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EDITORIAL

Bone and high-density lipoprotein: The beginning of a beautiful friendship

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Abstract

There is a tight link between bone and lipid metabolic pathways. In this vein, several studies focused on the exploration of high-density lipoprotein (HDL) in the pathobiology of bone diseases, with emphasis to the osteoarthritis (OA) and osteoporosis, the most common bone pathologies. Indeed, epidemiological and *in vitro* data have connected reduced HDL levels or dysfunctional HDL with cartilage destruction and OA development. Recent studies uncovered functional links between HDL and OA fueling the interesting hypothesis that OA could be a chronic element of the metabolic syndrome. Other studies have linked HDL to bone mineral density. Even though at epidemiological levels the results are conflicting, studies in animals as well as *in vitro* experiments have shown that HDL facilitates osteoblastogensis and bone synthesis and most probably affects osteoclastogenesis and osteoclast bone resorption. Notably, reduced HDL levels result in increased bone marrow adiposity affecting bone cells function. Unveiling the mechanisms that connect HDL and bone/cartilage homeostasis may contribute to the design of novel therapeutic agents for the improvement of bone and cartilage quality and thus for the treatment of related pathological conditions.

Key words: High-density lipoprotein; Cartilage; Bone; Osteoarthritis; Osteoporosis

Core tip: Recent evidence suggests that high-density lipoprotein (HDL) metabolic pathways are closely related to bone and cartilage homeostasis. In this editorial the authors briefly present the current knowledge concerning the mechanisms that link HDL and cartilage and bone metabolism and discuss the role of HDL result in the development of the most common bone

pathological conditions, osteoarthritis and osteoporosis. These data add to the appreciation of bone and lipid connection and pave the way towards the development of novel HDL-related strategies for the treatment of these diseases.

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It is now accepted that there is a strong connection between lipid metabolism and bone-cartilage homeostasis[1,2]. Indeed, it has been shown that lipid metabolic pathways differentially affect bone cells, leading to the development of pathological bone conditions, *via* both systemic and local phenomena. However, the molecular mechanisms that underline the bone-lipid connection have not been fully illuminated yet. The past few years several, epidemiological studies and studies on animal models focus on the implication of high density lipoprotein (HDL) in the development of bone-related diseases with emphasis to the most common bone pathologies, osteoarthritis (OA) and osteoporosis (OP).

HDL is a vital constituent of the lipoprotein transport system, regulating plasma and tissue lipid matabolism and homeostasis. Apolipoprotein A1 (ApoA1), the lipid transporter ATP-binding-cassette transporter A1 (ABCA1) and the plasma enzyme LCAT are required for the biosynthesis and maturation of HDL. Plasma ApoA-1 is a 243-residue protein, which synthesis takes place primarily in the liver and intestine. ApoA-1 is one of the major apolipoproteins of HDL, since it is responsible for the formation of discoidal HDL particles that mature and become spherical by the action of LCAT[3,4]. LCAT is synthesized and then secreted primarily by the liver catalyzing the esterification of free cholesterol of lipoproteins by transferring a fatty-acyl group from the C-2 position of lecithin to the 3-hydroxyl group of cholesterol. ApoA1 facilitates LCAT activation in plasma[4].

