese reference population. The coefficients of variation (precision) of measurements of the lumbar spine, femoral neck and radius were 0.9, 1.7 and 1.9 %, respectively. Body composition was measured by the DXA method in array mode and the coefficient of variation of fat body mass measurement was 2.0%.

Ascertainment of fractures

Vertebral fractures were assessed by lateral thoracic and lumbar spine radiographs and were defined using ratios of vertebral heights according to the diagnostic criteria provided by the Japanese Society of Bone and Mineral Metabolism [18]. Prevalent wedge fractures were defined by anterior heights more than 25% below posterior heights. Crush fractures were defined by midvertebral heights that were more than 20% below anterior or posterior heights.

Statistical analysis

BMD values, demographic, and biochemical paraimeters were expressed as mean±SD for each group. Statistical analysis was performed using the computer program Statview (Abacus Concepts, Inc., Berkeley, CA). Multiple regression analysis was used to assess the relationship between BMD values and plasma lipid levels. To evaluate the contribution of plasma lipid levels to the presence of vertebral fracture, multivariate logistic regression analysis was performed. Comparisons between two groups were made with unpaired *t*-tests. P-values less than 0.05 were considered significant.

Results

The characteristics of the participants are summarized in Table 1. The subjects enrolled in the present study had normal values of BMI and %fat, indicating that they had an average nutritional status. The Z scores of BMD values at each skeletal site were normal compared to the age-matched reference population provided by the manufacturer.

Since our statistical analysis showed that BMI and %fat were significantly correlated with each other and were significantly associated with both BMD and plasma lipid levels (data not shown), a multiple regression analysis was performed between BMD at each skeletal site and each plasma lipid level adjusted for age, years after menopause, BMI, and %fat (Table 2). Plasma LDL-C levels were significantly and inversely correlated with the absolute values of both one-third radial (1/3R) and distal radial (UDR) BMD ($p<0.01$), and tended to be inversely correlated with the absolute values of L-BMD ($p=0.051$). In contrast, plasma HDL-C levels were significantly and positively correlated with the absolute values of L, 1/3R and UDR BMD ($p<0.05$). Neither plasma total C levels nor TG levels were significantly correlated with BMD values at any skeletal sites, except for a significant inverse correlation between plasma total

Table 1. Baseline characteristics of the subjects

Number of subjects	214
Age (year)	62.7±8.1
Years since menopause	13.7±8.1
Body weight (kg)	51.9±8.1
Height (cm)	152.1±5.1
BMI (kg/m^2)	22.4±3.2
%fat	35.7±7.4
Alb (g/dl)	4.15±0.28
Ca (mg/dl)	9.29±0.35
P (mg/dl)	3.80±0.63
Alp (IU/l)	229±66
BUN (mg/dl)	16.1±3.5
Cr (mg/dl)	0.62±0.11
U-Ca/U-Cr	0.229±0.122
mPTH (pg/ml)	368±128
Total C (mg/dl)	220±35
LDL-C (mg/dl)	129±35
HDL-C (mg/dl)	66.7±19.0
TG (mg/dl)	122±63
L-BMD (g/cm^2)	0.763±0.134
L-BMD (Z score)	0.065±1.257
F-BMD (g/cm^2)	0.615±0.097
F-BMD (Z score)	0.262±1.348
1/3R-BMD (g/cm^2)	0.501±0.074
1/3R-BMD (Z score)	−0.703±1.210
UDR-BMD (g/cm^2)	0.301±0.062
UDR-BMD (Z score)	1.352±1.112
Total BMD (g/cm^2)	0.905±0.090

Abbreviations: C, cholesterol; L, lumbar; F, femoral neck; 1/3R, mid-radial; UDR, ultradistal radial

Table 2. Multiple regression analysis between BMD at each skeletal site versus each plasma lipid level adjusted for age, years after menopause, BMI, and %fat as independent variables
Numbers in each cell describe a correlation coefficient.

	Independent variables			
BMD region	Total C	LDL-C	HDL-C	TG
L (g/cm^2)	−0.074	−0.125	0.139*	−0.062
F (g/cm^2)	−0.014	−0.052	0.091	−0.024
1/3R (g/cm^2)	−0.079	−0.177**	0.154*	0.045
UDR (g/cm^2)	−0.127*	−0.204**	0.129*	0.023
Total (g/cm^2)	0.045	0.035	−0.008	0.042

*p<0.05, **p<0.01

C levels and the absolute values of UDR-BMD ($p<0.05$).

