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BISPHOSPHONATES AS A TREATMENT MODALITY IN OSTEOARTHRITIS

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Abstract

Osteoarthritis (OA) is affecting large proportions of the population worldwide. So far, no effective disease modifying drug has been developed for this disease, limiting the therapeutic options to pain medications, physiotherapy and ultimately surgical approaches, mainly joint implant surgery. In vitro and animal studies have demonstrated that bisphosphonates have the potential to become effective modalities for the treatment of OA. This group of pharmacological agents modulate crucial aspects of OA pathogenesis (subchondral bone turnover and loss, bone marrow edema formation, cartilage degeneration and synovitis, and have shown clear efficacy in animal models of OA. Human studies have, however, so far been disappointing with only one of six clinical studies showing clear short-term efficacy. Possible reasons for these discrepancies will be discussed.

Osteoarthritis

Definition, classification and epidemiology

Osteoarthritis (OA) is defined as a joint disorder characterized by cellular stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. This in turn manifests initially as a molecular derangement, abnormal joint tissue metabolism and subsequently by anatomic and physiologic perturbations [1]. These processes can present as cartilage degeneration, increased bone remodeling, and osteophyte formation accompanied by inflammation in joint tissue including synovitis, resulting in pain, and loss of normal joint function [2]. Structure-pain relationships in OA remain difficult to understand, however, because it is often unclear which structures may be contributing to pain in the individual patient. Intra-articular candidates include bone and synovium, though it is worth noting that the amount of pain that pathologies in these tissues explain is small [3] and extra-articular features (e.g. tendinitis and bursitis) may confound associations.

Clinically, OA refers to a syndrome of joint pain accompanied by varying degrees of functional limitations and reduced quality of life. At least 242 million people globally have hip/knee OA [4]. In addition, with an ageing population and rising risk factors such as obesity, this prevalence is growing [5]. As a result of the disability caused by OA, the cost to the global economy is significant [6].

Current management of OA involves pharmacological, non-pharmacological and ultimately surgical approaches. Conventional pharmacological treatments have limited efficacy and are associated with a number of side-effects, restricting the number of patients who can use them. New pharmacological therapies for managing

OA are required, in particular disease modifying osteoarthritis drugs (DMOADs), a putative class of therapies aimed at improving OA structural pathologies and consequent symptoms. Bisphosphonates have emerged as a possible treatment modality, and the aim of this review is therefore to summarize our current knowledge about the effects of bisphosphonates on joint cartilage, angiogenesis, subchondral bone and synovium. Subsequently we will review reported preclinical and clinical effects of bisphosphonates. Though this work did not include a systematic review, for the clinical studies of bisphosphonates that were included were accessed from a PubMed-based review of any randomized, placebo-controlled OA studies using a bisphosphonate alone as an intervention, up to and including 2019. We focused on knee OA, as this anatomical site provides the largest number of studies, and therefore gives a more consistent idea of possible benefits. Studies comparing bisphosphonate to another pharmacological agents and/or including mixed anatomical sites of OA were omitted. Small studies less with less than 50 participants (where there is greater potential for bias) were also excluded.

Bone remodeling in osteoarthritis

OA is not considered a typical disorder of bone remodeling like osteoporosis or other metabolic bone diseases, but bone remodeling in subchondral bone clearly affects the overlying cartilage. Generally bone turnover is increased progressively from mild to severe OA, based on the severity of the cartilage lesion [7], albeit some late stage OA patients may exhibit low bone turnover [8]. Increased bone turnover is also in line with the bone loss demonstrated in early stages of OA, while low bone turnover generally protects against bone loss. The increases in bone turnover have been related

to impact loading and microcracks resulting from it [9] [10]. As outlined below, increases in bone turnover rates may also be related to the formation of bone marrow lesions in the area [11].

An unresolved conundrum pertaining to OA pathogenesis is whether bone changes precede cartilage degeneration or vice versa. Numerous animal studies in various species (mice, rats, guinea pigs, dogs monkeys) have demonstrated, however, that alterations in the subchondral bone precede cartilage degeneration [12] [13-16] [17-20] [21].