Several lines of evidence associate reduced HDL levels with the development of OA. Indeed, it is now well received that OA is strongly connected to cardiovascular and metabolic pathologies namely hypertension hypercholesterolemia, diabetes type 2, which in turn are associated to altered fat metabolism[5]. Further to support this notion, recent epidemiological data propose that patients with OA have significantly reduced HDL levels compared to healthy individuals. Regrettably, however, the molecular mechanisms that link HDL to cartilage degeneration are still vague. A recent research work has shown that the OA patients have greatly reduced expression of ApoA1 in hyaline or articular cartilage, suggesting that ApoA1-depended HDL reduction affects hyaline cartilage homeostasis[6]. In addition, a very interesting *in vitro* study that used cartilage and synovial membrane joint cells from patients with OA having undergone joint replacement therapy, showed that ApoA1 has the ability to induce the expression of interleukin-6 (IL-6), mouse matrix metalloproteinase-1 (MMP-1) and MMP-3 by primary chondrocytes and fibroblast-like synoviocytes *via* the toll-like receptor 4 receptor. The authors proposed that the lipid metabolic profile is deregulated in the synovial fluid of OA patients and that apoA-1 exhibits pro-inflammatory properties responsible for the symptoms associated with OA[7]. Aiming at further investigating the HDL-OA connection, Collins-Racie *et al*[6], showed that LXR signaling is implicated in the pathobiology of OA. The liver X receptors (LXRα/NR1H3 and LXRβ/NR1H2) are oxysterol-activated transcription factors of the nuclear receptor family that regulate the homeostasis of cholesterol at both cellular and whole-body level and have robust anti-inflammatory functions. They also demonstrated that that the expression levels of LXRα and -β, as well as the expression levels of the LXR target genes ABCG1 and apolipoproteins D and E were altered, a finding implying that the LXR signaling cascade is dysfunctional in degenerated OA cartilage. Importantly, they propose that use of LXR signaling modulators as therapeutic alternative to standard joint glucocorticoid injections[6]. In the same vein Tsezou *et al*[8], studied the expression of genes that regulate cholesterol efflux in human OA chondocytes. In harmony with previous reports having demonstrated that distorted lipid metabolism is critically involved in OA they demonstrated that the expression of ABCA1, ApoA1, and LXRα and LXRβ genes that control cholesterol efflux is greatly reduced in OA compared to normal chondrocytes. Moreover they showed that treatment of osteoarthritic chondrocytes with the LXR agonist TO-901317 resulted in the enhancement of the ApoA1 and ABCA1 expression and cholesterol efflux[8].

In our further effort to explore the involvement of HDL-related metabolic pathways in the pathogenesis of OA we examined the effect of HDL deficiency and impaired maturation on OA development using ApoA1 and LCAT knock out, as well as wild-type mice. Both animal groups were fed both chow (standard) and Western-type (high-fat) diet. Our findings were intriguing. Indeed, we found that the LCAT$^{-/-}$ mice developed marked diet-induced obesity in comparison to the C57BL/6 and ApoA1$^{-/-}$ groups that were fed Western-type diet. Notably, both the LCAT and the ApoA1 knockout mice developed OA, even though the latter were not obese. These novel findings raise the challenging possibility that alterations in HDL rather than increased mechanical stimulation due to excess body weight most probably result in the development of OA in mice. Moreover, histomorphometrical analysis revealed that the bone marrow from LCAT$^{-/-}$ and ApoA1$^{-/-}$ mice contained remarkably enhanced number of fat cells, compared to the other groups adding to the prevailing notion that bone marrow fat is functionally involved in

the pathobiology of cartilage destruction, most plausibly *via* the production and secretion of adipokines, such as leptin, adiponectin and resitin[8]. Definitely, the role of HDL metabolic pathways in the development of OA warrants further investigation; however, the vast majority of the existing research data point towards a protective role of HDL against diet-induced OA and suggest that OA probably represents another facet of the metabolic syndrome[5,9].

