# Bone Health in Patients with Dyslipidemias

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Contributor: Panagiotis Anagnostis

Despite the high heterogeneity and the variable quality of evidence, dyslipidemia, mainly high TC and LDL-C and, to a lesser extent, TG concentrations, seems to be associated with low bone mass and increased fracture risk. This detrimental effect may be mediated directly through the increased oxidative stress and systemic inflammation that dyslipidemia is associated with, leading to increased osteoclastic activity and reduced bone formation, or through the atherosclerotic process, which affects bone's vascularization. Other mechanisms, such as low estrogen, vitamin D and K status, and increased concentrations of PTH, homocysteine, and lipid oxidation products, may also contribute to this interplay. Regarding the effect of lipid-lowering therapy on bone metabolism, statins may slightly increase BMD, with a tendency to reduce fracture risk as shown in case-control and cohort studies, although available RCTs have not shown any effect of statins on fracture risk. This is also the case for omega-3 FA, whereas inconsistent or insufficient evidence exists for other commonly used lipid-lowering medications, such as ezetimibe, fibrates, and niacin. There is an exigent need for prospective, well-designed studies in males and females to elaborate on the putative association between lipids and bone strength.

Keywords: dyslipidemia ; hypercholesterolemia ; bone mineral density ; osteoporosis ; fractures ; statins

## 1. Pathogenetic Mechanisms Linking Dyslipidemia and Atherosclerosis with Impaired Bone Metabolism

### 1.1. Direct Effect of Dyslipidemia on Bones

Several, though not all, lines of evidence have shown an inverse association of BMD with TC and LDL-C [1]. It has been suggested that increased cholesterol inhibits osteoblast differentiation, preventing bone formation [2]. Enhanced osteoclastogenesis may also be involved [2]. A differential effect of serum cholesterol on BMD at various skeletal sites has been suggested [1], explaining the inconsistency among studies. Furthermore, low HDL-C concentrations have been associated with the development of an inflammatory microenvironment and increased bone marrow adiposity, which restrains the differentiation and function of osteoblasts, leading to reduced bone mass [3].

Bones and vascular tissue share similar pathological features. As with atherosclerosis, increased lipids accumulate beneath the vascular intima and perivascular space in bones [4]. Furthermore, inflammatory bioactive lipids, which promote atherosclerosis, also induce bone loss [4], whereas oxidized LDL-C appears to play a major role in bone loss [5]. Lipid oxidation products, such as minimally oxidized LDL-C, promote arterial calcification, possibly by activating osteoblasts in the arterial pool, while their accumulation in the subendothelial space of skeletal bone arteries inhibits bone formation [6]. Dyslipidemias are also associated with impaired nitric oxide (NO) and enhanced endothelin production, leading to endothelial cell dysfunction and increased thrombotic risk [7]. Additionally, isoprostanes, present in atherosclerotic plaques, enhance vasoconstriction and endothelin-1 release in endothelium and modulate platelet aggregation [8]. Isoprostanes also inhibit osteoblastic differentiation of pre-osteoblasts and enhance osteoclastic differentiation and activity [8]. Overall, lipids appear to be involved in bone remodeling and atherosclerosis progression in opposite directions, explaining the simultaneous existence of osteoporosis and atherosclerosis in people with dyslipidemia [9].

Other mechanisms involve fat accumulation in the femoral head, which increases bone marrow microcirculation pressure and reduces bone vascularization, resulting in ischemia and hypoxia [10]. Moreover, increased blood viscosity also compromises bones' blood supply [10]. All these phenomena may lead to bone necrosis and fractures [10]. A summary of the direct and indirect mechanisms linking dyslipidemia with bone loss is provided in **Table 1**.

