Biochemical Pharmacology 83 (2012) 315–323

Contents lists available at SciVerse ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Subchondral bone as a key target for osteoarthritis treatment

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ARTICLE INFO

Article history:
Received 1 July 2011
Accepted 15 September 2011
Available online 22 September 2011

Keywords:
Subchondral bone
Osteoarthritis
Pathogenesis
Antiresorptives
New therapies

ABSTRACT

Osteoarthritis (OA), the most common form of arthritis, is a debilitating and progressive disease that has become a major cause of disability and impaired quality of life in the elderly. OA is considered an organ disease that affects the whole joint, where the subchondral bone (SB) plays a crucial role. Regardless of whether SB alterations precede cartilage damage or appear during the evolution of the disease, SB is currently recognised as a key target in OA treatment. In fact, bone abnormalities, especially increased bone turnover, have been detected in the early evolution of some forms of OA. Systemic osteoporosis (OP) and OA share a paradoxical relationship in which both high and low bone mass conditions may result in induction and/or OA progression. Recent findings suggest that some drugs may be useful in treating both processes simultaneously, at least in a subgroup of patients with OA and OP. This review focuses on the role of SB in OA pathogenesis, describing relevant underlying mechanisms involved in the process and examining the potential activity as disease-modifying anti-osteoarthritic drugs (DMOADs) of certain SB-targeting agents currently under study.

1. Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by uneven and gradual loss of articular cartilage, osteophyte formation, subchondral sclerosis and a variety of associated abnormalities of the synovial membrane and periarticular structures. OA is a multifactorial disease characterized by pain, stiffness and functional impairment ultimately resulting in chronic disability and significant economic burden, especially in people 65 years and older [1]. Although repetitive trauma plays a crucial role in the pathogenesis of primary OA, there are other important factors that must be considered. These include genetic factors, menopause-related estrogen deficiency and aging [2].

OA has traditionally been seen as a primary articular cartilage disorder; however, the role of subchondral bone (SB) is currently believed to be of particular importance in the pathogenesis of the disease [1,3–8]. Nevertheless, it remains controversial whether SB alterations precede cartilage degradation or follow the damage caused by loss of cartilage during the evolution of the disease. Recent data from animal models demonstrate that microstructural SB alterations may occur before, during or after cartilage damage [5–8].

In humans, the relationship between systemic bone mineral density (BMD), local subchondral BMD and OA is not clearly defined. Bone alterations may not be uniform and are dependent on the status of overlying cartilage, whether healthy or damaged, and the stage of the disease [4,9]. Recently, data from the Multicenter OA Study (MOST) indicate that high systemic BMD increases the risk of incident knee OA, but not radiographic progression of knee OA [10]. On the contrary, experimental studies show that systemic or local OP worsens OA progression [11]. Hence, different and opposite disturbances of SB mineral density may induce incident OA or aggravate previous disease. Furthermore, the presence of low bone mass in SB does not have the same influence on healthy and diseased cartilage [9].

Thus, SB may be a potentially interesting target for OA treatment, and therefore, bone-acting agents may have favorable consequences on cartilage structure, and subsequently on OA progression.

In this review, we discuss the role of SB in OA pathogenesis and analyze the main effects of various antiresorptive and bone-forming agents on SB remodeling and their potential suitability for treating OA.

2. Definition and functions of the subchondral bone

SB is the zone of epiphyseal bone just beneath the articular cartilage, and includes the SB plate and the underlying trabecular and subarticular bone. The SB plate comprises the deepest area of the articular cartilage, which is the calcified cartilage, and a thin

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0006-2952/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2011.09.018

cortical bone layer [12]. The calcified cartilage is separated from the overlying hyaline cartilage by a line of demarcation called the tidemark. There is an absence of clear anatomical boundaries between SB regions when examined by current imaging techniques, which impedes a thorough study of their properties.

Nevertheless, SB is recognised as a key factor in normal joint protection. In fact, SB has been shown to exert important shock-absorbing and supportive functions in normal joints. SB can attenuate about 30% of the joint load, providing a mechanical base for joint cartilage [13]. Moreover, SB supplies nutrients to cartilage and facilitates the removal of metabolic waste products.

Currently, there is clear evidence for biological crosstalk between SB and joint cartilage. In fact, there is a considerable amount of information indicating the presence of channels between these two tissues, providing a route for the active interplay of biochemical signals throughout both compartments [13]. Many authors therefore consider that SB and articular cartilage represent an authentic functional unit [12–14].

