Dyslipidemia and bone metabolism. A common bond of the osteoporosis and the atherosclerosis?

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Summary
The magnitude of the public health problem related to cardiovascular disease (CVD) and osteoporosis has been widely documented in the medical literature in the last decades, and common pathogenic links have been recently proposed. Dyslipidemia is one of the most important risk factors in the genesis and development of atherosclerosis, and therefore of CVD, which remains the leading cause of cardiovascular mortality in western countries. On the other hand, osteoporosis and its more serious consequence; fracture, represent a true epidemic nowadays. In this context, the relationship between dyslipidemia and bone metabolism has been addressed by several investigators, although results have been inconsistent. The purpose of this paper is to review the medical literature about the possible association between dyslipidemia and several aspects of bone metabolism.

Key words: Dyslipidemia, Arteriosclerosis, Cardiovascular disease, Osteoporosis, Fracture, Bone mineral density, Bone turnover markers.
Introduction

The common pathogenic basis of most cardiovascular diseases (CVD) is arteriosclerosis, a natural multifactorial process, in whose origin are implicated various risk factors, with dyslipidaemia being one of the most significant. Similarly to arteriosclerosis, osteoporosis has a high prevalence in the population, with significant associated morbimortality. It is for these reasons that there is great interest in studying the possible associations between the two, with the aim of promoting more strongly primary preventative activities and prioritizing interventions against the risk factors for both diseases.

The relationship between arteriosclerosis and osteoporosis appears to go further than a mere coincidence of common risk factors. What is more, in recent years, the possibility has been raised of the existence of pathogenic links and physiopathological interactions between bone metabolism and risk factors for CVD. This fact has been endorsed by the discovery of some of the molecular action mechanisms of the statins and the biphosphonates, which are attributed antatherogenic effects by means of a reduction in the accumulation of lipids and of fibrosis in the atheromatous plaques, as well as the inhibition of extra-bone calcification. On the other hand, the statins inhibit the limiting step of the biosynthetic route of cholesterol: the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, reducing its synthesis, and that of isoprenoids, which also affect osteoclast function, which is an effect in common with the aminobiphosphonates (Figure 1).3,5,10

Recently, it has been proposed that dyslipidaemia could be a common risk factor for CVD and osteoporosis. In vitro studies have shown that the products of lipid oxidation in the subendothelial space of the bone arteries inhibit osteoblast differentiation,11 and that hyperlipidaemia strengthens the activity of the osteoclasts. Also notable is the presence of products of the oxidation of the low density lipoproteins (LDL-C) in the atherosclerotic plaques.2 There has been discussion of a similarity between the processes of bone mineralisation and of vascular calcification, and the factors which may influence the development of both, such as, for example, the presence of oxidised LDL, with its high atherogenic potential.2 Although the precise intrinsic mechanism for this nexus is not yet known, recently it has been confirmed that the high density lipoproteins (HDL-C) have a regulatory effect on osteoblast differentiation and on vascular calcification. In fact, the prolonged treatment with HDL-C inhibits the calcification of the vascular cells and osteogenic activity induced by inflammatory cytokines, such as the interleukins IL-1β and IL-6. In addition, osteoclast activation appears to be favoured by other inflammatory cytokines, such as colony stimulating factor type 1 (CSF-1), tumour necrosis factor α (TNF-α), and the receptor activator of ligand NF-κB (RANKL), also present in the atherosclerotic plaque.10

Alterations to lipid metabolism and bone mineral density

Most of the studies have explored this association in postmenopausal women, and in addition, many of them have included patients being treated with hypolipidemic drugs, for which reasons the results have been less than consistent. The main question should probably be whether or not there exists a direct relationship between bone mineral density and blood lipids, or if this hypothetical association is due to confusion factors (principally their estrogenic state, in the case of the women).

So, the changes in the parameters of lipid metabolism have been related to BMD in different works, although with, in many cases, contradictory results. In the Framingham cohort Samelson et al.12 studied 712 women and 450 men with ages of between 32 and 61 years. In the first period of study (1953-55), a densitometric analysis was carried out in the hip, lumbar spine and distal radius, as well as laboratory tests and surveys of cardiovascular of risk factors, which were repeated in the study’s second phase (1988-89). No significant association was found between blood levels of cholesterol in both sexes and the BMD in the areas under consideration, save in the radial diaphysis, where the association with total cholesterol was inverse in the group of males. This study concluded that blood levels of total cholesterol did not appear to have a significant influence on the BMD, neither in men, nor in women.