Since an elevated circulating PTH level due to secondary hyperparathyroidism may be involved in cortical bone loss in aged women, we analyzed the relationship among LDL-C, HDL-C, PTH and radial BMD. Simple regression analysis revealed that there were no significant correlations between these factors (data not shown).

Next, we compared demographic and biochemical parameters including plasma lipids as well as BMD values at each site between women with and without vertebral fractures (Table 3). Women with vertebral fractures were significantly older in age ($P=0.0001$) and shorter in height ($P=0.0381$), and had signifi-

Table 3. Comparison of subjects with and without vertebral fractures

	Vertebral fractures		
	Yes	No	p value
Number of subjects	35	179	
Age (year)	69.7±7.3	61.3±7.6	0.0001*
Years since menopause	20.0±8.1	12.5±7.6	0.0001*
Body weight (kg)	49.3±8.8	52.4±7.9	0.0355*
Height (cm)	150.1±6.6	152.5±4.7	0.0108*
BMI (kg/m^2)	21.7±2.7	22.5±3.3	0.1739
%fat	33.5±7.3	36.1±7.4	0.0584
Alb (g/dl)	4.14±0.29	4.16±0.28	0.7383
Ca (mg/dl)	9.23±0.33	9.30±0.36	0.3104
P (mg/dl)	3.66±0.43	3.83±0.66	0.1438
Alp (IU/l)	252±87	224±61	0.0245*
BUN (mg/dl)	16.5±4.1	16.0±3.4	0.4051
Cr (mg/dl)	0.67±0.15	0.61±0.10	0.0026*
U-Ca/U-Cr	0.21±0.12	0.23±0.12	0.3494
mPTH (pg/ml)	385±168	365±119	0.4313
Total C (mg/dl)	214±35	222±35	0.2370
LDL-C (mg/dl)	128±34	130±35	0.7416
HDL-C (mg/dl)	66.9±18.2	66.6±19.2	0.9390
TG (mg/dl)	97.0±36.5	126.4±65.8	0.0110*
L-BMD (g/cm^2)	0.631±0.104	0.789±0.123	0.0001*
L-BMD (Z score)	−0.767±1.065	0.227±1.229	0.0001*
F-BMD (g/cm^2)	0.543±0.084	0.629±0.093	0.0001*
F-BMD (Z score)	0.012±1.255	0.311±1.364	0.2316
1/3R-BMD (g/cm^2)	0.437±0.069	0.514±0.068	0.0001*
1/3R-BMD (Z score)	−1.139±1.081	−0.617±1.218	0.0213*
UDR-BMD (g/cm^2)	0.239±0.047	0.313±0.057	0.0001*
UDR-BMD (Z score)	0.676±1.254	1.486±1.034	0.0001*
Total BMD (g/cm^2)	0.834±0.069	0.919±0.088	0.0001*

*p<0.05

Table 4. Associations between the presence of vertebral fractures and each plasma lipid level[a] in the subjects

	Presence of vertebral fractures	
	OR (95% CI)	p value
Total C	0.93 (0.58, 1.47)	0.7492
LDL-C	1.16 (0.74, 1.82)	0.5227
HDL-C	0.96 (0.61, 1.53)	0.8701
TG	0.51 (0.29, 0.89)	0.0187*

[a]Multivariate analysis adjusted for age, years after menopause, BMI, and %fat; unit of change = per SD increase.
*$p<0.05$

cantly lower absolute values and Z scores of BMD at each of the skeletal sites than women without vertebral fractures (mostly $P = 0.0001$) except for the Z scores of F-BMD. Among plasma lipids, only TG was significantly lower in women with vertebral fractures than in those without fractures ($p = 0.0110$).

When a multivariate logistic regression analysis was performed with the presence of vertebral fractures as a dependent variable and each lipid level adjusted for age, years after menopause, height, BMI, and %fat as independent variables (Table 4), only TG was found to be associated with the presence of vertebral fractures (odds ratio: 0.51, 95% confidential interval: 0.29–0.89 per SD increase, $p = 0.0187$).

Discussion

In this study, we found that plasma LDL-C and HDL-C levels were inversely and positively correlated with both R- and L-BMD values, respectively, after correction for age, BMI, and %fat in postmenopausal women. These relations are very similar to those between the two lipids and atherosclerosis, where plasma LDL-C and HDL-C levels are inversely and positively correlated with the incidence of atherosclerotic cardiovascular disease, respectively, and the correction of these lipid abnormalities by diet and drug therapies is the best way to protect against the disease [9].