3. Role of subchondral bone in OA pathogenesis

During the OA process, SB undergoes structural changes including increased bone turnover, microfractures, the appearance of new vessels (angiogenesis) and bone sclerosis in later stages. Furthermore, in terms of histopathology, the tidemark is duplicated, the hyaline cartilage is thinned, new blood vessels penetrate the calcified cartilage from SB and there is a subsequent increase in SB thickness [4,12]. These changes affect the biomechanical properties of the overlying joint cartilage and their intertwined biological relationship [12]. In addition, it may be possible that each SB anatomical region may respond differently during the OA process. Thus, SB alterations become a crucial contributor to OA pathogenesis.

The potential role of SB in the initiation and progression of OA was proposed by Radin and Rose [15]. The presence of SB stiffness may decrease its viscoelastic properties and produce a loss of SB shock absorbing capacity, which in turn causes significant extra mechanical load and subsequent breakdown of the overlying cartilage [15]. These same findings were also demonstrated in aged cynomolgus monkeys, where sclerosis of the tibial plateau was directly related to cartilage damage in the medial compartment of the knee [16]. In light of current knowledge on their close relationship, cartilage damage may in turn negatively influence subjacent SB, thus perpetuating a pathogenic circle in the OA joint.

The integrity of articular cartilage may depend not only on SB, which confers specific mechanical properties and influences cartilage remodeling, but also on subarticular bone beneath SB. More recent evidence has shown changes in the structure of bone beneath damaged cartilage in established OA in both humans and animals. This suggests that underlying bone and not just SB may contribute to the development of OA [8,17,18].

Several biological events confirming the presence of increased SB turnover have been described in OA using different study techniques (Table 1). First, several authors have demonstrated increased tracer uptake in subarticular bone scintigraphy [19,20], which has been found to be a good predictor of faster knee OA progression [19,20]. However, it is unclear in which SB region this increased turnover happens. Second, increased SB turnover and remodeling accompanied by specific structural changes in the subchondral trabecular bone have been identified in early stages of OA joints, while increased bone stiffness has been described as later finding [8,12]. Third, elevated levels of bone biomarkers have also been reported in patients with progressive knee OA [21,22]. Finally, magnetic resonance imaging (MRI) findings have indicated increased bone turnover, which are strong predictors of poor prognosis in knee OA [23]. Consequently, modulation of SB turnover may become an attractive approach to OA treatment.

Table 1
Main experimental methods to evaluate subchondral bone in OA.

SB evaluation method/technique	Parameters analyzed
Bone formation biomarkers	Bone alkaline phophatase, osteocalcin, PINP, PICP
Bone resorption biomarkers	TRAP, TRAP5b, pyridinolines (PYD) NTX-I, CTX-I
Bone isotopic scintigraphy	Isotopic tracer uptake
Image techniques: MRI, μCT	Bone microstructural variables Bone microarchitectural variables
Histomorphometry	Histomorphometric parameters

Abbreviations: MRI: magnetic resonance imaging; NTX-I/CTX-I: crosslinked C- (CTX) and N-terminal (NTX) telopeptides of type I collagen; PICP: C-terminal propeptide of type I collagen; PINP: N-terminal propeptide of type I collagen; PYD: pyridinolines; SB: subchondral bone; TRAP (5b): tartrate-resistant acid phosphatase (5b fraction); μCT: micro-computerized tomography.

Osteoblasts (OBs) and osteoclasts (OCs) are, respectively, the cellular effectors of anabolic and catabolic processes in SB and other skeletal regions [24], while chondrocytes preserve homeostasis in cartilage [25]. There is close biological communication between the osteoblasts and osteoclasts in SB and the chondrocytes in joint cartilage [5,26]. Various cytokines, growth factors, prostaglandins (PGs) and leukotrienes produced by SB cells, particularly OBs, seep through the SB-cartilage interface and promote cartilage breakdown [27]. It has therefore been proposed that OBs play a crucial role in this relationship. Indeed, some researchers characterize OA based on the subchondral OB phenotype and whether the OBs are low or high producers of endogenous PGE_2 and interleukin (IL)-6, which is related to the speed of OA progression [5,28].

Another interesting system that is clearly involved in cartilage and SB microarchitecture abnormalities in OA is the osteoprotegerin/receptor activator of nuclear factor (NF)-κB (RANK)/RANK-Ligand (OPG/RANK/RANKL) signaling pathway. The molecular triad OPG/RANK/RANKL is a common final regulator of bone remodeling, which has also been implicated in chondrocyte homeostasis [29–31]. In fact, RANKL expressed by subchondral OBs may be responsible for increased recruitment of active osteoclasts in osteoarthritic SB, thus leading to a rise in bone resorption observed in the early phase of experimental OA. Furthermore, human chondrocytes also express and produce each member of this molecular complex [32]. As a consequence, the RANKL/OPG system has a double mechanism of action in the pathogenesis of OA, through its effect on SB remodeling by stimulating osteoclastogenesis and by a direct effect on chondrocyte homeostasis. OPG has been proposed as a valid biomarker of hand OA [33], and high levels of synovial fluid OPG and increased serum RANKL/OPG ratio have correlated with disease severity in patients with primary knee OA [29]. These findings provide good evidence for the potential value of anti-RANKL therapy in OA.

