CLINICAL STUDY

Hyperlipidemia is not Associated With Low Bone Mineral Density in Postmenopausal Obese Women

Fatma Ferda **VERİT**

Department of Obstetrics and Gynecology, Faculty of Medicine, Harran University, Şanlıurfa, Turkey

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Abstract

Objective: There has been considerable debate about the potential role of cholesterol in the pathogenesis of both osteoporosis and atherosclerosis. The aim of this study was to investigate whether postmenopausal hyperlipidemic obese women had lower lumbar and femoral neck bone mineral density (BMD) and higher prevalence of osteoporosis than those with normal lipid levels.

Materials and Methods: The study population included 73 postmenopausal hyperlipidemic and 67 postmenopausal normolipidemic obese women. Total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL) levels were determined. BMD was measured at lumbar spine and femur neck by dual energy X-ray absorptiometry.

Results: The lumbar spine BMD was 0.82±0.15 g/cm^2 in women with hyperlipidemia and 0.84±0.16 g/cm^2 in those with the normolipidemic group (p>0.05); and femoral neck BMD was 0.72±0.12 g/cm^2 in the hyperlipidemic and 0.71±0.11 g/cm^2 in the normolipidemic groups (p>0.05). There was no significant difference in the prevalence of osteoporosis in the hyperlipidemic group when compared with the normolipidemic controls (52.1% vs. 53.7%, respectively, p>0.05). No significant association was found between the plasma triglyceride, total cholesterol, HDL, LDL levels and the lumbar spine BMD and femoral neck BMD in postmenopausal hyperlipidemic group in the study.

Discussion: In postmenopausal hyperlipidemic obese women, no increased risk of osteoporosis was observed. The lack of relationship between hyperlipidemia and BMD also suggests the lack of a link between atherosclerosis and osteoporosis.

Keywords: bone mineral density, hyperlipidemia, risk factor, osteoporosis

Özet

Postmenopozal Obez Kadınlarda Hiperlipidemi ile Kemik Kitle İndeksi İlişkili Değildir

Amaç: Kolesterolün, hem osteoporoz ve hem de aterosklerozun patogenezinde potansiyel bir rolü olduğu hakkında önemli bir görüş vardır. Çalışmamızın amacı, postmenopozal hiperlipidemik obez kadınlarda normal lipid seviyesi gösterenlere kıyasla daha düşük lomber spin ve femoral boyun kemik kitle indeksine (BMD) ve daha yüksek osteoporoz prevalansına sahip olup olmadığını araştırmaktı.

Materyal ve Metot: Çalışma popülasyonu, 73 postmenopozal hiperlipidemik ve 67 postmenopozal normolipidemik obez kadını içermekteydi. Total kolesterol, trigliserit, yüksek dansiteli lipoprotein (HDL), düşük dansiteli lipoprotein (LDL) seviyelerine bakıldı. BMD, lumbar spin ve femur boynunda dual enerji X-ray absorpsiyometri yöntemiyle ölçüldü.

Sonuçlar: Hiperlipidemik kadınlarda lumbar spin BMD'si 0.82±0.15 g/cm^2 ve normolipidemik grupta 0.84±0.16 g/cm^2 (p>0.05), femur boynu BMD'si ise, hiperlipidemik grupta 0.72±0.12 g/cm^2 ve normolipidemik grupta 0.71±0.11 g/cm^2 (p>0.05) idi. Osteoporoz prevalansı, hiperlipidemik grupta normolipidemik kontrollerle kıyaslandığında anlamlı değişiklikler göstermemekteydi (sırasıyla, 52.1% vs. 53.7%, p>0.05). Postmenopozal hiperlipidemik grupta, plazma trigliserit, total kolesterol, HDL, LDL ile lumbar spin BMD ve femur boynu BMD'si arasında da anlamlı bir ilişki bulunmamıştır.

