Acta Medica Mediterranea, 2011, 27:

MEVALONATE PATHWAY: ROLE OF BISPHOSPHONATES AND STATINS

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[Via del mevalonato: ruolo dei bifosfonati e delle statine]

SUMMARY

Cardiovascular diseases, i.e. high blood pressure, coronary heart disease, and stroke, and osteoporosis are public health problems, with several epidemiological links, and they might be related to each other in terms of pathogenesis and therapeutic agents. Bisphosphonates inhibit bone resorption and are used in the treatment of osteoporosis, whereas statins inhibit cholesterol biosynthesis and are used for the treatment of atherosclerosis and lipid metabolic disorders. Some late clinical studies suggested bisphosphonates may have beneficial effect in vivo on atherosclerotic progression, lipid profiles, and cardiovascular morbidity and mortality, whereas statins might increase bone density, and reduce fracture risk, even if properly designed prospective studies are needed to clearly define clinical effects and potential new roles for these old agents. Moreover mechanism by which these two classes of drugs act, at cellular level, may not be mutually exclusive, and the common target of action might be the mevalonate pathway. In this review, we focused on in *vitro* and in *vivo* interactions between mevolanate pathway, bisphosphonates, and statins, examining the possible therapeutic consequences of these links.

Key words: Mevalonate pathway, bisphosphonates, statins, osteoporosis, cardiovascular disease

RIASSUNTO

Le malattie cardiovascolari, quali l'ipertensione arteriosa, le coronaropatie e l'ictus, e l'osteoporosi rappresentano importanti problemi di sanità pubblica, con multipli collegamenti, sia di tipo epidemiologico, che patogenetico e terapeutico. I bifosfonati inibiscono il riassorbimento osseo e sono utilizzati per il trattamento dell'osteoporosi, mentre le statine inibiscono la biosintesi epatica del colesterolo e vengono utilizzate nel trattamento dell'aterosclerosi e dei disturbi del metabolismo lipidico. Alcuni recenti studi clinici hanno, però, evidenziato come i bifosfonati potrebbero possedere, anche, effetti positivi, in vivo, sulla progressione dell'aterosclerosi, sul profilo lipidico e sulla morbilità e mortalità cardiovascolare, mentre le statine potrebbero incrementare la densità minerale ossea e ridurre il rischio di fratture, anche se sono necessari ulteriori studi, prospettici e specificatamente progettati, per chiarire, definitivamente, il nuovo potenziale terapeutico di questi farmaci 'antichi'. Inoltre, i meccanismi molecolari attraverso cui queste due classi di farmaci agiscono sembrerebbero non escludersi mutualmente, ed il bersaglio comune della loro azione potrebbe essere la via del mevalonato. In questa review abbiamo concentrato la nostra attenzione sulle possibili interazioni, sia in vitro *che in* vivo*, fra la via del mevalonato, i bifosfonati e le statine, esaminandone le possibili conseguenze terapeutiche.*

Parole chiave: *Via del mevalonato, bifosfonati, statine, osteoporosi, malattie cardiovascolari*

Introduction

Osteoporosis and atherosclerotic disease are both pathology affecting the elderly. Even more evidences suggest existence of links between bone and vascular diseases. Osteoporosis is associated with both atherosclerosis and vascular calcification, whereas calcification is a common feature of atherosclerotic plaques[1-3].

Bisphosphonates (BPs) inhibit bone resorption and are used for the treatment of osteoporosis, whereas statins inhibit cholesterol biosynthesis and are used for the treatment of atherosclerosis and lipid metabolic diseases. However, the mechanism these two classes of drugs act, at cellular level, may not be mutually exclusive, and the common target of action might be the mevalonate pathway. Some early clinical data validate this hypothesis, suggest-

ing that BPs may have a beneficial in vivo effect on atherosclerotic process and on plasma lipid levels, whereas statins may increase bone density. Properly designed prospective studies, that examine effect of BPs on atherosclerotic progression, lipid profiles, and cardiovascular morbidity and mortality, as well as the effects of statins on bone density and fractures, are needed to clearly define the clinical effects and establish new potential therapeutic roles for these agents[4-6].