Poll et al.13, in a study which included 1,303 postmenopausal women, observed that those with blood levels of LDL-C ≥ 160 mg/dL had more than double the probability of having lumbar osteopenia than women with lower levels of LDL-C. Yamaguchi et al.14 found an inverse association between levels of LDL-C and BMD in the forearm and the spinal column, and a direct association between HDL-C and BMD in the aforementioned areas in 214 postmenopausal Japanese women. They observed also that women with earlier verte-
bral fractures had lower levels of triglycerides than the women without fractures.

Makovey et al.\textsuperscript{18}, carried out a longitudinal study in 497 female twins with ages of between 20 and 81 years (224 at the premenopausal stage, and 273 in the menopause; 156 in treatment with hormone replacement therapy (HRT), and 117 without it). They examined the influence of age, menopausal status, and HRT on blood cholesterol and BMD (measured in the lumbar spine, total hip, femoral neck and whole body, by means of double X-ray absorptiometry – DXA). They observed an inverse relation between levels of total cholesterol and of LDL-C with BMD in the lumbar spine and in the total body measurement, in the postmenopausal women, in addition to a negative relationship between HDL-C and BMD in the hip, which appeared to be modified by HRT.

Nuzzo et al.\textsuperscript{19}, investigated bone quality in 256 postmenopausal women stratified according to the absence (total cholesterol < 200 mg/dl; n = 180) or presence (cholesterol total ≥ 200 mg/dl; n = 76) of hypercholesterolemia (in turn, divided in subgroups as a function of whether they were receiving dietetic treatment or treatment with statins). The study was carried out using ultrasound (QUS) in the proximal phalanges of the hand, observing a statistically significant reduction in the velocity of the ultrasound (AD-SoS) in subjects with hypercholesterolemia, per se, could be a risk factor for bone deterioration and that the statins could have a protective effect on the bone, independently of the intake of calcium.
In a study of 52 postmenopausal women who were overweight, Orozco et al. 20 observed that those patients with an atherogenic lipid profile (total cholesterol $\geq$ 240 mg/dl or LDL-C $>160$ mg/dl) had a lower BMD in the lumbar spine and the femoral neck, as well as a higher risk of osteopenia, in comparison with those patients with a normal lipid profile, suggesting a possible association of hyperlipidemia with osteoporosis.

However, Solomon et al. 21, in a work which included 13,592 participants in the NHANES III study (1988-1994), and excluding those subjects receiving hyperlipidemic therapy, did not find any significant relationship between the parameters of lipid metabolism and BMD measured in the hip with DXA.

Adami et al. 22, studied this relationship with two cohorts of subjects: one clinical cohort which included 236 pre- and postmenopausal women of between 35 and 82 years of age who had attended a clinic specialising in osteoporosis, and a population cohort (265 males and 481 females aged between 68 and 75 years). In the clinical cohort there was evidence of a negative relationship between lumbar and hip BMD and levels of HDL-C, and a positive one with levels of blood triglycerides. In the community cohort the same correlations were found between these lipids and BMD in the hip and that measured in the whole body. In both, the relationship between the lipid profile and bone mass continued to be significant after adjusting for body mass index and weight.

In the Hertfordshire cohort 23 in Great Britain, which included 465 women and 48 males, a direct association was observed between the lumbar and total hip BMD and the levels of triglycerides in both sexes, as well as an inverse relationship between HDL-C and lumbar BMD in males, and BMD in the total hip in both sexes. However, these associations were neutralised by adjusting for the percentage of body fat. No associations were observed between BMD and total cholesterol or LDL-C.