In general, current data indicate that SB abnormalities are mainly resorptive in the initial phases of OA [8,34] and reparative (bone sclerosis, osteophyte formation) in later stages [35].

4. Osteoarthritis vs. osteoporosis

The paradoxical but unquestionable relationship between the two diseases, OA and OP, is another fascinating subject. Regardless of local communication between SB and joint cartilage and the influence of remodeling in subchondral and subarticular bone on the overlying cartilage, systemic OP may also be involved in OA pathogenesis. The current paradigm supports an inverse relationship between OA and OP [36,37]; however, the relationship has been shown to vary according to the location of BMD measurements and the type of OA (i.e., localized or generalized) [37,38]. As a point of fact, a direct relationship between both diseases has also been described [37,38], which has been used to show how

preceding OP aggravates cartilage lesions in an experimental model of OA in rabbits [11,31].

Cartilage damage can be induced not only by increased bone remodeling, but also by increased SB fragility and low quality [31]. In fact, accelerated bone turnover has been demonstrated in early stages of OA in several animal models, even prior to cartilage damage [6–8]. Although bone volume was increased, a reduction in the elastic modulus of trabecular SB from proximal tibiae was observed in cadaver specimens of subjects with early OA [7]. This local SB softening may occur due to a decrease in BMD, which in turn may be secondary to incomplete mineralization associated with increased bone remodeling [7]. Thus, a low-modulus SB will lead to disruption of the normal balance between bone and cartilage stiffness. Therefore, in a subgroup of patients, low bone mass or established systemic OP may be a deleterious factor for joint cartilage integrity.

In accordance with these findings, we have recently proposed that either high or low bone mass conditions could predispose patients to incident OA [9]. Moreover, current data suggest that antiresorptive drugs and bone-forming agents employed in OP treatment may also be useful in treating both processes (OP and OA) simultaneously.

5. Subchondral bone in different OA subgroups

As previously stated, OA is not a single homogeneous disease, but rather a heterogeneous disease with a number of risk factors able to induce or accelerate disease progression. These risk factors include genetics, anthropometric and anatomical characteristics, aging, hormonal status, obesity, malalignment, trauma and sports injuries to the joint [1]. It is plausible that each factor plays a different role in a particular patient with OA, and different subgroups of OA patients can be identified depending on the main implicated pathogenetic mechanism.

We recently proposed a new classification of primary OA, in which three subsets were postulated according to the predominant pathophysiological mechanism involved: genetic, menopause-related hormonal deprivation and age [2]. Among these subsets, the estrogen deficiency-dependent OA subgroup is of special interest because SB may be a differentiated primary therapeutic target [2,39]. Another typical subgroup is the post-traumatic OA, including OA secondary to repetitive microtrauma, instability-induced osteoarthritis and knee OA, which appears after meniscus or ligament injuries [40]. Experimental evidence indicates that SB turnover is especially increased after joint injury during early stages of this type of OA [8,41]. Consequently, antiresorptive drugs have a good potential for treating these patients in the first months after joint injury.

When searching for specific treatments and better therapeutic response, there is the temptation to classify patients with primary or secondary OA into subgroups according to the predominant pathophysiological mechanism involved. In this context, various agents could be examined within specific OA subgroups in order to establish their efficacy in controlling structural damage as well as modifying the progression of the disease.

6. Subchondral bone as a target in OA treatment

Current strategies for OA treatment include decreasing joint pain and stiffness, improving joint function and delaying surgery. So far, effective agents have not been found that significantly stop the progression of the disease. As with other rheumatic diseases, we need to find reliable disease-modifying OA drugs (DMOADs) capable of halting cartilage destruction. In this section, we will review the suitability in OA treatment of various therapeutic agents that may influence SB remodeling and their potential role as DMOADs. These agents include antiresorptives (e.g., estrogens, SERMs and bisphosphonates), bone-forming agents (e.g., parathormone/teriparatide), antiosteoporotic drugs with dual mechanisms of action (e.g., strontium ranelate) and other new drugs under study (Table 2).

Table 2
Potential disease modifying anti-osteoarthritic drugs working on subchondral bone.