In this review, we focused on in vitro and in vivo interactions between mevolanate pathway, BPs, and statins, examining the possible therapeutic consequences of these links.

The mevalonate pathway

One important biosynthetic route in eukariotes is the mevalonate pathway, leading to isoprenoid products, such as cholesterol, bile acids, dolichol, ubiquinone, carotenoids, vitamin D, and steroid hormones (Figure 1)[7-9].

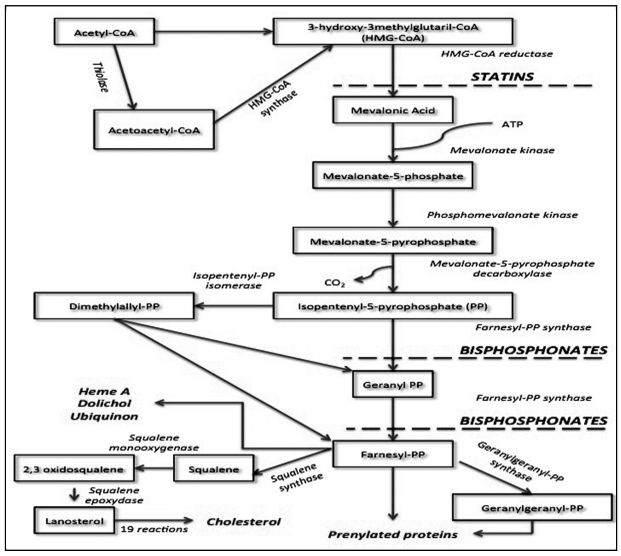

Figure 1: the mevalonate pathway

Membrane assembly, lipid uptake, glycoprotein synthesis, electron transport, and hormonal regulation are only possible if there is adequate production of isoprenoids. Isoprenoids synthesis begins from the precursor acetyl CoA, derived from intermediary metabolism. Most of acetate is converted to fatty acids, for energy storage, and much of the remainder is diverted to mevalonate for isoprenoids synthesis, via the 3-hydroxy-3-methylglutaryl-CoA (HMG CoA) synthase and the HMG CoA reductase. Mevalonate production is irreversible, and the enzyme HMG CoA reductase regulates this rate-limiting step. Mevalonate is subsequently phosphorilated, decarboxilated, and isomerized to isopentenyl pyrophosphate (IPP), the basic isoprenoid building block. Self-condensation of IPP produces geranyl pyrophosphate (GPP), and an additional IPP condensation step, mediated by the enzyme farnesyl pyrophosphate (FPP) synthase, yields FPP, the principal intermediate for all major isoprenoids. Particularly, subsequent synthesis of geranylgeranyl pyrophosphate (GGPP), mediated by the enzyme GGPP synthase, leads to ubiquinone, whereas synthesis of squalene leads, throughout lanosterol, to cholesterol[10,11].

Moreover, FPP and GGPP are essential for post-translational lipid modification (prenylation and geranylgeranylation) of low-molecular-weight guanosine triphosphate (GTP)-binding regulatory proteins of Ras superfamily (i.e. Rac, Rho, Rabs, Rans, Raps, Rals, and so on), which are also GTPases, with farnesyl or geranylgeranylisoprenoids groups. These post-translational modifications, or isoprenylation, need prenyltransferases farnesyltransferase (FTase) and geranylgeranyl transferase I (GGTase I), that catalyze the irreversible attachment of C15 farnesyl (Ras proteins) or C20 geranylgeranyl (Rho proteins) moieties, respectively, to the C-terminal region of these small GTPases, thus modulating their intrinsic, intracellular, activities. Ras superfamily proteins, usually, are placed into plasma membrane, and to be translocated here from cytoplasm, they need hydrophobic prenyl groups, which are able to anchor them to intracellular membranes. Only final cell-membrane fixation allows Ras proteins to participate in their specific interactions. Lack of protein isoprenylation leads to cytosolic sequestration and loss of biological activity[12-14].