**Table 1.** Pathogenetic mechanisms linking dyslipidemia and atherosclerosis with impaired bone metabolism.

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| **Direct effects** | • ↑ Cholesterol → ↓ osteoblast differentiation, ↑ osteoclastogenesis<br>• ↓ HDL-C → ↓ osteoblast differentiation and function<br>• Oxidized LDL-C → ↑ bone loss<br>• ↑ Fat accumulation in the femoral head → ischemia and hypoxia<br>• ↑ Blood viscosity, which compromises bones' blood supply |
| **Estrogens** | • ↓ Estrogens → ↓ osteoblast differentiation, ↑ osteoclastogenesis, ↓ bone mass, atherogenic dyslipidemia → ↑ atherosclerosis and fracture risk<br>• Inverse association between estrogen and serum homocysteine and oxidized LDL-C concentrations |
| **Vitamin D, PTH** | • Low vitamin D status → secondary hyperparathyroidism → ↓ bone mass, dyslipidemia, ↑ cardiovascular risk |
| **Inflammation** | • Dyslipidemia → systemic inflammation (↑ TNF-α, IL-1, IL-6, IL-17, C-reactive protein) → ↑ osteoclastogenesis, osteoporosis |
| **Gla proteins (MGP and osteocalcin)** | • Involvement in mineralization of bones and arteries |
| **Vitamin K** | • Essential co-factor for the formation of Gla proteins<br>• Protects against osteocalcin-induced calcification |
| **Osteopontin** | • ↑ Osteoclast activity, bone resorption<br>• ↑ Systemic inflammation, atherosclerosis, and plaque calcification |
| **BMPs** | • Involved in osteoblast differentiation and proliferation<br>• Vascular calcification promotion |
| **Homocysteine** | • ↑ Osteoclastogenesis, osteoclast activity, bone resorption<br>• ↓ Blood supply and impairment of bone biomechanical properties<br>• Association with premature atherosclerosis and thromboembolism |
| **Nitric oxide** | • ↑ Vascular smooth muscle relaxation, ↓ LDL-C oxidation, platelet aggregation, and adhesion<br>• ↑ Bone formation and fracture healing |
| **RANK/RANKL/OPG axis** | • ↑ Osteoclastogenesis, osteoclast activity, bone resorption<br>• Association with arterial and valve calcification |

| | |
|---|---|
| | • Involved in intracellular cholesterol trafficking |
| **Wnt pathway** | • Regulation of osteoblastogenesis and bone formation |

**Abbreviations:** BMPs—bone morphogenetic proteins; Gla—carboxyglutamic acid; HDL-C—high-density lipoprotein cholesterol; IL—interleukin; LDL-C—low-density lipoprotein cholesterol; MGP—matrix Gla protein, PTH—parathyroid hormone; RANK/RANKL/OPG—receptor activator of nuclear factor kappa-B//RANK ligand/osteoprotegerin; TNF-α—tumor necrosis factor-α; Wnt—Wingless-related integration site; ↑: increased; ↓ decreased.

## 1.2. Indirect Mechanisms

### 1.2.1. Estrogens

Bone and coronary arteries are target organs for estrogens. Indeed, estrogen receptors have been detected on osteoblasts, osteoclasts, and coronary artery smooth muscle cells [11]. Estrogen loss during the transition to menopause leads both to bone loss [12] and atherogenic dyslipidemia [13][14]. Reduced estrogen concentrations have also been associated with increased PTH secretion [15] and, subsequently, accelerated bone loss and soft tissue calcium deposition, including vascular and myocardial calcification [16]. Moreover, an inverse association between estrogen and serum homocysteine concentrations, as well as oxidized LDL-C, has been reported [17], which may partly explain the increased risk for both osteoporosis and atherosclerosis in menopause.

### 1.2.2. Vitamin D and PTH

Vitamin D and PTH are associated with the regulation of phosphorus metabolism, and dysregulated phosphorus metabolism is associated with bone mineral disorders and vascular calcification [18]. Vitamin D deficiency leads to decreased calcium absorption from the intestine and calcium release from bones to maintain normal serum calcium concentrations [19]. Moreover, low vitamin D status increases fracture risk via secondary hyperparathyroidism, leading to bone demineralization and the development of osteomalacia and osteoporosis [19]. On the other hand, vitamin D receptors (VDR) are present in endothelial and smooth muscle cells of the arterial wall [17][20]. Some, but not all, studies suggest that polymorphisms of VDR may be involved in the mutual risk between osteoporosis and atherosclerosis [17][20]. Moreover, increased PTH concentrations are associated with an increased risk of ASCVD [21].

### 1.2.3. Systemic Inflammation

Inflammation is an important component in the pathogenesis of atherosclerosis and osteoporosis, and inflammatory rheumatic diseases have been associated with secondary atherosclerosis and increased bone loss [22]. Several inflammatory mediators are involved in both clinical entities. Furthermore, high concentrations of some inflammatory mediators [e.g., tumor necrosis factor α (TNF-α), interleukin (IL)-1, IL-6, IL-17, and C-reactive protein] have been associated with increased risk of myocardial infarction and non-traumatic fragility fractures [21].