Therapeutic Agents	Main mechanisms of action					Observations and references
	Bone resorption	Bone formation	Osteophyte formation	OPG/RANKL pathway	Biomechanical properties	
Inhibitors of bone remodeling						
Estrogens	– –	+	– –	↑ OPG levels ↓ RANKL	Improves	Ham et al. [42]; Ho et al. [43]; Turner et al. [44]
SERMs	– –	±			Not well established	Sniekers et al. [45]; Yan et al. [46]; Canpolat et al. [47]
Bisphosphonates	– – –		– –		Improves	Hayami et al. [48]; Doschak et al. [49]; Karsdal et al. [50]; Kadri et al. [51]; Moreau et al. [52]
Calcitonins	– –		–		Not well established	Behets et al. [74]; Nielsen et al. [76]
OPG	– –			↓ RANKL action	Improves	↓ osteoclast survival ↑ osteoclast apoptosis Kadri et al. [18]
Blocking RANKL antibodies	– –			↓ RANKL action	Improves	Similar effects to OPG, more long-lasting action
Bone forming agents						
PTH (1–34), intermittent administration		+++			Improves	Bellido et al. [82]
PTH (1–84), intermittent administration		+++			Not well established	There are not studies regarding this point
Agents with dual mechanism of action						
Strontium ranelate	– –	+			Improves	Tat et al. [85]

Abbreviations: OPG: osteoprotegerin; RANKL: receptor activator of NF-κB ligand; SERMs: selective estrogen receptor modulators; PTH: parathyroid hormone. (–): inhibitory effect of variable intensity; (+): stimulatory effect depending on intensity. All these signs refer to clearly demonstrated effects.

6.1. Blocking the remodeling process

Various antiresorptive agents such as estrogens, calcitonin, alendronate and other bisphosphonates (BP) have been shown to have a chondroprotective function/role and a favorable effect in stopping OA progression in animal models of OA [42–52] (Table 2). Recently, selective estrogen receptor modulators (SERMs) have also demonstrated similar positive effects in OA treatment [45].

The current predominant belief is that antiresorptive agents could modify OA progression as modulators of SB remodeling, regardless of their systemic bone effects [53–55]. Due to their chondroprotective effects observed in animal models, antiresorptive agents have also been assayed in humans (Tables 3 and 4). However, results from clinical trials using these drugs have been contradictory, which is not surprising due to the lack of proper selection of certain subgroups of OA patients [2].

6.1.1. Estrogen and SERMs in OA treatment (Table 3)

The role of estrogen in maintaining cartilage integrity has long been the subject of study [39,56,57]. Various authors have demonstrated the expression of two estrogen receptors (α and β) in both healthy and OA cartilage [56]. Furthermore, there is strong evidence of the positive effect of estrogen at multiple levels, not only on articular cartilage but also on SB, synovium and other joint tissues [39].

Estrogen exerts a beneficial effect on bone remodeling, and has become an established therapy in OP treatment. As a consequence, estrogen may also decrease SB remodeling. However, few studies have addressed the potentially restorative effects of estrogen on SB. In an ovariectomized (OVX) female Cynomolgus monkey model of knee OA, Ham et al. reported that long-term estrogen treatment decreased histological damage in both articular cartilage and SB when compared with phytoestrogen or placebo [42]. In another study on OVX sheep, the detrimental effects of ovariectomy on the mechanical properties of cartilage were ameliorated by the implantation of estradiol pellets [44]. Recently, we observed that estrogen deprivation induces cartilage damage in a combined model of OA and OP in rabbits, and this negative effect could be partially explained by the direct effect of estrogen absence on SB [58].

Observational studies and clinical trials have shown a beneficial effect from estrogen on the progression of some forms of OA [59,60] (Table 3). In the Chingford study, Spector et al. found an inverse relationship between the use of hormonal replacement therapy (HRT) and X-ray findings in knee OA [61]. In a recent study, Ravn et al. found that both oral and transdermal treatment of estradiol decreased the release of collagen degradation products from SB and articular cartilage, thus suggesting a protective effect of estradiol against OP and OA [62]. In this regard, estrogens have been proposed as effective modifiers of structural progression in OA, especially in lower limbs. In fact, by analyzing the data from the Women's Health Initiative study aimed at determining the risk of joint replacement in knee and hip OA, Cirillo et al. found that unopposed estrogen decreased OA severity, particularly in the hip, [63]. However, other authors have failed to show the potential benefit of estrogens in OA [64].

SERMs act in a manner similar to estrogens on estrogen receptors. However, their action can be estrogen agonistic or antagonistic, depending on the tissues. Remarkably, SERMs, such as tamoxifen, levormeloxifene and raloxifene, have shown effects similar to estrogen on SB and bone remodeling [39,45–47].

A secondary analysis of a 2-year double blind, randomized, placebo-controlled study demonstrated that tibolone, a synthetic steroid with estrogenic, androgenic and progestogenic properties, also suppresses bone resorption, whereas cartilage degradation remained unchanged [50].