In a recent work which analysed 289 males included in the Camargo cohort 24, we observed a direct association between blood levels of total cholesterol, LDL-C and the quotient LDL-C/HDL-C and BMD in the lumbar spine and hip. There was no evidence of any relationship with HDL-C or triglycerides. After controlling for confusion variables it was seen that the males with hypercholesterolemia had a higher BMD in measurements taken in the hip, with respect to those normocholesterolemic males. In addition, in the bone ultrasound study, a positive correlation was found between levels of triglycerides and the LDL-C/HDL-C relationship and the broadband ultrasound attenuation (BUA), and between the total cholesterol/HDL-C quotient and the quantitative ultrasound index or consistency index (QUI) and the BUA. Only one other work, published by Buizert et al. 25, has analysed the value of ultrasounds in patients with dyslipidemia. These authors found a positive association between the total cholesterol/HDL-C quotient and the SOS and BUA, and an inverse relationship with HDL-C in both sexes. Our data, and those of Buizert et al., indicate that a high “good/bad” cholesterol quotient may not only be in relation to BMD but also to bone quality.

**Alteration of lipid metabolism, markers for bone remodelling and calcitropic hormones**

Various studies, in vitro and with animal models, have shown some harmful effects of dyslipidemia on bone metabolism 22. The in vitro studies, for example, have indicated that the osteoblast differentiation is inhibited by the products of lipid oxidation 26. Recently, the participation of the mevalonate pathway has been proposed in both the synthesis of cholesterol and the regulation of the proliferation or apoptosis of bone cells 27. Also, the regulatory role of the LRP5 gene in osteoblast proliferation 28, whose mutation causes a significant reduction in BMD both in rats and in humans 29. The same has been suggested of the mutations in the gene LRP6, a homolog of LRP5, demonstrating its role in the reduction in bone mass in rats 30 and its genetic link with early coronary disease, metabolic risk factors and osteoporosis in humans 31. In addition, Parhami et al. 32 demonstrated that hypercholesterolemia increases osteoclast activity and the reduction in BMD in rats.

**Markers for bone remodelling**

In this context, there are few works which have studied the effects of hypercholesterolemia or lipid parameters on markers for bone remodelling (MBR), and the results have also not been very consistent, and have even been contradictory. Majima et al. 33, analysed the blood levels of alkaline phosphatase, bone alkaline phosphatase (BAP), and collagen type I N-terminal telopeptide (NTx) in 281 Japanese patients with hypercholesterolemia and 267 controls. In the women, there was evidence of values of BAP significantly higher in the cases than in the controls. The levels of NTx in those subjects with hypercholesterolemia were significantly higher than those of the controls, in both sexes. In addition, blood levels of BAP and NTx in males showed an inverse correlation with HDL-C, whilst this correlation was direct with total cholesterol and LDL-C in the case of the women. In both sexes, the relationship between the MBRs and the lipid profile continued to be significant after adjusting for confusion variables. These data indicate an elevation in levels of MBR in dyslipidemic patients independent of sex.

