

Lipids and Bone Mineral Density in Patients with Vascular Disease

José-Luis Pérez-Castrillón^{1,4}, Manuel Gonzalez-Sagrado^{2,4}, Marta Gonzalez-Rozas¹, Maria Andres-Calvo¹, Elena Izquierdo-Delgado¹, Marcelino Mendo³, Daniel de Luis^{2,4}, and Antonio Dueñas-Laita¹

¹Department of Medicine, University Hospital Río Hortega University of Valladolid, Spain. ²Research Unit, University Hospital Río Hortega University of Valladolid, Spain. ³Department of Radiology, University Hospital Río Hortega University of Valladolid, Spain. ⁴RETICEF (Thematic Network of Cooperative Research into Aging and Fragility).

Abstract

Objective: To evaluate the relationship between cholesterol and triglycerides and bone mineral density in patients with vascular disease (hypertension and acute coronary syndrome).

Methods: The study included 217 patients (83 men and 134 women), aged between 36 and 76 (mean age 59 ± 10), with hypertension and acute coronary syndrome. Information obtained included anthropometric measurements, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides; bone mineral density (BMD) was recorded at the lumbar spine.

Results: BMD was significantly lower in patients in the higher tertiles of cholesterol ($p = 0.041$). The effect was maintained after adjustment for age and Body Mass Index (BMI). However, there was no association between the range of triglycerides, LDL cholesterol, HDL cholesterol and bone mass.

Conclusions: A relationship was found between total cholesterol and bone mineral density in patients with vascular disease.

Keywords: Cholesterol, Triglycerides, Bone Mineral Density

Introduction

Atherosclerosis and osteoporosis are chronic degenerative diseases with a high incidence in developed countries, whose prevalence will increase as the population ages(1,2). They are silent processes with a high economic cost that becomes evident when the acute complications, including vascular accidents and osteoporotic fractures become overt. Various epidemiological studies have shown an age-independent association between the two diseases(3,4).

Atherosclerosis, which plays a role in heart disease, cerebrovascular accidents and peripheral arterial disease, is responsible for most cardiovascular disease. It is characterized by chronic arterial inflammation caused and exacerbated by disorders of the lipid metabolism and other clearly-identified risk factors (5). Calcification, induced by an active process in which inflammatory cytokines and other mediators that regulate the phospho-calcium metabolism, is characteristic of atherosclerosis(6). In contrast, the same mechanisms can intervene at the level of the bone, reducing bone mineral content and altering the bone microarchitecture, leading to osteoporosis. Therefore, the two diseases, although with a different expression, share common mechanisms.

There are various well-known risk factors for cardiovascular diseases, some of which can also influence bone metabolism, modifying bone mass and facilitating osteoporosis. Lipids can play an important role in both processes. Few studies have evaluated plasma lipids (a surrogate marker of atherosclerosis) with bone mineral density (BMD) and/or osteoporotic fractures and the results are not concordant.

The objective of this study was to evaluate the relationship between cholesterol and triglycerides in patients with vascular disease (hypertension and acute coronary syndrome).

Correspondence: José Luis Pérez-Castrillón, Hospital Río Hortega, Rondilla Santa Teresa 9, 47010 Valladolid, Spain. Tel: (+34) 983-420400; Fax: (+34) 983-331566; Email: castrv@terra.es



Copyright in this article, its metadata, and any supplementary data is held by its author or authors. It is published under the Creative Commons Attribution By licence. For further information go to: <http://creativecommons.org/licenses/by/3.0/>.

Matherial and Methods

Subjects and study protocol

The study included 217 patients (83 men and 134 women), aged between 36 and 76 (mean age 59 ± 10), with systolic and/or diastolic stage I-II hypertension, according to JNC VII criteria or acute coronary syndrome according to European Society of Cardiology guidelines. The exclusion criteria were: alcoholism, neoplasia, secondary arterial hypertension, chronic renal failure, hyper- and hypocalcemia, diabetes, hyperparathyroidism and use of drugs modifying BMD (calcium, vitamin D, estrogens, calcitonin, bisphosphonates, and fluorine).

Measurements

Blood samples were obtained after 8 fasting hours in the morning. Total serum cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Roche Diagnostics GmbH, Mannheim, Germany), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. LDL-cholesterol was calculated using the Friedewald formula.

Densitometry studies were conducted in the lumbar spine (L2–L4) using an X-ray densitometer (DEXA, Lunar Corporation, Madison, Wisconsin, U.S.A.). The BMD results were expressed in g/cm^2 and as peak percentage of bone mass in normal subjects (T-score) and percentage of subjects of the same age and sex (Z-score), depending on the software used in the device.