When activated, they are involved in the receptor-coupled transduction of signals from extracellular stimuli to cytoplasm and nucleus. Multitudes of directly interacting targets have been identified, including protein kinases, and a whole range of "adaptor" proteins, so-called because they bring together other proteins. There is yet no evidence of function of these targets, and the way Rac and Rho regulate their activities, but everything is under feverish investigation. However, regulatory proteins of Ras superfamily are implicated in regulation of mitogen-activated protein (MAP) kinase cascades, activation of transcription factors, gene transcription, cytoskeletal rearrangement, vesicle transport, secretion, phagocytosis, neurite outgrowth, osteoclasts apoptosis, and malignant transformation[15-17].

Particularly, various cellular processes, including gene transcription, cytoskeletal rearrangement, and malignant transformation are regulated by activity of the small GTPase, Rac1, of the Ras superfamily proteins[18-20].

Activation of STAT3, a member of the family of signal transducers and activators of transcription (STATs) has been proved to be stimulated by constitutively active Rac1 (Rac V12). Rac V12 induces STAT3 activation through an indirect mechanism involving autocrine production and action of interleukin (IL)-6, a known mediator of STAT3 response. Particularly, induction of IL-6 secretion and IL-6 receptor (IL-6R) expression result from Rac V12 activity[21-23].

Therefore, IL-6 activates multiple signalling pathways, i.e. STAT-3 homodimer pathway, STAT1-STAT3 heterodimer pathway, and Ras dependent MAP kinase cascade. Several other cytokines, belonging to IL-6 family (i.e. IL-11, oncostatin M, leukemia inhibitor factor (LIF), ciliary neurotrophic factor (CNTF), and cardiotropin-1 (CT-1)), use gp130, the signal transducer of IL-6R, as a common signal-transducing molecule, having, in this way, similar biological activities[24-27].

In turn, IL-6 mediated inflammation is the common causative factor and therapeutic target for atherosclerotic vascular disease and age-related disorders, including osteoporosis, dementia, Alzheimer's disease, and type 2 diabetes. People affected with conventional risks factors, i.e. smoking, high blood pressure, high cholesterol, and like, have higher incidence of cardiovascular diseases. However, inflammation-related molecules are better predictor of heart disease in subjects without those risk factors. In the health, IL-6 levels are associated with the highest risks for subclinical as well as for clinical cardiovascular disease[28-30].

Moreover, isoprenoids generation, via mevalonate pathway, is required for in vitro activated monocytes IL-8 production, at least in part through attenuation of the increase in mRNA in response to lipopolysaccharide, granulocyte-macrophage colony-stimulating factor, and phorbol myristate acetate[31,32].

Isoprenoids are also required, in granulocytes, for reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex activation, involved in pathogen killing during phagocytosis, via the low-molecular-weight GTP-binding protein Rac isoprenylation[33,34].

Bisphosphonates and mevalonate pathway

Currently, bisphosphonates (BPs) are the treatments of choice, being powerful inhibitors of bone resorption, among the therapeutic options for treatment of osteoporosis, and other excessive bone resorption disease, including Paget's disease of bone, myeloma and osteolytic bone metastases[35-39].

They are synthetic compounds, with high affinity for calcium containing crystals, and selectively concentrate into the bones, binding to hydroxyapatite crystals. They subsequently are locally and selectively taken up, and absorbed to the bone mineral surfaces, where they are able to remain for long, and to be, again and slowly, released during phases of bone remodelling, interfering with the action of the bone-resorbing osteoclasts. In particular, yet unidentified mechanism, which can lead to osteoclast apoptosis, seem to be the grounding BPs may, after internalization, suppress osteoclast-mediated bone resorption by[40,41].

BPs are chemically stable analogues of inorganic pyrophosphate, and are resistant to breakdown by enzymatic hydrolysis. They consist of two side chains, R(1) and R(2), and two atoms of phosphorus linked to a single atom of carbon, forming a P-C-P structure, which is totally resistant to enzymatic hydrolysis. As the longest chain is responsible of the effectiveness of the drugs, shortest one binds to mineral content of bone tissue. Requires a simple change of the side chains to produce different BPs, including currently used in the clinical practice ones[42,43].

BPs can be classified, at least, into two groups, with different molecular mechanisms, depending on the nature of the R(2) side chain[44,45].