Although the studies are difficult to compare for obvious reasons, our data in the study of the Camargo cohort do not support these findings and, in fact, we found lower blood levels of PINP and β-CTX in those individuals with hypercholesterolemia with respect to the controls, although the difference did not reach statistical significance. However, in stratifying by age, the blood levels of both MBRs were significantly lower only in those...
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<th>Author(s)</th>
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<th>Study</th>
<th>Cases</th>
<th>Controls</th>
<th>Treatment</th>
<th>Results (OR with CI 95%) after adjustment</th>
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<tr>
<td>Meier et al.</td>
<td>♂ and ♀ 50-89 years (Great Britain) N=27,519, average age 77/76 years</td>
<td>Cases and controls</td>
<td>3,940 subjects with previous bone fractures in any location</td>
<td>23,379 subjects without a history of fracture</td>
<td>Statins, fibrates, other lipid-lowering</td>
<td>↓ risk of fractures with statins (OR 0.55; 0.44-0.69) No effects with other hypolipidemics (OR 0.87; 0.7-1.08)</td>
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<td>Wang et al.</td>
<td>♂ and ♀ &gt;65 years (US) N=6,119, average age: 82/82 years</td>
<td>Cases and controls</td>
<td>1,222 subjects with hip fracture</td>
<td>4,888 subjects without fracture</td>
<td>Statins</td>
<td>↓ risk of hip fracture (OR 0.29; 0.10-0.81) ↓ risk of hip fracture (OR 0.50; 0.4-0.76) ↓ risk of hip fracture (OR 0.57; 0.40-0.82)</td>
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<tr>
<td>Chan et al.</td>
<td>♀ &gt;60 years (US) N=3,675, average age: 77/76 years</td>
<td>Cases and controls</td>
<td>928 ♀ with fracture in any location</td>
<td>2,747 ♀ without fracture</td>
<td>Statins</td>
<td>♀ ≥13 pharmacological dispensations of statins: ↓ risk of fracture 52% (OR 0.48; 0.27-0.83) ♀ &lt;13 dispensations: no effect</td>
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<td>Ray et al.</td>
<td>♂ and ♀ with an average age of 62 years (US) N=34,864, average age: 62/62 years</td>
<td>Retrospective study Tennessee Medicaid Programme Cohort</td>
<td>12,506 subjects on statins, 4,798 subjects on other hypolipidemics 17,280 subjects without hypolipidemic treatment</td>
<td></td>
<td>Statins, other lipid-lowering</td>
<td>RR in subjects using statins: 0.62 (0.45-0.85) RR using other hypolipidemics: 0.44 (0.26-0.95) Statins are not better than other hypolipidemics in ↓ the risk of fracture</td>
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<tr>
<td>Scranton et al.</td>
<td>♂ and ♀ older than 65 years (1998-2001) in US N=91,052, average age: 65/59 years</td>
<td>Retrospective study US Veteran Population Cohort</td>
<td>86,731 ♀ and 4,321 ♀ (28,063 in treatment with statins, 2,195 with other hypolipidemic treatment)</td>
<td></td>
<td>Statins, other lipid-lowering</td>
<td>↓ risk of fracture 36% (OR 0.64; 0.58-0.72) in subjects in treatment with statins in comparison with other hypolipidemics (32%, OR 0.67; 0.50-0.91)</td>
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<td>Bauer et al.</td>
<td>8 observational studies (4 prospective studies - SOF, FIT, HERS, Rotterdam-) 2 clinical trials</td>
<td>Meta-analysis</td>
<td>SOF: N=9,704 ♀, average age 75/77 years, cases=1,083, follow up 4 years FIT: N=6,459 ♀, average age 69/69 years, cases 1,241, follow up 3.6 years HERS: N=2,763 ♀, average age 66/67 years, cases=271, follow up 4.5 years Rotterdam: N=4,878 ♀, average age 66/72 years, cases=726, follow up 5.3 years</td>
<td></td>
<td>Statins</td>
<td>◼ risk of fracture OR=0.43 (0.25-0.75) and non-vertebral fracture: 0.69 (0.55-0.88). Clinical trials: use of statins for hip fracture: OR 0.87 (0.48-1.50) and non-vertebral fracture: OR 1.02 (0.85-1.26)</td>
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<td>Toh et al.</td>
<td>Database: Medline, Embase and Cochrane N=522,507 subjects</td>
<td>Meta-analysis 15 articles (6 case-control studies, 8 cohorts -6 prospective, 2 retrospective-, 4 post hoc analyses of randomised controlled trials)</td>
<td>N=522,507 subjects, with 109,919 fractures included in the analysis</td>
<td></td>
<td>Statins</td>
<td>◼ risk of fracture OR=0.77; 0.66-0.90 [use of statins vs non-use]. The protective effect of statins was found in case-control studies (OR=0.62; 0.45-0.85) and in cohort studies (OR=0.77; 0.50-1.00), not in randomised clinical trials. ◼ risk of hip fracture: OR=0.58 (0.40-0.74), vertebral column: OR=0.65 (0.48-0.88), other locations: OR=0.77 (0.6-1.00). The evidence does not support the use of statins in the prevention of fractures: what is missing is an association in clinical trials, heterogeneity in observational studies, confusion factors and possible publication bias</td>
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</table>
patients with hypercholesterolemia of between 70 and 74 years of age. Neither did Brownbill et al., in a transversal analysis of 136 healthy postmenopausal women, with no hypolipidemic treatment, find any association between the MBRs (blood osteocalcin and NTX in urine) and BMD.