Statistical analyses

A descriptive statistical analysis, including central and dispersion trends, was conducted for quantitative categories, and absolute and relative variables were analyzed for the different categories. The Student's t-test was used to analyze the data that matched the aim of the study and the Anova method was used to compare multiple groups. The relationship between variables was assessed using Pearson's correlation coefficient. Multiple regression analysis was used to assess the relationship between BMD and plasma lipid levels. The results are expressed as mean $\pm$ standard deviation.

Ethical issues

This study was approved by the hospital's ethics committee and the patients signed an informed consent form.

Results

Two-hundred and seventeen patients (83 men and 134 women) were analysed, 134 with hypertension and 83 with acute coronary syndrome. There were no significant differences between the two groups at baseline (age 59 ± 10 years vs. 61 ± 10 years, BMI 28 ± 4 vs. 28 ± 4 and BMD $1.089 \pm 0.16 \text{ g}/\text{cm}^2$ vs. $1.136 \pm 0.22 \text{ g}/\text{cm}^2$). There were 41 osteoporotic patients (19%). Table 1 shows the baseline data of the whole study population, males and females. BMD was significantly lower in patients in the higher tertiles of cholesterol ($p = 0.041$) (Fig. 1). However there was no association between the range of triglycerides and bone mass (Fig. 2). We found a relationship between cholesterol and BMD in men ($r: -0.213$, $p = 0.0021$) but not in women. The effect disappeared after adjusting for weight. We found no relationship between HDL-cholesterol ($r: -0.232$, $p = 0.075$) and LDL-cholesterol ($r: -0.122$, $p = 0.352$) and bone mineral density.

When a multivariate logistic regression analysis was performed with BMD as a dependent variable and each lipid level, age and BMI as independent variables (Table 2), cholesterol, age, and BMI were associated with spine BMD.

Discussion

We found evidence for a weak association between total cholesterol and spine BMD in patients with vascular disease. Patients with higher levels of total cholesterol had lower BMD. Few clinical studies have investigated the link between plasma lipids and BMD. Broulik et al.(7) reported that osteoporotic women had higher cholesterol levels than female controls. Yamaguchi et al.(8) found that LDL cholesterol was inversely and significantly related to BMD while the reverse occurred with HDL cholesterol. Furthermore, patients with a low bone mass had higher plasma lipid levels associated with more severe vascular disease(9). Other studies found differing results. The Framingham Osteoporosis Study found no association between cholesterol levels and subsequent osteoporosis(10). Similarly, Tanko et al.(11), in a study of 340