Table 3
Summary of main clinical studies using steroidal hormones with subchondral bone remodeling activity for OA treatment.

Therapeutic agents	Study design	Dose	Effect on OA disease activity	OA location	References
Hormonal treatment					
ERT	Cross sectional	Standard dose	Protective effect[a] (by X-ray)	Hip	Nevitt et al. [59]
ERT	Prospective cohort study	Standard dose (non-specified)	Protective effect (by X-ray)	Knee	Zhang et al. [60]
HRT	Cross sectional	Standard dose (non-specified)	Protective effect on the knee (by X-ray)	Knee and hand	Spector et al. [61]
Oral or transdermal estradiol	2 different randomized, DB, P-C trials	PO: 1 mg 17-β-estradiol + PG TD: 45 μg 17-β-estradiol + PG	Moderate protective effect on cartilage/bone biomarkers	Postmenopausal women	Ravn et al. [62]
CEE + MHP	P-C, DB randomized trial (WHI)	0.625 mg/day CEE ± 2.5 mg/day MHP	Lower rates of hip arthroplasties	Hip and knee	Cirillo et al. [63]
Estrogen + MHP	Randomized, DB, P-C 4-year trial (HERS)	0.625 mg of CEE + 2.5 mg MHP	Pain and disability: no improvement	Knee	Nevitt et al. [64]
Oral estrogen	Cross sectional	Non-specified	Positive effect on WOMAC and MRI findings	Knee	Carbone et al. [72]
SERMs					
Raloxifene	Cross-sectional	60 mg/day	No effect on knee pain severity neither in WOMAC nor MRI	Knee	Carbone et al. [72]
Synthetic steroid hormones					
Tibolone	Post-hoc analysis of 2-year DB, P-C study	1.25–2.5 mg/day	Decrease of cartilage and bone biomarkers		Karsdal et al. [50]

CEE: conjugated equine estrogens; DB: double-blind; ERT: estrogen replacement therapy; HERS: Heart and Estrogen/Progestin Replacement Study; HRT: hormone replacement therapy; MHP: medroxy progesterone acetate; MRI: magnetic resonance imaging; OA: osteoarthritis; P-C: placebo controlled trial; PG: progestagens, progesterone; PO: oral administration; SERMs: selective estrogen receptor modulators; TD: transdermal administration; WHI: Women's Health Initiative Study; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; X-ray: radiographic evaluation.

[a] Only in current users of estrogen for ≥10 years.

Table 4
Summary of main clinical studies using other antiosteoporotic agents for OA treatment.

Therapeutic agents	Study design	Dose	Effect on OA disease activity	OA location	References
Bisphosphonates					
Risedronate	1 year prospective DB, P-C study (BRISK study)	5 mg or 15 mg/day PO	Improvement of X-ray, WOMAC index and PGA	Knee	Spector et al. [68]
Risedronate	2 parallel 2-year studies	5–15 mg/day, 35 mg/wk or 50 mg/wk	1- No improvement of WOMAC, PGA neither X-ray 2- Improvement of bone/cartilage biomarkers	Knee	Bingham et al. [69] Garnero et al. [73]
Risedronate	2-year DB, multi-centre, P-C study	5–15 mg/day or 50 mg/wk	Positive effect on X-ray and on FSA	Knee	Buckland-Wright et al. [70]
Alendronate	Post-hoc analysis of the FIT	5 mg/day (first 2 years); 10 mg/day (3rd year)	Positive effect on X-ray progression	Spine	Neogi et al. [71]
Alendronate	Cross-sectional		Positive effect on knee pain severity, WOMAC and MRI findings	Knee	Carbone et al. [72]
Calcitonins			Positive effect in animals. Their efficacy in humans has not been yet proved		Chesnut et al., 2008 [79] Karsdal et al., 2010 [80] ID: NCT00486434 (*ClinicalTrials.gov*)
Cathepsin K inhibitors					
Balicatib (AAE-581)	Phase II, 1 year, DB, P-C, randomized	10, 25 or 50 mg/day PO	Favorable effect on WOMAC, OARSI score and X-ray progression	Knee (Kellgren-Lawrence Gr. 3)	ID: NCT00371670 (*ClinicalTrials.gov*) Completed, 2009
Strontium ranelate					
Strontium ranelate	Post-hoc analysis of pooled data from SOTI and TROPOS, 3 years	2 g/day	Improvement of pain and reduction X-ray progression	Spine	Bruyere et al. [86]

BRISK: British study of risedronate in structure and symptoms of knee OA; DB: double-blind; FIT: Fracture Intervention Trial; FSA: fractal signature analysis; MRI: magnetic resonance imaging; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; P-C: placebo controlled trial; PGA: Patient Global Assessment; PO: oral administration; SOTI: Spinal Osteoporosis Therapeutic Intervention; TROPOS: TReatment Of Peripheral Osteoporosis; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; X-ray: radiographic evaluation.