Calcitropic hormones
With respect to the relationship between vitamin D and CVD, the results are again contradictory. On the one hand, an excess of vitamin D favours the development of arteriosclerosis in animal models, while on the other, its deficiency is related to ischemic cardiopathy. Other authors did not find an association between vitamin D and vascular disease.

Something similar occurs with parathyroid hormone (PTH). Hangstrom et al., in the ULSAM study, carried out in 958 males, observed a direct relationship between levels of PTH and cardiovascular mortality. Whilst Reis et al., in a transversal study carried out in 654 subjects aged between 55 and 96 years, did not find an association between blood levels of PTH and carotid arteriosclerosis. In a cohort of 410 males and 660 females, participants in the Rancho Bernardo study, the same authors found evidence of the existence of a direct relationship between levels of PTH and metabolic syndrome in the males.

However, we have not found any works which explicitly analyse the possible relationship between vitamin D and/or PTH with lipid profile or dyslipidemia. In the NHANES III study, already mentioned, levels of 25OHD did not vary in any of the quintiles of total cholesterol, LDL-C or HDL-C in the blood. The levels of PTH were not measured. In the Camargo cohort, also, no significant differences were found with respect to blood levels of 25OHD or intact PTH in males with or without hypercholesterolemia, which suggests perhaps that these calcitropic hormones do not play a significant role in the association between bone and lipid metabolisms.

Alterations in lipid metabolism and bone fractures
Over the last few decades epidemiological studies have provided evidence of an increase in mortality by CVD both in patients with osteoporotic fractures, and in non-fractured subjects with reduced bone mass. The mechanism which underlies the relationship between cholesterol and osteoporotic fracture may be directly related to the contribution of the cholesterol metabolism to bone structure.

Once again, the relationship found in those few relevant publications, between alterations in lipid metabolism and fractures, is not very conclusive.

Yamaguchi et al. analysed the lipid profile in 214 postmenopausal women and its relationship to BMD and the presence of vertebral fractures. They observed a direct relationship between HDL-C and BMD in the lumbar spine and forearm, and a positive association between triglyceride values and previous vertebral fractures.

Another nested case-control study from the SOF cohort, which analysed 271 women with fracture of the proximal femur (n= 133) and radiological vertebral fracture (n= 138), did not find any association between blood levels of total cholesterol, LDL-C or HDL-C, and the incidence of vertebral or hip fracture, once the statistical model was adjusted for age and body weight.

Ahmed et al. studied the effect of some components of metabolic syndrome, among them lipid profile, on the risk of non-vertebral fracture in a prospective cohort of 12,780 males and 14,211 females of between 25 and 98 years of age, followed for 6 years (1994-2001). They observed that the low levels of HDL-C protected against the risk of fracture in obese females and males.

Sivas et al. reviewed the relationship between lipid profile, osteoporotic vertebral fractures and BMD in 107 postmenopausal women, aged between 45 and 79 years. They analysed lateral dorso-lumbar X-rays, BMD in the proximal femur, radius and lumbar spine by means of DXA, and lipid profile (total cholesterol, triglycerides, LDL-C and HDL-C). The values of the first three lipid parameters were lower in those postmenopausal women who had at least one vertebral fracture in comparison with those who had none, this relationship staying the same after adjusting for the principal confusion variables (age, duration of the menopause, BMI, among others). An increase of 1 mg/dl of total cholesterol reduces the risk of having a vertebral fracture by 2.2%, there being also a weak association between the levels of total cholesterol, LDL-C and HDL-C in the distal radius.

In the Camargo cohort study we did not observe any association between blood lipids and earlier vertebral fractures. However, we found that blood levels of total cholesterol (p< 0.03) and of LDL-C (p= 0.04) were lower in males with existing non-vertebral fractures.