The simple non-nitrogen-containing BPs (such as clodronate and etidronate) can be intracellularly metabolized into a nonhydrolyzable, toxic, analogue of adenosine triphosphate (ATP), which inhibits ATP-dependent intracellular enzymes. Metabolite of clodronate adenosine-5'-(β,γ-dichloromethylene) triphosphate (AppCCl2p) can inhibits adenosine diphosphate (ADP)/ATP translocase, with subsequent reduction of mitochondrial oxygen consumption; this is, probably, the route by which clodronate causes apoptosis of osteoclasts[46-49].

Most powerful nitrogen-containing BPs (such as pamidronate, alendronate, risedronate, ibandronate, and zoledronate) are not metabolized in this way, but can inhibit enzymes of mevalonate pathway, in particular FPP synthase, thereby preventing biosynthesis of isoprenoid compounds, that are essential for the post-translational modification of

Ras superfamily regulatory proteins. Late discover of FPP synthase crystal structure may explain how BPs can bind to active site and inhibit this enzyme, via their critical N atoms. So the loss of osteoclast activity and induction of their apoptosis can be explained by inhibition of protein prenylation and disruption of function of these key regulatory proteins. Actually, these regulatory factors, as intracellular "signal" proteins, transducing extracellular signals, regulate a variety of cellular processes required for osteoclasts functions, including determination of cellular morphology, cellular adhesion, formation of "ruffled border", and apoptosis. This mechanism is responsible for nitrogen-containing BPs suppression of osteoclastic bone resorption and reduction of bone turnover, which leads to prevent fractures[49-52].

In addition, lately, it has been demonstrated proinflammatory mediators regulation, monocyte /macrophage system suppression, and anti-atherosclerotic properties seem to be controlled by BPs activity[53].

Nitrogen-containing BPs inhibit mevalonate pathway and particularly FPP synthase leading to depletion of isoprenoid products and, therefore, to suppression of IL-6 mediated inflammation[54-57].

Moreover, vascular calcifications, such as coronary and aortic calcification, are significant feature of vascular pathology, and contribute to several cardiovascular problems, such as systolic hypertension, myocardial and peripheral ischemic disease, and heart failure. Vascular calcification may be divided, at least, in two different class, according to the features of calcification itself: first is medial calcification, between the cell layers of smooth muscle cells, related to aging, diabetes and chronic renal failure; the other is atherosclerotic calcification, in the intima, formed in the progression of atheromatous disease. Process of calcification, based on matrix vesicle formation and mineralization, similar to bones one, initiates vascular calcification. In addition, a lot of bone regulatory factors have been shown to be present in calcified atherosclerotic lesions[58-60].

Evidences indicate BPs can inhibit in vitro experimental development of atheromatous plaque, and propose mechanisms for this action including: inhibition of arterial mineralization and calcification, by their marked accumulation and concentration in human healthy and atherosclerotic arteries, their strong affinity to hydroxyapatite, and their subsequent ability to inhibit ectopic calcification (calcium deposition in soft tissues), or by enhancing production of parathyroid hormone-related peptide from vascular smooth muscle cells[40,61-64]; inhibition of cellular (macrophage) metabolism of atherogenic, modified, low-density lipoprotein (LDL)[65,66]; foam cell development shortening[65,67]; and, latter, reduction of atherogenic LDL-cholesterol, and increasing of protective high-density lipoprotein (HDL)-cholesterol, in the plasma[68-70].

In addition, BPs reduce human arterial contractile force to alpha-adrenergic and depolarizing stimuli, and exert an addictive inhibitory effect, on human arterial contractions, with a Ca2++-channel blocker[71].

A recent study, pointed out, how treatment, for 1 year, with cyclicl administration of etidronate, conducted in 57 patients affected by type 2 diabetes associated with osteopenia, leaded to statistically significant reduction of carotid intima-media thickness, demonstrated, by ultrasounds examination. This affect occurred even though serum lipid levels and cardiovascular parameters were unaffected[72,73].

Contrariwise, two 3-year, randomized, placebo-controlled clinical trials, including 417 elderly osteoporotic women, treated with ibandronate, given either orally, or intravenously, demonstrated no significant differences in atherosclerosis both in yearly progression rate and in 3-year change, between the different intervention groups. These findings suggest that 3-year treatment with effective doses of ibandronate does not pose any cardiovascular risk in terms of altering vascular calcification[74].