Tartışma: Postmenopozal hiperlipidemik obez kadınlarda osteoporoz riskinde artış gözlenmemiştir. Hiperlipidemi ve BMD arasında bir ilişkinin olmaması, ateroskleroz ve osteoporoz arasında kayıp bir bağlantı olduğu izlemini uyandırmaktadır.

Anahtar sözcükler: kemik kitle indeksi, hiperlipidemi, risk faktörü, osteoporoz

Corresponding Author: Dr. Fatma Ferda Verit
Harran Üniversitesi Tıp Fakültesi,
Araştırma ve Uygulama Hastanesi,
Kadın Hastalıkları ve Doğum Bölümü
63100 Şanlıurfa, Türkiye
Phone : +49 414 316 8821
Fax : +49 414 315 11 81
E-mail : fverit@harran.edu.tr

Introduction

Osteoporosis and atherosclerosis are two of the major causes of morbidity and mortality in the world and the incidence is expected to rise given the population demographics and increased life expectancy. Growing evidence links vascular and bone disease. It has been reported that osteoporosis is associated with increased risk of cardiovascular mortality (1,2) and aortic calcification (3-5). Moreover, a population based longitudinal study demonstrated that progression of atherosclerotic calcification is associated with bone loss in women during menopause (3). Patients with lower bone density and osteoporosis also have higher lipid levels, more severe coronary atherosclerosis, and have a greater risk of stroke and death (5,6).

Given that the relationship between cardiovascular disease and cholesterol is well established, one possibility was that high cholesterol might be associated with low bone mass. One possible mechanism involves the cholesterol biosynthetic pathway, which determines cholesterol levels and contributes to the activity of the osteoclasts (7). A study found that the low density lipoprotein (LDL)/high density lipoprotein (HDL) ratio was negatively associated with BMD in postmenopausal women without risk factors for cardiovascular disease and osteoporosis (8). Another longitudinal study in postmenopausal women aged 50-75 years, those with the largest increases in serum cholesterol showed the greatest decreases in spine BMD independently of the change in the body mass index (9).

There has also been interest in whether medicines used to lower blood lipids, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG co-A) reductase inhibitors (statins), may also increase bone mineral density (BMD). Statins inhibit steps in the mevalonate pathway and have been shown to increase BMD when applied directly to the rat calvaria (10). Several large observational epidemiologic studies suggest that persons taking statins are at a significantly reduced risk of fractures and have an increased BMD, (11-15) but other epidemiologic studies have found no relationship (16,17). More importantly, randomized controlled clinical trials of lipid lowering for cardiovascular disease have not shown any reduction in fracture risk associated with statins (16-18).

Therefore, concerning the possible role of lipids in osteoporosis, the aim of the study was to investigate whether postmenopausal hyperlipidemic obese women had lower lumbar and femoral neck BMD and higher prevalence of osteoporosis than those with normal lipid levels.

Materials and Methods

Subjects

The study population consisted of 73 postmenopausal hyperlipidemic women aged 48-64 years (mean±SD age, 54.89±4.34 years) and 67 postmenopausal normolipidemic women aged 48-64 years (mean±SD age, 54.16±4.05 years). All the patients gave written informed consent. The menopause was defined as the absence of menstruation for at least 12 months and serum FSH levels of higher than 40 IU/L. All the subjects were naturally menopausal, hyperlipidemic, obese, but did not smoke or drink. Exclusion criteria were, above age 65, surgical menopause, hypertension, bone disorders other than primary osteoporosis, rheumatological or endocrine conditions such as diabetes, hyperparathyroidism, acute-chronic liver diseases, renal dysfunction, or with any history of cancer in the past 5-years. Also excluded were subjects who received therapeutic interventions known to influence serum lipids and/or BMD such as statins or other lipid lowering agents, sex steroids such as hormone replacement therapy, bisphosphonates, calcitonin, corticosteroids, thiazide, fluoride and raloxifene. None of these women had previous BMD problems.