6.1.2. Bisphosphonates

Besides their well-established role in OP treatment, BPs have some chondroprotective effects by direct action on both cartilage and SB [53–55]. Experimental studies have shown the beneficial effect of various BPs in OA through their effects on SB [48,51,52,65] (Table 2). BPs decrease vascular invasion of calcified cartilage, inhibit SB remodeling and osteophytogenesis [48,51] and modulate the OPG/RANKL system. Although the exact mechanism of BP action on cartilage is not understood, this mechanism may be due to the promotion of chondrocyte proliferation, inhibition of matrix metalloproteinases (MMP), chondrocyte apoptosis and endochondral ossification, and its possible anti-inflammatory effects [41].

Similar positive findings have been demonstrated with different BPs (etidronate, clodronate, pamidronate, tiludronate, risedronate, alendronate, neridronate and zoledronic acid) [41,48,49,51,52]. Hayami et al. showed the clear chondroprotective effect of alendronate by assaying biomarkers of cartilage degradation in the rat anterior cruciate ligament transection (ACLT) model of OA [48]. Alendronate blocked osteoclast recruitment in SB, and it also inhibited both the vascular invasion of calcified cartilage and osteophyte formation in a dose-dependent manner [48]. For its part, pamidronate reduced the OA score by inhibition of bone resorption in Runx2-Tg mice with high bone remodeling [51]. Other studies have confirmed the beneficial effect of zoledronic acid and risedronate on experimental OA in various animal models [49,66]. In contrast, a study of primary OA in guinea pigs showed that alendronate inhibited bone remodeling and significantly increased bone mineral content and density in SB, thus aggravating OA progression, which was probably due to changes in mechanical properties [67].

BPs have not demonstrated a clear disease-modifying effect in humans, but there are several studies that show a potential benefit of risedronate and alendronate in OA in decreasing SB lesions and improving symptoms and progression of the disease at various locations [68–71] (Table 4). In a cross-sectional study, Carbone et al. reported that both alendronate and estrogen therapy were associated with a lower incidence of MRI-assessed edema and osseous cysts in SB in an elderly female population with knee OA [72]. Moreover, alendronate decreased pain severity in the same population, as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale [72]. In a post-hoc analysis of the Fracture Intervention Trial (FIT), alendronate decreased both osteophyte progression and disc space narrowing at the thoracic and lumbar spine between the 3- and 4-year follow-ups [71] (Table 4).

The BRISK study demonstrated that risedronate 15 mg/day for a year has a beneficial effect on pain and the WOMAC index, as well as significantly decreases markers of both bone resorption and articular cartilage degradation [68]. Risedronate has also been shown to decrease urinary levels of type II collagen C-telopeptide at 6 months of treatment, correlating with slower knee OA progression [73]. In another study, Buckland-Wright et al. demonstrated that risedronate, 15 mg daily or 50 mg weekly for 2 years, maintains the trabecular structure of the cancellous subarticular bone, while the 50 mg weekly dose also increases the number of vertical trabeculae preserving the structural integrity of SB, particularly in patients with marked cartilage loss [70] (Table 4). However, the effects of risedronate on symptoms and functions of knee OA, assessed by the WOMAC OA index and the Patient Global Assessment score, were inconsistent. Therefore, proper meta-analysis and systematic reviews of this topic need to be carried out.

Finally, although BPs have not shown a clear structural effect in clinical trials, they may be useful in early stages of the disease and in some subtypes of OA that progress with high SB remodeling. They could even have some benefit in advanced OA with marked

cartilage loss when administered at doses higher than those used in OP treatment.

6.1.3. Calcitonin

Calcitonin (Ct), a drug already in use for OP treatment, may also act as a DMOAD. Behets et al. reported a beneficial effect of Ct on cartilage damage in ACLT-induced knee OA in dogs [74]. Specifically, the authors reported that Ct administered intranasally inhibited bone remodeling and subsequent bone loss in SB, thus avoiding OA damage in knee joint cartilage [74]. Other studies have also found beneficial effects from the preventive and therapeutic intramuscular administration of salmon Ct in cartilage and SB lesions in a surgically induced model of OA in rabbits [75]. In addition, the preventive use of Ct restored chondrocyte metabolism, increased the number of cartilage layers and decreased osteophyte volume, while therapeutic administration decreased subchondral cysts, regenerated hyaline cartilage and restored chondrocyte metabolism [75]. Recently, Nielsen et al. demonstrated that oral salmon calcitonin counteracts the loss of cartilage thickness, and reduces both SB damage and type II collagen degradation in a combined model of OA induced by meniscectomy associated with ovariectomy in rats [76].