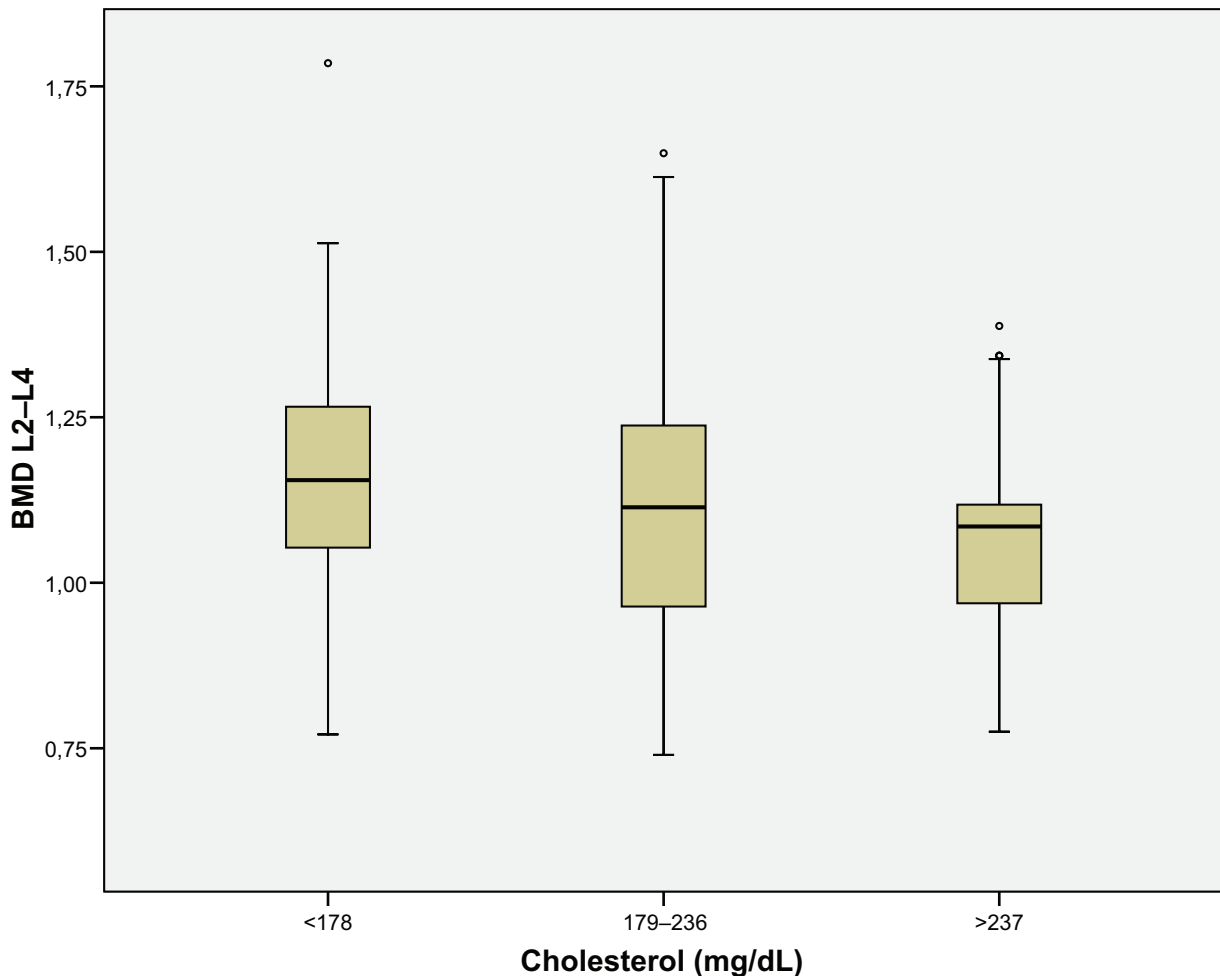
Table 1. Baseline data of the study population.

Population	Total (n: 217)	Men (n: 83)	Women (n: 134)
Age (years)	60 ± 10	59 ± 9	61 ± 11
Body Mass Index (g/cm ²)	28 ± 4	28 ± 4	28 ± 4
Cholesterol (mg/dl)	207 ± 45	199 ± 43	212 ± 46
Triglycerides (mg/dl)	125 ± 60	123 ± 60	131 ± 80
BMD L2–L4 (g/cm ²)	1.106 ± 0.19	1.116 ± 0.20	1.099 ± 0.18

postmenopausal women aged <76 years, found no relationship between cholesterol and mean BMD 8 years later. Our group found no relationship between plasma lipids and bone mass in type 2 diabetic patients(12).

Recently, Solomon et al.(13) have analyzed 13592 participants in the National Health and Nutritional Examination Survey (NHANES) III

in whom BMD and lipid levels were recorded. In the crude analysis, higher total cholesterol and LDL levels were associated with lower BMD whereas higher HDL-levels were associated with lower BMD. However, in fully adjusted models, there was no significant relationship. Dennison et al.(14), in a British study, demonstrated a relationship between lipid profile and BMD that was greatly