Hyperlipidemia was defined as follows: serum LDL cholesterol ≥160 mg/dl or total cholesterol ≥240 mg/dl or triglyceride ≥200 mg/dl or HDL cholesterol <40 mg/dl (19). A patient was considered as diabetic with a fasting plasma glucose level ≥126 mg/dl and obese if body mass index (BMI) ≥30 kg/m^2.

Lipid parameters

Blood samples were drawn in the morning from the subjects after an overnight fast. The levels of triglyceride, total cholesterol, HDL and LDL were determined by using commercially available assay kits (Abbott) with an autoanalyzer (Aeroset, Abbott).

Bone density measurements

Bone mineral density of lumbar spine and femoral neck were measured by Hologic QDR 4500 W (Hologic Inc, Bedford, MA, USA) fan beam dual energy x-ray absorptiometry. The "within subject" coefficient of variations were both 1% for lumbar spine and the femoral neck. The results were given in g/cm^2. Osteopenia was defined as *t*-score <-1 SD, and osteoporosis was defined as *t*-score <-2.5 SD in accordance with the WHO criteria. Given that lumbar spine and femoral neck BMD are considered the more representative measures of bone mass in clinical practice in osteoporosis, we used only these measurements to define BMD.

Statistical evaluation

Values shown in the text and tables are mean±SD. The prevalence of osteoporosis in both groups was assessed by χ^2 tests. Correlations between plasma lipids and BMD in postmenopausal hyperlipidemic patients were performed by Pearson correlation analysis. $P<0.05$ was considered as statistically significant.

Results

Demographic findings and lipid profiles of the two groups were shown in Table 1. There were no significant differences in terms of age, BMI, duration of menopause and lumbar spine BMD and femoral neck BMD between the postmenopausal hyperlipidemic and normolipidemic groups (Table 1). Triglyceride, total cholesterol and LDL were significantly

Table 1. Baseline characteristics of the study population

	Hyperlipidemic group (n=73) (mean±SD)	Normolipidemic group (n=67) (mean±SD)	p
Age (y)	54.89±4.34	54.16±4.05	NS
BMI (kg/m^2)	32.41±1.60	32.17±1.46	NS
Duration of menopause (y)	2.54±1.81	2.49±1.68	NS
BMD (g/cm^2)			
LS BMD	0.82±0.15	0.84±0.16	NS
FN BMD	0.72±0.12	0.71±0.11	NS
TG (mg/dl)	190.75±92.67	116.08±42.51	<0.0001
TC (mg/dl)	211.19±48.13	187.76±29.72	0.001
HDL (mg/dl)	40.14±11.58	51.75±10.75	<0.0001
LDL (mg/dl)	114.69±38.98	97.94±33.59	0.008

BMI: body mass index, **BMD**: bone mineral density, **LS BMD**: lumbar spine bone mineral density, **FN BMD**: femoral neck bone mineral density, **TG**: triglyceride, **TC**: total cholesterol, **HDL**: high density lipoprotein, **LDL**: low density lipoprotein

higher and HDL was significantly lower in hyperlipidemic group in Table 1.

Thirty-eight women (52.1%) were osteoporotic and 35 (47.9%) women were nonosteoporotic in the hyperlipidemic group (p>0.05). In the normolipidemic group, 36 (53.7%) women were osteoporotic and 31 (46.3%) women were non-osteoporotic (p>0.05). The number of osteoporotic patients were not significantly different in both groups (p>0.05, for both).

Correlations of lipids with BMD in postmenopausal hyperlipidemic group were shown in Table 2. There were also no correlations between plasma triglyceride, total cholesterol, HDL, LDL levels and lumbar spine BMD and femoral neck BMD in postmenopausal hyperlipidemic women in the study (Table 2). No correlations were found between plasma triglycerides, total cholesterol, HDL, LDL levels and lumbar spine BMD and femoral neck BMD in postmenopausal normolipidemic women (p>0.05, for all of them).