### 1.2.4. Carboxyglutamic Acid (Gla) Proteins

Gla proteins, including matrix Gla protein (MGP) and osteocalcin, encompass a part of a family of mineral-binding proteins. Gla residues bind and incorporate calcium into hydroxyapatite crystals [23]. MGP is a secretory protein with widespread tissue expression, including bones and vascular walls, inhibiting the osteoid formation and mineralization [24] [25]. Osteocalcin, an abundant protein in bones, also inhibits calcification. Data from animal studies suggest that depletion or dysregulation of these proteins leads to abnormal mineralization of bones and arteries [24]. Regarding humans, MGP is integrally expressed in the normal aorta, while it is up-regulated in atherosclerotic plaques [26], probably to limit vascular osteogenesis. Osteocalcin resembles MGP expression in normal and atherosclerotic human vessels [27]. Indeed, increased serum osteocalcin concentrations have been observed in women with both atherosclerosis and osteoporosis [28][29].

### 1.2.5. Vitamin K

Vitamin K is an essential co-factor for the formation of Gla proteins. Accordingly, reduced availability of vitamin K has been associated with functionally defective Gla proteins, which cannot properly form the matrix in which calcium and phosphorus bind together to make solid, well-mineralized bone; thus, low BMD ensues [30]. On the other hand, impaired vitamin K status has been associated with the presence of atherosclerotic calcification [17]. A possible underlying mechanism is that, by increasing MGP in the arterial wall, vitamin K protects against the calcification induced by osteocalcin [30].

#### 1.2.6. Osteopontin

Osteopontin (OPN) is an extracellular, non-collagenous bone matrix glycoprotein, which binds to integrins, especially the αvβ3 one. Integrins are transmembrane proteins that facilitate cell–cell and cell–extracellular matrix adhesion [31]. In bone, upon OPN binding, integrin αvβ3 activates signal transduction pathways that mediate osteoclast attachment to resorption sites [23][32], subsequently promoting bone resorption [32][33][34]. Apart from bones, OPN appears to be involved in vascular inflammation and atherosclerosis [35]. Several lines of evidence suggest that OPN promotes atherosclerotic plaque formation, leading to artery calcification [36][37][38]. In patients with CHD, OPN was found to be localized in calcified atherosclerotic lesions [27] and calcified cardiac valves [39]. Several possible underlying mechanisms regarding the association of OPN expression with increased atherosclerotic risk have been proposed, such as enhanced endothelial cell migration via αvβ3 ligand, increased macrophage activation, and cytokine release by OPN [40][41].

## 2. The Effect of Hypolipidemic Medications on Bone Metabolism

### 2.1. Statins

The 3-hydroxy-3-methylglutarylo-CoA (HMG-CoA) reductase inhibitors (statins) are the most widely prescribed lipid-lowering agents, constituting the mainstay of treatment both in adults and children with hypercholesterolemia [42][43]. Preclinical and clinical data suggest a potential beneficial effect on bone metabolism. In particular, statins may inhibit osteoclastic activity since HMG-CoA blockade reduces the production of downstream products in the mevalonate pathway, such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) [44]. The same pathway is also shared by nitrogen-containing bisphosphonates, thus preventing the prenylation of guanosine triphosphate (GTP)-ases, such as Ras, Rho, and Rac, which are essential for the survival and function of osteoclasts [45]. Another mechanism could be the inhibition of RANKL, which is essential for osteoclast differentiation by averting the production of reactive oxygen species [46]. Statins may also increase 25-hydroxy-vitamin D concentrations [20].

Statins also exert osteoanabolic properties, inhibiting osteoblast apoptosis and fostering osteoblast activity. This mechanism is mediated through increased expression of the BMP-2 gene, which promotes osteoblast differentiation [47]. The latter is also induced by the depletion of FPP and GGPP, as mentioned above [48]. Statins may also promote embryonic stem cell differentiation towards the osteogenic lineage, through activation of increased mRNA expression of runt-related gene 2 (Runx2), osterix (OSX), and osteocalcin (OCN), as osteogenic transcription factors [49].

However, data in humans regarding the effect of statins on bone mass and, more importantly, fracture risk are not robust and consistent. A meta-analysis of randomized controlled trials (RCTs), published in 2016, including seven studies involving a total of 27,900 subjects, showed an increase in BMD by 0.03 g/cm$^2$ (95% CI 0.006–0.053; $I^2$ 99.2%; $p < 0.001$) with statins. Concerning the skeletal site, four studies assessed BMD in LS, one in the distal radius and two in any of multiple skeletal sites. Regarding fracture risk, no association with statin use was observed [pooled hazard ratio (HR) 1.00, 95% CI 0.87–1.15; $I^2$ 0; $p = 0.396$]. These findings remained consistent and significant in sensitivity analysis [50].