In general, the potential of Ct as a DMOAD has been shown in animal models during early stages of the disease [75,77,78] whereas its chondroprotective effect in humans is anecdotal [79,80] (Table 4).

6.2. Increasing SB mineral density: bone-forming agents in OA

The role of bone forming agents in OA treatment has just begun to be explored. Due to the relevance of SB remodeling in early stages of OA pathogenesis, it is reasonable that any drug capable of modifying bone microarchitecture may also have consequences in chondrocyte biology and, subsequently, in cartilage health. This is particularly important with bone forming agents such as the amino-terminal fragment parathyroid hormone (PTH) (1–34), known as teriparatide in drug form, and the complete PTH (1–84) molecule. Since these therapies can form new bone by increasing bone volume and bone mineral content, they may be able to modify the biomechanical properties of SB. This may be associated with increased SB thickness and stiffness, and paradoxically with overload and mechanical stress on the overlying joint cartilage (Table 2).

There are few studies on the use of bone-forming agents in animal models of OA. Chang et al. demonstrated that PTH (1–34) inhibits terminal differentiation of human articular chondrocytes in vitro and reduces the progression of cartilage damage in a model of papain-induced OA in rats, although the characteristics of bone remodeling and SB properties were not studied in this model [81]. We recently demonstrated that intermittent administration of PTH (1–34) reverses cartilage lesions in a combined model of OP and OA induced by ovariectomy associated with meniscectomy plus anterior cruciate ligament (ACL) sectioning of the knee in rabbits [82]. The decrease in cartilage damage was partially explained by improvements in SB microstructure [82]. In fact, these data demonstrate that increasing subchondral BMD in OP halts OA progression in OP patients, and show the need for classifying OA patients into appropriate pathogenic subgroups. Although more research needs to be carried out, this approach opens new horizons in targeting SB for the treatment of OA.

6.3. Agents with double mechanism of action: strontium ranelate

Strontium ranelate (Sra) is an agent with dual mechanisms of action on bone metabolism, exerting antiresorptive and new bone forming effects [83]. Since Sra increases cartilage matrix formation [84], and produces favorable effects on bone remodeling, it may also have certain value as a DMOAD. Recently, Tat et al. demonstrated that Sra decreases MMP-2 and MMP-9 expression, as well as increases expression and synthesis of osteoprotegerin (OPG) in human SB cells [85]. Sra inhibited key factors affecting bone remodeling in human osteoarthritic SB osteoblasts, and OA osteoblasts treated with Sra had significantly decreased resorbed bone surface at the different concentrations tested [85].

However, very few studies have explored the efficacy of Sra in OA. Recently, Bruyere et al. carried out a post-hoc analysis to determine if Sra could delay the progression of spinal OA in women with OP who were included in the Spinal Osteoporosis Therapeutic Intervention (SOTI) and the Treatment Of Peripheral Osteoporosis (TROPOS) trials [86]. This analysis showed that Sra reduced back pain, regardless of the presence of vertebral fractures, and reduced spinal OA progression, especially by decreasing disc space narrowing [86] (Table 4). In another study, Sra significantly decreased urinary excretion of CTX-II, a marker of cartilage destruction [87].

These early findings suggest that strontium ranelate may have both symptom- and structure-modifying activities in women with osteoporosis and OA (Table 2).

6.4. Targeting OPG/RANK/RANKL system as OA treatment

OPG/RANK/RANKL system is a well-known regulatory system for bone remodeling and bone homeostasis [88,89]. This molecular triad is also produced and expressed in healthy and OA chondrocytes, and may have a role in cartilage homeostasis [30]. In fact, high levels of synovial fluid OPG and increased serum RANKL/OPG ratio have correlated with disease severity in patients with primary knee OA [29].

In an OA model of mice that underwent medial meniscectomy, Kadri et al. found that intraperitoneal administration of OPG inhibited cartilage degradation in vivo, and this effect was attributed to the improvement in SB quality [18]. In fact, OPG increased bone volume and reduced trabecular separation of SB in operated OA knees. In contrast, OPG had no effect on cartilage in vitro [18]. Thus, the prevention of mechanically induced cartilage degradation may be related to a direct effect on SB. In our rabbit model of OA associated with OP, SB microstructural damage induced by increased local remodeling was also related with decreased OPG expression and increased RANKL expression in SB, which led to the reduction of the OPG/RANKL ratio [31]. Interestingly, RANKL produced by human knee OA chondrocytes can diffuse through cartilage matrix and reach SB, thereby probably influencing SB remodeling [26]. Since OP exacerbates cartilage damage, the potential neutralization of RANKL may be doubly beneficial, since anti-RANKL therapy also improves systemic OP (Table 2).