**Figure 1.** Cholesterol levels (tertiles) and BMD.

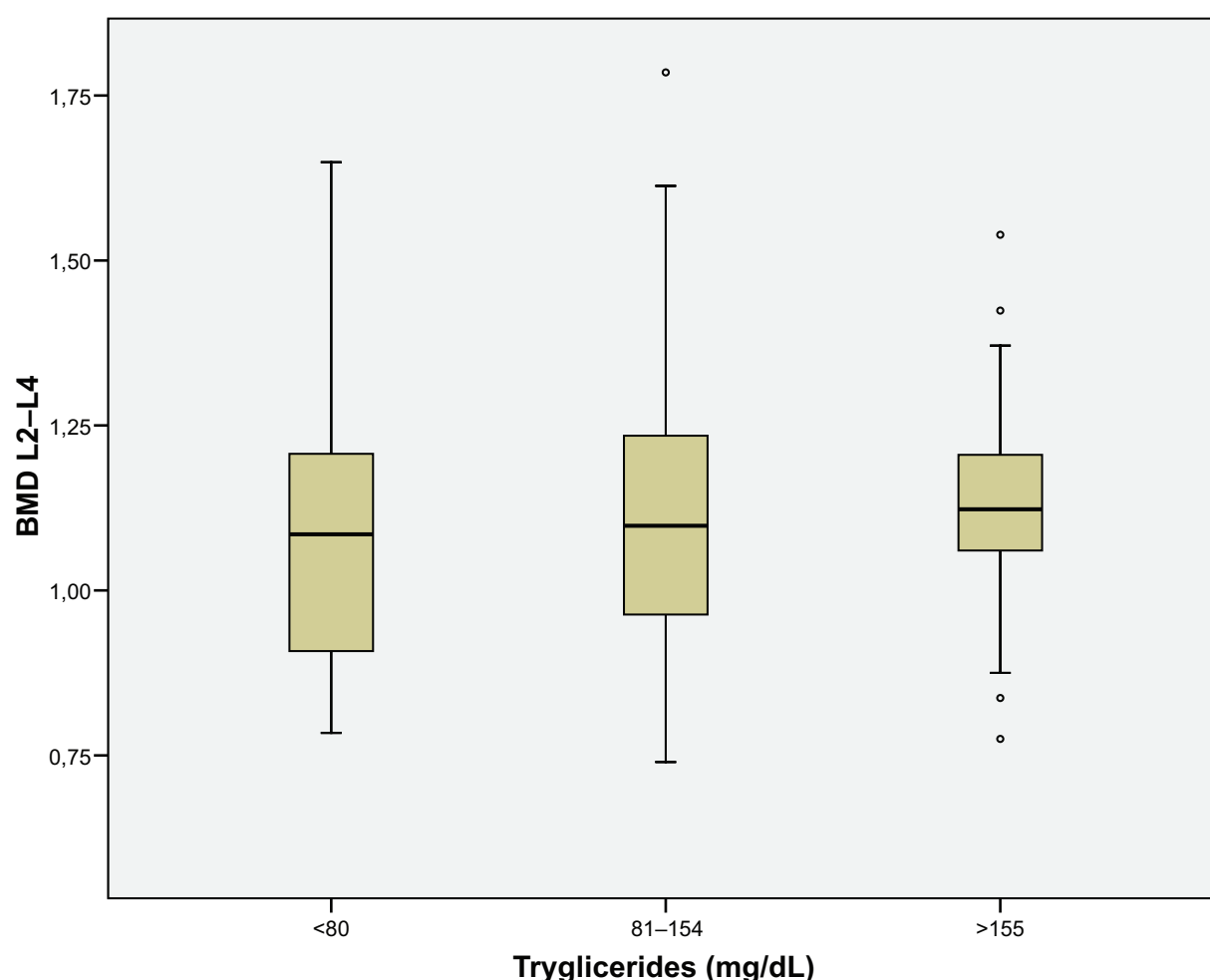


Figure 2. Triglyceride levels (tertiles) and BMD.

attenuated by adjustment for total body fat. Our results are similar. There was a relationship between total cholesterol and BMD but the relationship remained significant in the adjusted model, although weak (Table 2).

The results of other studies are not concordant, probably due to the heterogenous nature of the study populations, which vary from healthy cohorts to patient series. Key factors are body fat and BMI, which attenuates the relationship and makes the comparison of results difficult.

Table 2. Association between bone mineral density and plasma lipid levels.

	B	p
Constant	1.294	0.0001
Age (years)	−0.005	0.0001
BMI	0.008	0.013
Cholesterol (mg/dl)	−0.001	0.029
Triglycerides (mg/dl)	0.0009	0.661

Both direct and indirect reasons may explain the possible association between bone mass and the lipid profile. During the menopause there is an abrupt fall in estrogens accompanied by greater bone mass loss and an increase in cholesterol and triglycerides. In addition, various drugs (estrogens, statins, estrogen receptor modulators, and bisphosphonates) can act on both parameters. On the other hand, osteoblasts and adipocytes share common progenitor cells in the bone marrow. Some authors, such as Parhami et al.(15), suggest a possible lipid etiology for osteoporosis. The coexistence of vascular calcification and osteoporosis is not infrequent, and a significant role is attributed to oxidized low-density lipoproteins. This author suggests that these proteins would act in pluripotential stem cells of the bone marrow, enhancing their progression to adipocytes instead of osteoblasts. Furthermore, oxidized lipids induce the expression of chemotactic factors for monocytes and M-CSF in the endothelium, a significant catalyst of osteoclastic differentiation(16).

Our study had several limitations. The study population was small and there were two groups of participants, patients with hypertension and those with coronary syndrome, who could have different regulation of BMD and lipidic metabolism.