These results were replicated by another meta-analysis published in 2017, including 33 studies (23 observational and ten RCTs) with 314,473 patients on statin therapy and 1,349,192 controls [51]. In particular, statins increased LS BMD (standardized MD (SMD) 0.20, 95% CI 0.07–0.32; $p = 0.002$; $I^2$ 43%), as well as TH BMD (SMD 0.18, 95% CI 0.00–0.36; $p < 0.05$; $I^2$ 62%). In subgroup analyses, these associations remained significant only for data derived from cohort studies but not for RCTs. Notably, there was no gender difference regarding TH, but LS BMD increased only in males. Concerning FN BMD, no association with statin use was found. Regarding fracture risk, statins decreased the risk of overall (odds ratio (OR) 0.81, 95% CI 0.73–0.89; $p < 0.0001$; $I^2$ 87.5%) and hip fractures (OR 0.75, 95% CI 0.60–0.92; $p = 0.007$; $I^2$ 77.2%), however, with no effect on vertebral and upper extremity fractures (data from 16 cohort and case-control studies). The authors also assessed the effect of statins on markers of bone turnover, showing a positive effect on osteocalcin concentrations (SMD 0.21, 95% CI 0.00–0.42; $p = 0.04$; $I^2 = 0\%$), but no effect on bone-specific alkaline phosphatase (bALP) and serum C-terminal peptide of type I collagen (CTX) concentrations [51].

Interestingly, a recent Mendelian randomization (MR) study showed that the effect of statins on BMD was dependent on the degree of their LDL-C-lowering action. MR explained this by utilizing 400 single nucleotide polymorphisms, which provided evidence for a causal effect of LDL-C on BMD [52].

Another recent meta-analysis assessed the effect of statin use exclusively on fracture risk in older adults [53]. The authors included 21 observational studies and two RCTs (n= 1,783,123 participants). Data from the observational studies showed an overall decreased fracture risk with statin use [pooled relative risk (RR) 0.80, 95% CI 0.72–0.88; $I^2$ 93.1%]. In subgroup analysis, this association was more evident in men (RR 0.75, 95% CI 0.59–0.95) than in women (RR 0.87, 95% CI 0.76–

0.99) and only for hip (RR 0.73, 95% CI 0.64–0.82) and low extremity fractures (RR 0.69, 95% CI 0.54–0.88). In terms of statin type, only atorvastatin was associated with a reduction in fracture risk (RR 0.77, 95% CI 0.71–0.84) compared to other statins. Interestingly, this beneficial effect was shown only for a short duration of statin use (<1 year) (RR 0.66, 95% CI 0.47–0.93), but not for a higher duration (1–3 or >3 years). Of note, it must be emphasized that the evidence for an anti-fracture efficacy for statins was based only on data derived from observational studies. In the two RCTs, there was no evidence for reducing fracture risk with statin use (RR 1.00, 95% CI 0.87–1.15; $I^2$ 0%) [53].

### 2.2. Ezetimibe

Ezetimibe acts by blocking the cholesterol transport protein Nieman-Pick C1-like 1 (NPC1L1) protein, inhibiting the intestinal absorption of cholesterol. This increases the expression of the LDL-C receptor in hepatocytes, resulting in reductions in serum LDL-C concentrations by 20% [54]. However, due to the concomitant upregulation of cholesterol biosynthesis, mevalonate concentrations may increase. Scarce data exist concerning its effect on bone metabolism. In particular, the inhibition of NPC1L1 protein has raised the hypothesis of reduced vitamin D absorption since NPC1L1 is an important sterol transporter [55]. Although experimental data have shown a decrease in 25(OH)D concentrations [56], this has not been shown in human studies [57]. Moreover, in an open-label study (n = 54 patients with hypercholesterolemia), no effect in LS and TH BMD, as well as in bone turnover markers (bALP and CTX), was observed with ezetimibe [58].

### 2.3. PCSK-9 Inhibitors

No data concerning the effect of proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors on bone metabolism are currently available.

### 2.4. Fibrates

Fibrates are proliferator-activated receptor (PPAR)-α agonists, mostly used in patients with hypertriglyceridemia. They are moderately effective agents in reducing plasma TG (by 50%) and, to a lesser extent, LDL-C (≤20%), as well as in increasing HDL-C concentrations (≥20%) [59].

Concerning bone metabolism, preclinical data have demonstrated that fibrates and, in particular, fenofibrate promote BMP-2 gene expression, thus, stimulating the osteoblast differentiation [60]. Fenofibrate has been shown to maintain FN and whole-body BMD and bone architecture in ovariectomized rats, compared with pioglitazone [61]. However, others have shown a detrimental effect on bone quality in mice with diabetes mellitus, through decreased collagen I and osteocalcin secretion, due to down-regulation of Runx2 gene expression [62].