One study in human OA patients reported signs of increased remodeling in weight bearing regions, but not in non-weight bearing regions [22]. Studies using other modalities (bone turnover markers, in vivo (99m)Tc-DPD-SPECT/CT studies and μCT analyses of excised femoral heads) have all corroborated increased remodeling activity in OA [23, 24]

Furthermore, several studies have demonstrated that blocking subchondral bone resorption and transforming growth factor-β (TGF-β) signaling, attenuate cartilage damage and prevent OA progression [20, 21] [25]. Subcutaneous injection of osteoprotegerin (OPG) a pivotal modulator of osteoclast differentiation has also been shown to reduce pain behavior and joint pathology in rats [26] and clinically, increased levels of synovial OPG, have been shown to correlate with Kellgren-Lawrence scores in knee OA [27].

Late stage bone changes in OA

Late stage bone changes in OA involve increases in subchondral cortical bone thickness (sclerosis), formation of marginal joint osteophytes, development of bone cysts and advancement of the zone of calcified cartilage between the articular cartilage and subchondral bone ensues [28] [29]. Late stage changes further include hypertrophy and apoptosis of articular chondrocytes, degradation of cartilage matrix, angiogenesis and calcification of hyaline cartilage, replication of tidemark, degeneration of ligaments and, in the knee, the menisci, hypertrophy of the joint capsule and increased permeability of the osteochondral interface [30]

Bone marrow lesions

The increasing use of magnetic resonance imaging in clinical practice, has led to increasing recognition of bone marrow lesions (BML) as being central components of many different diseases affecting the musculoskeletal system including OA.

BMLs give rise to a fairly consistent water signal on MRI, causing hypodense lesions on T1 weighted sequences and hyperdense lesions on T2 weighted sequences. The best modality for detecting such lesions are water sensitive sequences such as fat suppressed T2-weighted, proton density-weighted, intermediate-weighted fast spin echo or short tau inversion recovery (STIR) sequences. In hip OA Taljanovic et al reported ,that the amount of BMLs in the OA hip, correlated with the severity of pain, radiographic findings, and number of microfractures on histology[31]. BMLs are not visible on plain X-ray or computed tomography (CT), but show uptake on scintigraphy [32]

A myriad of terms have been used in the literature when referring to bone marrow lesions reflecting the wide range of conditions associated with these lesions (trauma,

infections, ischemia, neoplasms, autoimmune arthritis and degenerative conditions like osteoarthritis [33]. Initially, such lesions were denoted Bone Marrow Edema (BME). No tissue edema has, however, been conclusively demonstrated in histological studies of such lesions. We therefore prefer the term bone marrow lesion (BML) as originally proposed by Felson[34] [35] [33] .

A crucial factor in the development of BMLs seems to be microdamage in subchondral bone[34] . In joints BMLs are related to malalignment, joint pain, and disease progression[34]. Moreover, it seems that BMLs are involved in bone-cartilage crosstalk in joint disease[34, 36]. The clinical symptoms in most of the cases of trauma-related BMLs resolve over 6 weeks, while the MR-signal changes resolve over an average of 3 months. A minority, less than 5% in one study fail to resolve by 3 months probably secondary to repetitive trauma [35, 37].

Bone marrow lesions in OA patients are usually longer lasting due to the chronic nature of the disease, and they have been linked to increased pain, enhanced cartilage loss and worsening of prognosis [37] [24, 33]. Our own histological studies based on tetracycline double labelling have revealed that BMLs are characterized by pronounced increases in bone turnover (40- and 18-fold increase of bone formation rate and mineralizing surface, respectively) and 4-fold increase in angiogenesis as reflected in the expression of angiogenesis markers like CD31 and von Willebrand factor. Additionally, bone samples with BML demonstrated a 2-fold reduction of marrow fat and a 28-fold increase of woven bone. We therefore concluded that BMLs represent a skeletal repair phenomenon, probably related to microdamage accumulation as suggested by Alliston et al.[34]. Moreover our studies suggest, that the water signal on MR,, is most probably reflecting increased tissue vascularity [38]. A recent microarray study by Kuttapitiya et al. studying gene expression in BMLs

found the lesions to be characterized by increased metabolic activity expressing a wide variety of genes related to nociception, and neuronal activity, inflammation and extracellular matrix synthesis signalling[36]