Although both R- and L-BMD values were correlated with LDL-C and HDL-C in this study, R-BMD was more significantly correlated with these lipids than L-BMD. Other researchers have also reported the significant association of BMD with aortic calcification, stroke, and cardiovascular death at the radial site but not at other sites [3, 4, 8, 19]. Thus, there might be a difference in the association with plasma levels of the two lipids or the incidence of lipid-related disorders between the appendicular and axial bones.

On the other hand, this study showed that plasma TG but not LDL-C or HDL-C were significantly lower in women with vertebral fractures than in those without fractures. A logistic regression analysis indicated that every 1 SD increase in plasma TG levels in the patients reduced the chance of having vertebral fractures by nearly half. The mechanisms underlying this relation are unclear. A search of the literature failed to find other reports of the association of TG with vertebral fractures. Since this association was observed even after correction for BMI and %fat, it is unlikely that differences in the nutritional status of the subjects affected the statistical outcome.

Although no method for evaluating bone quality or bone geometry is clinically available at present, the presence of a vertebral fracture might be useful as a crude indicator of bone quality in individual patients. A large study on the incidence of vertebral fractures in postmenopausal osteoporosis showed that patients with previous vertebral fractures were more likely to suffer new vertebral fractures [20, 21] and hip fractures [20] than those without vertebral fractures during several-year study periods. We found that high TG was associated with the lower incidence of vertebral fractures, or possible better bone quality, in postmenopausal women. In contrast, recent large-scale clinical studies showed that TG was an independent risk factor for major coronary events after controlling for LDL-C and HDL-C [22]. Thus, this study suggests that circulating TG might have opposite impacts on the bone and the vessel wall, while LDL-C and HDL-C have similar effects on both tissues.

Accumulating evidence shows that patients with lower bone density or osteoporosis are prone to have more severe atherosclerosis and a greater risk of cardiovascular death [1–8]. It is well known that oxidized LDL can contribute to the pathogenesis of atherosclerosis by many mechanisms [10, 11]. Oxidized LDL attracts monocytes to the vessel wall and facilitates their conversion into macrophages. In turn, macrophages express scavenger receptors that take up oxidized LDL, leading to lipid-laden foam cells and fatty streak lesions. The products of oxi-

dized LDL are toxic, producing endothelial damage and initiating thrombosis and smooth muscle cell proliferation by releasing platelet-derived growth factors from platelets attracted to the lesion. Since the bone is also abundant in such cells and growth factors, it is possible that oxidized LDL could evoke similar reactions in its microenvironment and could eventually cause bone loss and osteoporosis. Indeed, recent *in vitro* studies showed that LDL oxidation products had the abilities to inhibit osteoblast differentiation and to promote adipocyte differentiation [13, 14], suggesting that the products could be harmful to both the vessel wall and bone structure. However, few clinical studies have examined the association of plasma lipids with bone mass or fragility. Although Broulik and Kapitola [23] reported that women with osteoporosis diagnosed by low BMD had higher total C levels than control subjects, it was not determined whether BMD values were correlated with plasma LDL-C or HDL-C levels. The present study is the first to show that both high LDL-C and low HDL-C are clinically associated with low bone mass in postmenopausal women, similar to the way in which such lipid derangements are linked to the incidence of atherosclerotic cardiovascular disease. Thus, our clinical study together with previous experimental studies [13, 14] suggest that disturbances in plasma lipids might induce both atherosclerosis and osteoporosis. Alternatively, it is interesting that statins, estrogens, and nitrogen-containing bisphosphonates have similar stimulatory effects on bone mass, because all of them are known to reduce LDL-C and increase HDL-C in the plasma [24].

This study has some limitations. First, we only analyzed the subjects who attended Kobe University Hospital, a tertiary care center, for the evaluation of osteoporosis. Therefore, the patients enrolled in this study might not be representative of normal Japanese postmenopausal women. Second, the analysis of effects of plasma lipids on vertebral fractures only included 35 fracture cases and, thus, the statistical power to detect meaningful differences for LDL-C or HDL-C was probably not large.

In conclusion, our study suggests that high LDL-C and low HDL-C are associated with low bone mass as well as atherosclerosis, and that high TG is associated with the lower incidence of vertebral fractures in postmenopausal women. Thus, abnormalities in lipid metabolism might be the common factors underlying both osteoporosis and atherosclerosis. Our study together with recent basic and clinical studies suggest that plasma lipids play some physiological role in maintaining bone mass and better bone quality in postmenopausal women.