Table 2. Correlations of lipids with BMD in postmenopausal hyperlipidemic group

	LS BMD	FN BMD
TG	r=0.11	r=–0.17
	p=0.33	p=0.14
TC	r=0.11	r=–0.16
	p=0.32	p=0.17
HDL	r=0.09	r=–0.08
	p=0.41	p=0.41
LDL	r=–0.02	r=–0.10
	p=0.83	p=0.38

TG: triglyceride, **TC**: total cholesterol, **HDL**: high density lipoprotein, **LDL**: low density lipoprotein, **LS BMD**: lumbar spine bone mineral density, **FN BMD**: femoral neck bone mineral density

Discussion

We assessed the relationship between lipids and BMD in postmenopausal hyperlipidemic obese women compared with normolipidemic group. Our results yielded that there was no significant relationship between any of the lipid parameters and BMD in this study.

The hypothesis that hyperlipidemia might adversely affect BMD was demonstrated by previous epidemiologic studies (20-22). It has been reported that cholesterol and its metabolites influenced the functional activity of osteoblasts under both *in vivo* and *in vitro* conditions (2,23). Oxidized LDL and other bioactive oxidized lipids, which promote atherogenesis, could inhibit osteoblastic differentiation of bone and marrow derived preosteoblasts *in vitro*, suggesting that an atherogenic diet could contribute as a common risk factor for both diseases (24). Postmenopausal women with atherogenic lipid profile have lower lumbar spine BMD and femoral neck BMD and have an increased risk of osteopenia than those with normal lipid profiles (8). However, it has been reported that there was significant correlation between serum lipids and BMD in only unadjusted analyses (10). Fully adjusted models that included variables such as age, BMI, menopausal status, smoking status, calcium intake, showed no significant relationship between lipid parameters and BMD (10). In one study, Adami et al. found a relationship between serum lipids and BMD, but important covariables such as functional status, thiazide use, alcohol intake, and tobacco were not included in multivariable models (25). Exclusion of such variables might have produced misleading results. Another study found no relationship between serum cholesterol levels and BMD (26). In a longitudinal follow-up study, although there was a significant increase in cholesterol levels measured at baseline and 8 years later, no association between serum cholesterol levels and BMD was evaluated in that time period at spine, distal forearm and total hip sites in postmenopausal women (9). There was also no correlation between serum cholesterol levels and bone turnover markers

such as osteocalcin and C-terminal telopeptide of type I collagen (CTX) in the same study (9).

Previous studies demonstrated conflicting results on the effects of statins on BMD (14,27-31). In several studies treatment with statins has been associated with an increased BMD (14,27,28). Other studies were unable to show an effect of statins on BMD in hypercholesterolemic patients (18, 29-31). Most recently, in an analysis from the Women's Health Initiative (WHI) Observational Study, BMD at the lumbar spine, total hip, or whole body did not differ between statin users and nonusers, after adjustment for multiple confounders (31). Rejnmark et al. found no effect of 1 year simvastatin treatment on BMD at the lumbar spine, total hip, femoral neck, or whole body in a randomized controlled trial in postmenopausal women (18). Moreover, simvastatin did not affect bone turnover as assessed by plasma levels of biochemical bone markers (18). A recent prospective study by Chan et al. demonstrated that lipid-lowering therapy resulted in slight increases in osteocalcin without changes in CTX (32).

There were several limitations in this study. It included only one referral center and the number of the women in the study was small. Research with larger groups is needed to obtain further support for the study. A more powerful study design would include longitudinal data to assess changes over time in lipids and bone mineral density. The discrepancy between our findings and those from other earlier studies may suggest that the potential relationship between lipids and bone mineral density could be modified by genetic heritage.

In conclusion, we demonstrated that there was no relationship between serum lipids and BMD in hyperlipidemic, obese postmenopausal women in this study. The lack of relationship between hyperlipidemia and BMD also suggest a missing link between atherosclerosis and osteoporosis.

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