Angiogenesis in OA

Angiogenesis is the formation of new blood vessels from preexisting vasculature, and constitutes an essential adaptive response to physiological stress and an endogenous repair mechanism after injury [39]. It has been well established that bone remodeling occurs in close proximity to blood vessels and these vessels carry perivascular stem cells that differentiate into osteoblasts [40]. Bisphosphonates exhibit anti-angiogenic properties, with zoledronic acid being the most potent [41], which also may be of interest in relation to treatment of OA. Not only may anti-angiogenesis exert a positive impact on vascularization and pain from bone marrow lesions [33], but also other features related to OA as outlined below (Fig. 1).

Contrary to bone, which is a highly vascular tissue, most of the normal articular cartilage is mostly avascular. This feature has been linked to the presence of anti-angiogenic factors such as chondromodulin-1 (ChM-1) and thrombospondin-1 (TSP-1) within the cartilage [42, 43]. Studies have revealed, however, that the osteochondral junction exhibits significant upregulation of angiogenetic factors, nerve growth factor and proinflammatory cytokines in OA [44] [40]. Increased angiogenesis has also been implicated in the development of pain in OA. The principal regulators of angiogenesis, vascular endothelial growth factors (VEGFs), are, like proinflammatory cytokines (IL-1, IL6. IL-11), well documented modulators of nociception. Late stage changes in OA (osteophyte development, subchondral bone remodeling, and cartilage mineralization) are closely linked to angiogenesis [45] [46, 47]. Finally,

atherosclerosis of intraosseous vessels has been implicated in the pathogenesis of OA [48].

Bisphosphonate effects on synovitis

Cinar et al. studied the effects of intra-articular zoledronic acid in a rat OA model created by anterior cruciate ligament transection (ACLT). The group treated with zoledronic acid showed less cartilage deterioration and less synovitis by histology [49].

Bisphosphonate effects on bone and cartilage in OA

Preclinical studies

Subchondral bone plays a role in maintaining hyaline articular cartilage integrity and its pathology is integral to the OA process [50]. A number of antiresorptive therapies used for osteoporosis, targeting increased bone turnover in the subchondral region, have therefore been explored as OA therapies, targeting increased bone turnover in the subchondral region, which is seen primarily in early OA [51, 52].

Bisphosphonates have demonstrated significant protection against subchondral bone loss and cartilage loss in various animal models of osteoarthritis (Fig. 1). Most models have studied changes after induction of OA changes following transection of the anterior cruciate ligament or chemical induction using monosodium acetate. In such models treatment with bisphosphonates like tiludronate, pamidronate, alendronate and zoledronic acid were shown to reduce subchondral bone turnover and bone loss and preserve articular cartilage [53, 54] [55] [56].These effects have been linked to reduced expression of metalloproteinases, changes in the OPG/RANKL ratio affecting osteoclast recruitment, angiogenic factors and proinflammatory

cytokine[57]. The bisphosphonate clodronate has been shown to upregulate the transcription factor SOX-9, which is important for chondrogenic commitment. This was associated with increased extracellular matrix synthesis [58].

In this context it is of significant interest, that Alendronate was found to inhibit vascular invasion into the calcified cartilage in rats with OA and blocked osteoclast recruitment to subchondral bone and osteophytes. ALN treatment reduced the local release of active TGFβ, possibly via inhibition of MMP-13 expression in articular cartilage and MMP-9 expression in subchondral bone [59].