Recent data suggest that serum HDL levels and bone mass are connected. Nevertheless, whether this association is positive or negative, is not clear. Indeed, in a relative recent review article on human subjects Ackert-Bicknell very nicely describe a large number of epidemiological studies exploring the link between HDL and bone mineral density. He proposed the that the inconsistent results that were presented are attributed to a number of parameters including age, dietary habits, sex, endocrine status and genetic background[10]. It seems that the research data are clearer in molecular, *in vitro* and animal model studies. Indeed, studies in mice have shown that specific genes such as *APOE, PPARγ, ESR1, IL-6* that regulate both BMD and HDL exhibit chromosomal co-localization[10]. In addition, studies on transgenic mice uncovered specific genes that regulate both BMD and HDL serum levels. One of these genes is apolipoprotein E (apoE) that is involved in HDL metabolic pathways. The role of apoE in bone regulation is very intriguing. Indeed, a few years ago an animal model study showed that apoE deficiency is associated with increased bone mass and elevated osteoblastic function, whereas bone resorption is not affected[11]. Interestingly, however, a few years later the same group showed that when stressed with diabetogenic high-fat diet, the apoE deficient mice develop decreased bone mass and lower body weight[12]. In addition, these animals display lower serum glucose, insulin and leptin levels compared to the control group. Less is know about the role of apoE in osteoclast function. A recent *in vitro* study unveiled that apoE halts osteoclast differentiation and proposed that this effect is possibly mediated through the inhibition of the RANL-dependent nuclear factor κB activation and the c-Fos and NFATc1 induction[13]. Genetic analyses in mice also demonstrated that human apoE isoforms have different effects on bone mass and bone turnover. More specifically, Kim *et al*[14], showed that human apoE2 strongly influences trabecular (but not cortical) bone metabolism in knock-in mice and highlighted the possibility that apoE ε2 allele might serve as a genetic risk factor vertebral fractures in humans[15].

Scavenger receptor class B type Ⅰ is the product of *Scarb1* gene, and its major function is the uptake of cholesteryl esters of HDL by the liver and other tissues. The implication of *Scarb1* in bone metabolism has very recently started to be investigated. However, the results generated seem to be very interesting. Using static and dynamic histomorphometric analyses, Martineau *et al*[16] showed that *Scarb1* deficiency results in augmented bone mass that was more evident in the trabecular bones of 2 mo old female mice[14]. In symphony with the histomorphometry data, *in vitro* assays revealed that the expression levels of the osteoblastic transcription factor *Osx/Sp7* were enhanced, whereas the mRNA levels of the cavelin 1, a gene that halts osteoblastic progenitor differentiation, were reduced. Notably, the number of TRAP-positive surface remained unaffected in these KO mice. In an effort to further explore the role Scarb1 in osteoblastogenesis, the same group performed a series of *in vitro* assays on mesenchymal stem cells obtained from Scarb1 deficient and wild-type mice and concluded that the enhanced osteogenic function that was observed in the Scarb1 knock-out mice can be attributed to stimulation of the Wnt signaling cascade[16].

As mentioned previously, studies have shown that HDL deficiency results in the congregation of lipoblasts in the bone marrow of mice. It is also accepted that bone marrow accelerates osteoclastogenesis, while stunts osteoblastogenesis. These data spark the question whether HDL may have an implication in the pathogenesis of other bone pathological conditions, including neoplastic bone diseases. Since bone marrow microenvironment possesses a cardinal role in the development of bone metastasis we are tempted to speculate that HDL may have a protective role towards metastatic bone disease a hypothesis that definitely merits further exploration. In addition, the tight link between bone and fat raises the challenging possibility that the development of drags that will effectively target lipid-specific metabolic pathways may enhance osteoblast function, improving bone quality.

Collectively, gradually accumulating research evidence suggests that HDL serves as a requirement for normal cartilage and bone function and that it most probably has a protective role against the development of degenerative and metabolic conditions such as OA and OP. Nevertheless, additional epidemiological, molecular, and *in vitro* studies in animal models are needed to substantiate this hypothesis. Furthermore, the role of other molecules that are tightly involved in the HDL metabolic pathways (such as ABCA1), should be carefully examined. Except from HDL-C levels, HDL functionality should also be determined in bone diseases. Indeed, mounting evidence supports the notion that the functionality of HDL particles is plausibly more significant than simply HDL-C levels in plasma and in many instances the anti-inflammatory and anti-oxidant properties of HDL cannot be evaluated only by the determination of HDL-C plasma levels[17].

Unfolding the molecular mechanistic events that connect HDL and bone metabolism may pave the way towards the development of HDL-directed therapies that could add to the armamentarium against bone-related diseases.

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