In conclusion, we found a relationship between total cholesterol and BMD in patients with vascular disease. Cholesterol and BMD are only two of the variables associated with atherosclerosis and osteoporosis and other parameters can play a key role in the association between the two diseases(17).

References

- [1] Kado, D.M., Browner, W.S., Blackwell, T., Gore, R. and Cummings, S.R. 2000. Rates of bone loss are associated with mortality in older women: a prospective study. *J. Bone Miner. Res.*, 15:1974–80.
- [2] Bauer, D.C., Palermo, L., Black, D. and Cauley, J.A. 2002. Quantitative ultrasound and mortality: a prospective study. *Osteoporosis. Int.*, 13:606–12.
- [3] Hofbauer, L.C., Brueck, C.C., Shanahan, C.M., Schopper, M. and Dobnig, H. 2007. Vascular calcification and osteoporosis, from clinical observation towards molecular understanding. *Osteoporosis. Int.*, 18:251–9.
- [4] Bagger, Y.Z., Rasmussen, H.B., Alexandersen, P., Werge, T., Christiansen, C. and Tankó, L.B. 2007. Links between cardiovascular disease and osteoporosis in postmenopausal women: serum lipids or atherosclerosis per se? *Osteoporosis. Int.*, 18:505–12.
- [5] Hansson, G.K. 2005. Inflammation, atherosclerosis and coronary artery disease. *N. Engl. J. Med.*, 352:1685–95.
- [6] Doherty, T.M., Fitzpatrick, L.A., Inoue, D., Quiao, J.H., Fishbein, M.C., Detrano, R.C. et al. 2004. Molecular, endocrine and genetic mechanisms of arterial calcification. *Endocr. Rev.*, 25:629–72.
- [7] Broulik, P.D. and Kapitola, J. 1993. Interrelations between body weight, cigarette smoking and spine bone mineral density in osteoporotic Czech women. *Endocr. Regul.*, 27:57–60.
- [8] Yamaguchi, T., Sugimoto, T., Yano, S., Yamauchi, M., Sowa, H., Chen, Q. et al. 2002. Plasma lipids and osteoporosis in postmenopausal women. *Endocr. J.*, 49:211–7.
- [9] Cui, L.H., Shin, M.H., Chung, E.K., Lee, Y.H., Kweon, S.S., Park, K.S. et al. 2005. Association between bone mineral densities and serum lipid profiles of pre and post-menopausal rural women in South Korea. *Osteoporosis. Int.*, 16:1975–81.
- [10] Samelson, E.J., Cupples, L.A., Hannan, M.T., Wilson, P.W.F., Williams, S.A., Vaccarino, V., Zhang, Y. and Kiel, D. 2004. Long-term effects of serum cholesterol on bone mineral density in women and men: The Framingham Osteoporosis Study. *Bone*, 34:557–61.
- [11] Tanko, L.B., Bagger, Y.Z., Nielsen, S.B. and Christiansen, C. 2003. Does serum cholesterol contribute to vertebral bone loss in postmenopausal women? *Bone*, 32:8–14.
- [12] Pérez-Castrillón, J.L., De Luis, D., Martín-Escudero, J.C., Asensio, T., Del Amo, R. and Izaola, I. 2004. Non-insulin-dependent diabetes, bone mineral density, and cardiovascular risk factors. *J. Diabetes Complications*, 18:317–21.
- [13] Solomon, D.H., Avorn, J., Canning, C.F. and Wang, P.S. 2005. Lipid levels and bone mineral density. *Am. J. Med.*, 118:1414.e1–1414.e5.
- [14] Dennison, E.M., Syddall, H.E., Sayer, A.A., Martin, H.J., Cooper, C. and the Hertfordshire Cohort Study Group. 2007. Lipid profile, obesity and bone mineral density: the Hertfordshire Cohort Study. *QJM*, 100:297–303.
- [15] Parhami, F., Garfinkel, A. and Demer, L.L. 2000. Role of lipids in osteoporosis. *Arterioscler. Thromb. Vasc. Biol.*, 20:2346–8.
- [16] Parhami, F., Jackson, S.M., Tintut, Y. et al. 1999. Atherogenic diet and minimally oxidized low density lipoprotein inhibit osteogenic and promote adipogenic differentiation of marrow stromal cells. *J. Bone Miner. Res.*, 14:2067–78.
- [17] Perez-Castrillón, J.L., De Luis, D. and Dueñas, A. 2008. Atherosclerosis and osteoporosis. *Minerva. Med.*, 99:45–54.