Impact of the statins on bone metabolism and of the bisphosphonates on lipid metabolism
Recent in vitro and in vivo studies have described possible beneficial effects of statins on the bone. In 1999, in a study in rats, it was suggested that the statins could promote osteoblast differentiation through the stimulation of BMP-2. Subsequently, in an observational study an inverse association was found between hip fracture and the use of statins. Since then, various works have analysed the relationship between the statins, BMD and osteoporotic fractures, although with disparate results. A protective effect of the statins on the bone has been observed in different case and control studies, and in various cohort studies. However, the data coming from randomised controlled (post hoc) trials, and other observational studies, does not show such findings. In Table I are presented the studies most relevant to the possible association between the use of statins and osteoporotic fractures.
Table 2. Studies which relate to the hypolipidemic effect of the biphosphonates

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Population</th>
<th>Study</th>
<th>Cases</th>
<th>Controls</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiloglu et al.</td>
<td>72 ♀ (52/51 years) Follow up: 1 year</td>
<td>Prospective</td>
<td>39 ♀ with osteoporosis in treatment with alendronate</td>
<td>♀ 33 without treatment</td>
<td>Alendronate 70 mg/week</td>
<td>Positive effect of alendronate on ApoB/ApoAI quotient (p&lt;0.01); ↓ reduction in thickness of the carotid intima-media a year from the start of treatment (p&lt;0.05)</td>
</tr>
<tr>
<td>GuneY et al.</td>
<td>49 ♀ postmenopausal (54 years), Follow up: 6 months</td>
<td>Prospective</td>
<td>49 ♀ with osteoporosis and dyslipidemia</td>
<td></td>
<td>Alendronate 10 mg/day</td>
<td>↓ CT, triglycerides and LDL-C. No significant differences in HDL-C, ApoA1 nor Apo B</td>
</tr>
<tr>
<td>Adami et al.</td>
<td>87 ♀ postmenopausal (53-72 years) Follow up: 1 year</td>
<td>Cases and controls</td>
<td>44 ♀ with osteoporosis in treatment with neri- dronate</td>
<td>♀ 43 without treatment</td>
<td>Neridronate 50 mg/2 months</td>
<td>↑ HDL-C in 17-18% at 12 months (p&lt;0.0001); ↑ 24% HDL-C/LDL-C at 12 months (p&lt;0.01); ↑ ApoAI/ApoB (p&lt;0.001); ↓ LDL-C at 4, 8 and 10 months (p&lt;0.05)</td>
</tr>
<tr>
<td>Iwamoto et al.</td>
<td>121 ♀ postmenopausal, (69 years) Follow up: 1 year</td>
<td>Prospective</td>
<td>61 ♀ with osteoporosis in treatment with alen- dronate</td>
<td>61 ♀ with osteoporosis in treatment with alendronate</td>
<td>Alendronate 5 mg/day</td>
<td>No difference in lipid profile of the group in treatment with alendronate</td>
</tr>
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</table>

On the other hand, some works have suggested that the biphosphonates, in addition to reducing bone resorption and risk of fracture, could slow the arteriosclerotic process, due to their effect on the synthesis of cholesterol, the progression of inflammation and oxidative stress. Although the majority of the studies in animals show the clear antiatherogenic activity of the biphosphonates, the data in humans are not consistent. In relation to the lipid metabolism, some authors have described a positive effect of alendronate on the ApoB/ApoAI quotient, and a reduction in the thickness of the carotid intima-media (CIM) in women with postmenopausal osteoporosis. Koshimaya et al., showed evidence in 57 subjects with type 2 diabetes mellitus and osteopenia of a reduction in CIM at 12 months from the initiation of cyclical treatment with etidronate. Other recent studies did not find this hypolipidemic effect of alendronate in women with postmenopausal osteoporosis. GuneY et al., in an analysis of 49 women with osteoporosis and dyslipidemia, found a reduction in concentrations of total cholesterol, triglycerides and LDL-C 6 months after the start of treatment with alendronate. Another study carried out by Adami et al., showed the hypolipidemic effect of endovenous neridronate, which continued with an increase in HDL-C, of the HDL-C/LDL-C quotient and the ApoA-I/Apo B relationship, as well as a reduction in LDL-C. The main studies which have analysed the hypolipidemic action of the biphosphonates are summarised in Table 2.

Conclusion

The relationship between osteoporosis and dyslipidemia probably goes further than the mere presence of joint risk factors, and in this relationship are probably implicated common pathogenic mechanisms which favour the development of both diseases. Despite the fact that the results obtained by the studies carried out to date are not definitive, future studies should establish the magnitude of this relationship, especially at the level of tissue.