The evidence for any clinical effect of fibrates on bone health is generally poor. In a case-control study, including 124,655 fracture cases and 373,962 age- and gender-matched controls, an increased risk for non-statin lipid-lowering agents (mainly cholestyramine and fibrates) was demonstrated. In contrast to statins, the use of these non-statin drugs was associated with an increased crude risk of vertebral (OR 2.25; 95% CI 1.22–4.16) and total fractures (OR 1.14, 95% CI 1.00–1.30). However, this association lost significance after adjustment for potential confounders [63].

### 2.5. Omega-3 Fatty Acids

The omega-3 fatty acids (FA) and, in particular, docosahexaenoic (DHA) and eicosapentaenoic acid (EPA) are essential polyunsaturated FA, derived mainly from fish oil [59]. They are moderately efficacious in lowering serum TG concentrations in a dose-dependent manner, with usual doses of 2–4 g/day, although their effect on other lipoproteins is trivial [59]. A cardiovascular benefit has been shown in patients at very high CVD risk with high doses (2 g of EPA twice a day) [59].

Preclinical data suggest a protective effect of omega-3 FA on bone metabolism since a high dietary intake increases the rate of bone formation [64]. They also reduce osteoclastic activity and the ensuing bone resorption by 80%, as shown in rats fed with a purified diet rich in omega-3 FA [65]. Furthermore, fat-1 transgenic mice, which can convert omega-6 to omega-3 FAs, demonstrate significant acceleration in callus formation and fracture healing compared with controls [66].

Epidemiological data in humans regarding the effect of omega-3 FA on musculoske-letal outcomes have provided inconsistent results. A meta-analysis of observational stu-dies (including seven prospective and three case-control studies; n = 292,657 participants) showed an inverse association between fish consumption and the risk of hip fractures (pooled effect size 0.88, 95% CI 0.79–0.98, for the highest compared with the lowest quartile) [67]. However, in subgroup analysis, this association was evident only in case-control studies and in prospective studies with a sample size of ≥ 10,000 participants. Moreover, an inverse association between omega-3 FA intake and the risk of hip fracture was observed (pooled effect size: 0.89, 95% CI 0.80–0.99) [67].

In a systematic review and meta-analysis of ten RCTs published in 2012, a favorable effect of omega-3 FA on BMD or bone turnover markers was demonstrated in four studies, but only when co-supplemented with calcium, whereas three studies showed no effect. No data on fractures were available [68]. Another meta-analysis of 28 RCTs (23 studies on omega-3 FA; 0.4–5.8 g/day of EPA and/or DHA, 3.5–9.1 g/day of alpha-linoleic acid) showed no effect on LS (mean difference 0.03 g/cm$^2$, 95% CI from −0.02 to 0.07) or FN BMD (mean difference 0.04 g/cm$^2$, 95% CI from −0.00 to 0.07) (low or very low quality of evidence, respectively) [69]. A high omega-3 dose induced a slight increase in osteocalcin concentrations, but no effect was observed on other bone formation or bone resorption markers [69]. No data on fractures were available from both meta-analyses [68][69].

### 2.6. Niacin

Niacin (nicotinic acid) is effective in reducing serum TG concentrations by inhibiting the secretion of very-low-density lipoprotein (VLDL) particles from the liver [59]. It also increases HDL-C concentrations due to increased production of apolipoprotein-A1 in the liver [59]. However, its cardiovascular benefit has not been proven, and therefore, it is currently not available in Europe [59].

Very little data exist concerning the effect of niacin on skeletal outcomes. A prospe-ctive community-based study, the Cardiovascular Health Study (CHS), including 5187 men and women ≥ 65 years, showed a U-shaped association between dietary niacin consumption with hip fracture risk. In particular, both lowest (3.6–21.8 mg/day) and highest (41.0–102.4 mg/day) consumption were associated with increased risk of hip fracture [HR 1.31 (95% CI 1.04–1.66) and 1.53 (95% CI 1.20–1.95), respectively] compared with daily intakes of 21.9–40.9 mg. A trend for an inverse association with hip BMD was also found ($p = 0.06$) [70]. However, the latter was not confirmed in another study in 243 pre- and 137 postmenopausal Japanese women, showing a positive association between dietary niacin intake and calcaneus BMD [71].

### 2.7. Bile Acid Sequestrants

Very few data exist with regard to the effect of bile acid sequestrants, such as cholestyramine, colestipol, or colesevelam, on bone metabolism. In a prospective study, cholestyramine 24 g/day, administered either as monotherapy or in combination with pravastatin, had no effect on PTH, 25-hydroxy-vitamin D, and 1,25-dihydroxy-vitamin D concentrations [72].

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