Eighty-seven postmenopausal women, with moderate to severe osteoporosis, in another randomized, placebo-controlled clinical trial, were treated with intravenous infusion of neridronate. Patients' serum total cholesterol and serum triglycerides showed marginal decreases, which were occasionally significant. LDL-cholesterol and Apo B significantly fell, whereas Apo AI and HDL-cholesterol rose progressively. Similar findings were obtained in four postmenopausal women administering pamidronate or alendronate high intravenous doses[75].

In conclusion BPs, at least when given intravenously, induce remarkable and unexpected effects on lipid metabolism leading to a final profile that might be clinically relevant.

Statins and mevalonate pathway

Beyond cholesterol lowering, HMG CoA reductase inhibitors (statins) have several others actions. These pleiotropic actions include direct effects on vascular tissue, inflammation, glucose

metabolism, and bone[76-78]. Many of these might be mediated by inhibition of post-translational modification (isoprenylation) of the GTP-binding regulatory proteins of Ras superfamily[79-81].

Vascular endothelia may benefit of statins effects. In this setting, activated Ras proteins are primary component in kinase signal-transducing cascades, negatively involved in NO production. As a matter of fact, there is effective reduction of Ras proteins membrane concentration and activity, due to statins inhibition of enzymes isoprenylation[82-84].

Particularly, statins improve basal and stimulated endothelium-dependent forearm blood flow responses, by increasing endothelial NO production and consequent NO-dependent vasorelaxation[85].

Statins up-regulate endothelial NO synthase (eNOS) expression, and not less, reducing concentrations of LDL cholesterol, improve endothelial derived vasodilation[86-89].

In detail, statins, binding to endothelial and vascular smooth muscle cells, activate Akt, a serine-threonine kinase, also activated by insulin/insulin-like growth factor-I (IGF-I), which, in turn, promotes phosphorilation and subsequent activation of eNOS[89,90], and increases endothelial progenitor cells[91].

In addition to affecting post-translational regulatory mechanisms, statins increases eNOS transcription, stability, and protein level[92].

Moreover, statins, not only increase endothelial cell NO production, but also up-regulate the inducible form of NOS (iNOS) in vascular smooth muscle cells. Generally this enzyme is expressed after vascular injury, and its induction, in these states, seems to be beneficial for vascular function[93,94].

Finally, statins modulate actions and release of vasoconstrictors agents (i.e. angiotensin II and endothelin-1)[95,96].

Statins, in hypercholesterolemic men, reverse hypertensive responses to infused angiotensin II[97], and reduce, in dose- and time-dependent way, the expression of endothelin-1 in endothelial cells, thus, reducing vascular resistance, and improving blood flow in coronary and systemic vascular beds[96,98].

Late evidences pointed out anti-inflammatory action of statins, as these drugs are able to decrease C-reactive protein serum levels, independently from LDL-cholesterol reduction[99,100].

Effectively, statins might affect many of the events in the inflammatory cascade by inhibiting receptor-dependent activation of signal-transducing cascades. Actually, statins seem to: reduce leukocyte rolling, adherence, and transmigration in rodent model of NO deficiency[101,102]; reduce monocyte chemoattractant protein-1 (MCP-1) expression, and monocyte infiltration and proliferation in rat model of coronary inflammation[100,103]; attenuate adhesion molecule expression on endothelial cells (i.e. P-selectin, and intracellular adhesion molecule [ICAM]-1)[104], and monocytes (CD11b)[105], in absence of lipid lowering; reduce serum levels of soluble P-selectin in patient affected with acute coronary syndromes[106]; reduce serum levels of TNF-α and IL-1β in rat model associated with elevated serum levels of these markers[107].

Reduction of nuclear factor (NF)-$\varkappa$B activity in vascular and inflammatory cells may suppress adhesion molecules and cytokines production[100,108].

The complex of these observations points out importance of statins in attenuating the inflammatory process and the consequent impact on cardiovascular risk reduction.