References

1. Fujita T, Okamoto Y, Sakagami Y, Ota K, Ohata M (1984) Bone changes and aortic calcification in aging inhabitants of mountain versus seacoast communities in the Kii Peninsula. *J Am Geriatr Soc* 32: 124–128.
2. Frye MA, Melton LJ 3rd, Bryant SC, Fitzpatrick LA, Wahner HW, Schwartz RS, Riggs BL (1992) Osteoporosis and calcification of the aorta. *Bone Miner* 19: 185–194.
3. Vogt MT, San Valentin R, Forrest KY, Nevitt MC, Cauley JA (1997) Bone mineral density and aortic calcification: the study of osteoporotic fractures. *J Am Geriatr Soc* 45: 140–145.
4. Ouchi Y, Akishita M, de Souza AC, Nakamura T, Orimo H (1993) Age-related loss of bone mass and aortic/aortic valve calcification-reevaluation of recommended dietary allowance of calcium in the elderly. *Ann N Y Acad Sci* 676: 297–307.
5. Uyama O, Yoshimoto Y, Yamamoto Y, Kawai A (1997) Bone changes and carotid atherosclerosis in postmenopausal women. *Stroke* 28: 1730–1732.
6. Barengolts EI, Berman M, Kukreja SC, Kouznetsova T, Lin C, Chomka EV (1998) Osteoporosis and coronary atherosclerosis in asymptomatic postmenopausal women. *Calcif Tissue Int* 62: 209–213.
7. Browner WS, Pressman AR, Nevitt MC, Cauley JA, Cummings SR (1993) Association between low bone density and stroke in elderly women. The study of osteoporotic fractures. *Stroke* 24: 940–946.
8. 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.
9. Plutzky J (2000) Emerging concepts in metabolic abnormalities associated with coronary artery disease. *Curr Opin Cardiol* 15: 416–421.
10. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL (1989) Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 320: 915–924.
11. Witztum JL, Steinberg D (1991) Role of oxidized low

density lipoprotein in atherogenesis. *J Clin Invest* 88: 1785–1792.
12. Miller NE, La Ville A, Crook D (1985) Direct evidence that reverse cholesterol transport is mediated by high-density lipoprotein in rabbit. *Nature* 314: 109–111.
13. Parhami F, Demer LL (1997) Arterial calcification in face of osteoporosis in aging: can we blame oxidized lipids? *Curr Opin Lipidol* 8: 312–314.
14. Parhami F, Jackson SM, Tintut Y, Le V, Balucan JP, Territo M, Demer LL (1999) Atherogenic diet and minimally oxidized low density lipoprotein inhibit osteogenic and promote adipogenic differentiation of marrow stromal cells. *J Bone Miner Res* 14: 2067–2078.
15. 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.
16. Fukase M, Fujita T, Matsumoto T, Ogata E, Iijima T, Takezawa J, Saito K, Ishige H, Fujimoto M (1989) A clinical study using radioimmunoassay for midregion and carboxylterminus of parathyroid hormone in normal, hypo- and hypercalcemic states. *Folia Endocrinol Jpn* 65: 807–827.
17. Nakaoka D, Sugimoto T, Kobayashi T, Yamaguchi T, Kobayashi A, Chihara K (2000) Evaluation of changes in bone density and biochemical parameters after parathyroidectomy in primary hyperparathyroidism. *Endocr J* 47: 231–237.
18. Orimo H, Sugioka Y, Fukunaga M, Mutoh Y, Hotokebuchi T, Gorai I, Nakamura T, Kushida K, Tanaka H, Igai T (1996) Diagnostic criteria for primary osteoporosis (in Japanese). *Osteoporosis Jpn* 4: 643–653.
19. Browner WS, Seeley DG, Vogt TM, Cummings SR (1991) Non-trauma mortality in elderly women with low bone mineral density. Study of Osteoporotic Fractures Research Group. *Lancet* 338: 355–358.
20. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR (1999) Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res* 14: 821–828.
21. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW Jr, Dequeker J, Favus M (1995) Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 333: 1437–1443.
22. Cullen P (2000) Evidence that triglycerides are an independent coronary heart disease risk factor. *Am J Cardiol* 86: 943–949.
23. Broulik PD, Kapitola J (1993) Interrelations between body weight, cigarette smoking and spine mineral density in osteoporotic Czech women. *Endocr Regul* 27: 57–60.
24. Adami S, Braga V, Guidi G, Gatti D, Gerardi D, Fracassi E (2000) Chronic intravenous aminobisphosphonate therapy increases high-density lipoprotein cholesterol and decreases low-density lipoprotein cholesterol. *J Bone Miner Res* 15: 599–604.