These findings suggest that therapeutic approaches aimed at modulating the OPG/RANK/RANKL system could be an interesting option for treating OA in the near future.

6.5. Other possible targets involving subchondral bone in OA

Other possible targets in the treatment of OA involving SB include prostaglandin E_2 (PGE_2) and the Ephrin-B2/EphB4 receptor complex.

PGE_2 is one of the major catabolic mediators involved in cartilage degradation and OA progression [90]. PGE_2 intracellular signals are transduced through four separate E prostanoid (EP) receptors (EP1–EP4), which produce different and sometimes opposite effects on cell metabolism, depending on the type of activated cell/tissue [91]. We demonstrated that PGE_2 increased synthesis of RANKL by human OA chondrocytes to a greater extent

than OPG, and moreover, induced RANKL transport to the chondrocyte membrane [26]. It is plausible that there is bidirectional crosstalk between articular cartilage and SB, and that chondrocytes also send signals to control SB cell activity in a paracrine manner [26]. In this context, PGE_2 produced in the cartilage could increase SB remodeling by signaling through EP receptors, mainly EP2/EP4 [26,92,93]. Hence, EP2/4 receptor antagonists may represent effective therapeutic agents for controlling bone remodeling and treating OA [26,92]. Several researchers have recently demonstrated that selective antagonism of E prostanoid receptor relieves inflammation and pain in rodent models of experimental arthritis and OA [94,95].

Interestingly, some nonsteroidal anti-inflammatory drugs (NSAIDs) may have a potential role as DMOADs due to their ability to reduce PGE_2 levels and the expression of EP2/EP4 receptors in osteoarthritic joints [96]. In this line, we have demonstrated that some NSAIDs, such as celecoxib and aceclofenac, decreased EP2/EP4 gene expression in cultured human OA chondrocytes [96]. However, this effect has not yet been demonstrated in subchondral bone.

Another novel mechanism involving SB is the Ephrin-B2/EphB4 receptor signaling pathway. Ephrin-B2/EphB4 receptor is a membrane-bound protein complex that leads to bidirectional signaling between OBs and OCs [97,98]. Thus, signal transduction through EphB4 receptors promotes osteoblast differentiation, whereas reverse signaling through Ephrin-B2 ligand suppresses osteoclast differentiation by inhibiting the osteoclastogenic c-Fos-NFATc1 cascade [97,98]. The overall result of such interaction favors bone formation. In SB, OBs and osteocytes express EphB4 receptors. Remarkably, EphB4 receptor levels in osteoarthritic OBs were significantly upregulated by PGE_2 and IL-17. EphB4 activation by Ephrin-B2 inhibits the expression of IL-1β, IL-6, several MMPs and RANKL, but not MMP-2 and OPG [99]. Thus, Ephrin-B2 could be classified as another specific therapeutic approach to DMOAD development.

7. Concluding remarks: the search for a single molecule to treat two diseases

Diverse experimental and observational data strongly support the relevant role of SB in OA pathogenesis. Indeed, findings in studies carried out in different animal models suggest increased bone turnover, which leads to a pro-resorptive status in SB during early stages of OA. Due to technical limitations in determining the initial OA event, early exploration of SB changes in humans has been difficult. However, similar pathophysiological events are likely to occur in different forms of OA. Thus, the appropriate identification of phenotypic subgroups of OA, determined from a pathogenic perspective, becomes crucial for optimizing and individualizing the clinical response of future agents in the OA treatment.

There may be a systemic effect of bone quality in the development and/or progression of OA, which has been assumed from the study of the relationship between OP and OA. Both high and low systemic BMD conditions may influence the incidence and/or progression of OA through their indirect effect on SB.

Therefore, it is reasonable to assume that drugs affecting SB remodeling may hold a prominent role as DMOADs. However, the beneficial effect of these agents in animal models has not been confirmed in clinical studies. Pharmacodynamic properties of each agent, different doses used in animals, critical pharmacokinetic drug characteristics, and the stage of OA evolution may partially explain the differential effects of bone-acting drugs in experimental models of OA when compared with humans.

Recent findings in both pathogenic mechanisms shared by OP and OA, and new mechanisms exerted on articular cartilage and SB by bone-acting drugs already in use, such as BP and bone-forming agents, as well as the launch of OPG/RANKL system-targeting antiresorptive drugs open new horizons in OA treatment. Therefore, new molecules with DMOAD properties that act on bone remodeling may soon be established and integrated into the therapeutic armamentarium for treating both OP and OA.

Conflicts of interest

The authors declare that they have no competing interests related to the present study.

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