Moreover, statins seem to reduce the risk of developing diabetes. Both substrate delivery to insulin-sensitive tissue, and modulation of insulin-activated signalling cascades, which mediate glucose uptake, might be controlled by statins. As aforesaid, statins increase eNOS expression, which may result in increased capillary recruitment and glucose disposal. Insulin also activates a series of kinase cascades, which involve Akt and PI3K, resulting in translocation of glucose transporters to cell membrane and enhanced glucose uptake. These cascades are inhibited by circulating cytokines. Statins, like insulin, activate Akt and PI3K, thus improving glucose uptake[109].

In addition, statins decrease cytokine levels, and inhibit cellular cascades, such as Rho kinase, that inactivate insulin receptor and signalling (90).

However, mechanisms which link together statins and glucose metabolism and insulin sensibility, are, yet, no totally understood, so further studies are required[77,110,111].

As described above, BPs, especially nitrogen-containing ones, exert their cytotoxic effects on osteoclasts by interfering with mevalonate pathway, a step further downstream from the site of statins action[112].

Therefore, protective effect on bone metabolism has been described as possible effect of therapy with HMG CoA reductase inhibitors. Precisely because of their widespread use and the average age of patients taking these drugs, prevention of

bone loss and fractures would be a desirable side effect. However, mechanisms how statins may regulate bone metabolism are, yet, poorly defined.

Mundy et al. demonstrated that statins enhance new bone formation, both in vitro and in rodents. This effect was associated with increased expression of the bone morphogenetic protein-2 (BMP-2) gene, an osteoblast growth factor, in bone cells. Furthermore, statins increased bone formation when injected subcutaneously over the calvaria of mice, and increased cancellous bone volume when orally administered to rats[113,114].

Sugiyama et al. showed simvastatin, a lypophilic BPs, with elevated bone affinity, activate the BMP-2 promoter, in human osteosarcoma cells, whereas pravastatin, a hydrophilic BPs, do not. Mevalonate, the downstream metabolite of HMG CoA reductase, completely inhibit BMP-2 promoter statin-mediated activation, indicating this last one was result of enzyme inhibition[115].

Potential role of statins in bone formation, probably by inducing the BMP-2, has been indicated by above-mentioned studies[116-119]. However, new, fascinating, mechanisms of statins action have been recently proposed, referring to Rho kinase[120] and Akt/PI3K pathways[91,121].

Another study evaluated effect of atorvastatin on osteoblastic production of osteoprotegerin (OPG) and receptor activator of the nuclear factor κB ligand (RANKL), essential cytokines for osteoclast cell biology. Whereas RANKL promotes osteoclast formation and activation, thus promoting bone resorption, OPG acts as soluble decoy receptor that antagonized the effects of RANKL. Mentioned study pointed out, atorvastatin increased OPG mRNA levels and protein secretion in human osteoblasts, and enhanced expression of osteoblastic differentiation markers, osteocalcin and alkaline phosphatase. Human osteoblasts treated with substrates of cholesterol biosynthesis, which are downstream of HMG CoA reductase reaction (mevalonate, and geranylgeranyl pyrophosphate), reversed atorvastatin-induced enhancement of OPG production. We can, therefore, conclude that atorvastatin enhances production of OPG and osteoblastic differentiation[122].

Contrariwise, few clinical trials have been published to date on statins therapy effect on fracture risk and bone metabolism marker levels. The first case-control studies, managed by Wang et al[123], and Meier et al.[124], on a large number of patients, showed reduction in osteoporotic fractures risk in the group of patients treated with statins, compared to using other lipid-lowering drugs and to control ones.

Bias in selection of analysed populations may explain controversial results of few other observational studies managed to analyse reduction of osteoporotic fractures risk and statins therapy[125-128]. Moreover, all studies presented an undoubted limitation: they were not randomised and so all information they provided could not be considered as unequivocal basis begin prescribing statins for osteoporosis treatment on.

Post-hoc analyses of two, large, secondary prevention with statins interventional trials, the Scandinavian Simvastatin Survival Study (4S) and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study, displayed different results. Both studies were randomised, double-blind, placebo-controlled, multicentric trials, performed in patients with coronary artery disease, the former (4S) using simvastatin (20 to 40 mg/day), with a median of 5.5 years of follow-up, the latter (LIPID) using pravastatin (40 mg/day) for 7 years of follow-up. There was no successful secondary analysis of these studies able to demonstrate positive effects on reduction of fracture risk[129,130].

Bone formation (serum osteocalcin, and bone-specific alkaline phosphatase), and of bone resorption (urinary deoxypyridinoline, and C- and N-terminal cross-linked telopeptides of type I collagen) marker levels have been analysed in few studies, trying to appreciate possible activity of statins administered at different dosis, with controversial results[131-133].

Treatment with simvastatin 20 mg/day, for a period of 4 weeks, led to significant increase of serum osteocalcin, but not anyone of other bone markers evaluated (bone-specific alkaline phosphatase, and urinary deoxypyridinoline, and C- and N-terminal cross-linked telopeptides of type I collagen) had similar ongoings[131].

Contrariwise, fluvastatin 40 mg/die, for a period of 12 weeks, did not show any beneficial effect on the aforementioned markers of bone remodelling[132].

Another multicentric randomised trial, evaluated effect of different statins, at different doses (atorvastatin 20 to 40 mg/day, and simvastatin 40 to 80 mg/day), for 12 weeks period, valuing serum bone-specific alkaline phosphatase and urinary C- and N-terminal cross-linked telopeptides of type I collagen. The only significant effect was a dose-

dependent reduction of serum bone-specific alkaline phosphatase levels in patients treated with simvastatin[133].

Yet another randomized, placebo-controlled study, showed no effects of simvastatin, 20 to 40 mg/day, administered in osteopenic women, for 12 weeks, on bone formation (bone-specific alkaline phosphatase) and resorption (C- and N-terminal cross-linked telopeptides of type I collagen) markers[134].

Late meta-analysis (MA) collected results from 21 studies valuating statins activity on total hip (TH), femoral neck (FN) and lumbar spine (LS) bone mineral density (BMD). Twelve studies concluded to beneficial effect, six to absence of activity and one to deleterious effect. MA pointed out statins users had real increase of TH and FN BMDs, but no effect on LS BMD. Moreover, this meta-analysis compared different activity of lipophilic and hydrophilic statins, concluding first one had real effect, whereas the other seemed not to have same activity, even if data did not reach statistic significance[135].

Finally, another study demonstrated statins (atorvastatin) have, in hypercholesterolemic postmenopausal women with established osteoporosis-osteopenia, modest additive effects to BPs (risedronate) in improving lumbar spine bone mineral density. Moreover, atorvastatin plus risedronate had favourable effects on the serum lipid profile: LDL and total cholesterol[136].

Conclusion

Cardiovascular disease and osteoporosis are public health problems with several epidemiological links and important economic consequences. Recent studies have demonstrated that cardiovascular disease and mortality are associated with reduced bone mineral density and bone fracture. It is also interesting that statins and nitrogen-containing BPs have similar stimulatory effects on bone mass, and all of them are known to reduce LDL-cholesterol and increase HDL-cholesterol in the plasma. So, cardiovascular disease and osteoporosis might be related to each other in terms of pathogenesis and therapeutic agents. Remedies for primary osteoporosis are increasing in brands, but not always with concomitant improvement in efficacy and safety. Clinical studies suggest that nitrogen-containing BPs alone display sufficient practical effectiveness to survive as effective therapy. However, their ineffectiveness in highly osteopenic patients, due to their lack of genuine bone anabolic effect, waits improvements. Statins are cholesterol-lowering drugs as they inhibit HMG CoA reductase, which is a rate-limiting enzyme in mevalonate pathway.

Lately, mevalonate metabolites are also shown to play pivotal roles in the regulation of osteoclast and osteoblasts proliferation and function. However, there have been great controversies in pleiotropic statins effect on bone metabolism. Although in vitro and in vivo animal studies have shown positive effects on bone mineralization and reduction in bone resorption, clinical data on fracture rates and surrogate markers are conflicting. However, while incomplete and contradictory, these studies indicate the possibility that, if bioavailability to bone could be improved simply changing dosing methods and/or deliberate derivatization, the statins genuine anabolic properties in bone could be extracted and put into therapeutic use.

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