Bagi, C. M., et al. Studied the effects of osteoanabolic (Teriparatide) and antiresorptive therapies (zoledronic acid) on cartilage in an OA model using meniscectomy in rats. Although both Zol and PTH improved subchondral bone mass and Zol reduced serum CTX-II level, both treatments failed to prevent or correct cartilage deterioration, osteophyte formation and mechanical incapacity [60].

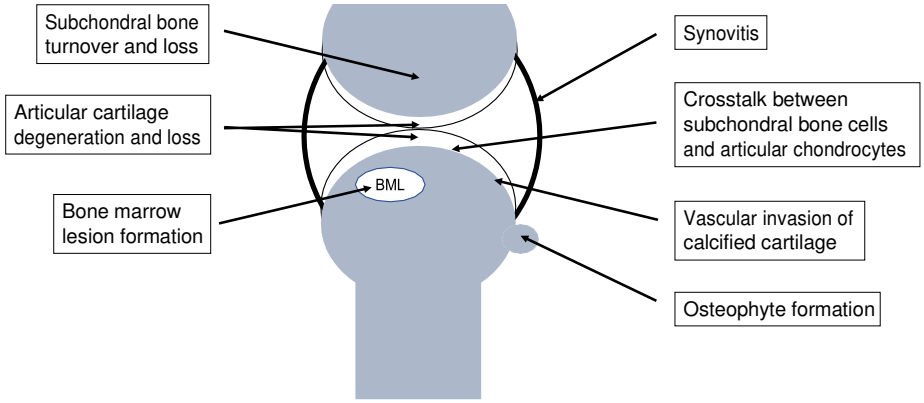

Fig. 1. Schematic presentation of aspects of OA pathogenesis, where bisphosphonates have demonstrated significant inhibitory effects in animal and human studies, based on the studies reviewed.

Human studies

Table 1 shows randomized controlled trials comparing bisphosphonates to placebo in knee OA. Evidence of symptomatic improvement and reduction of radiographic progression with bisphosphonates was limited and inconclusive. However, reduced MRI BML size was demonstrated in two studies.

Recent studies have focused recruitment on patients with definite subchondral bone abnormalities, specifically MRI-detected bone marrow lesions (BMLs). BMLs are commonly seen on MRI scans of OA knees, represent areas of trabecular loss, microfracture and marrow fibrosis, and have associations with both pain and progressive cartilage loss [61-64]. Zoledronic acid (ZOL) was compared with placebo in a double blind, parallel group trial of 59 patients aged 50-80 with knee pain and at

least one BML on MRI [65]. Results were promising, demonstrating a significant symptomatic benefit and reduction in BML size at 6 months. The preliminary report from the larger follow-up multicenter, randomized controlled trial has been recently presented. In this study, 223 knee OA patients with significant knee pain and MRI-detected BMLs received annual intravenous infusion of ZOL 5mg or placebo over 2 years [66]. Unfortunately, no significant improvement was detected at 24 months in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale, WOMAC function scale, or BML size change with ZOL.

Table 1: Human bisphosphonate knee OA intervention studies (adapted from [67])

Intervention vs comparator	Study duration	Number of participants	Main symptom outcome	Structural Outcome	Summary of results
Risedronate 5 or 15 mg/day vs oral placebo [68]	12 months	284	WOMAC pain and function	X-Ray mean joint space width change (mm)	No significant difference between treatment groups
Risedronate 5 or 15 mg/day or 35 mg/week vs oral placebo [69]	24 months	1251	WOMAC pain and WOMAC function; patient global assessment	Proportion of patients experiencing X-Ray progression (defined as ≥0.6 mm of JSN over 24 months)	No significant difference between treatment groups
Risedronate 5 or 15 mg/day or 50 mg/week vs oral placebo [69]	24 months	1232	WOMAC pain and WOMAC function; patient global assessment	Proportion of patients experiencing X-Ray progression (defined as ≥0.6 mm of JSN over 24 months)	No significant difference between treatment groups
Zoledronic acid 5 mg vs IV placebo [65]	12 months	59	Visual analogue scale (VAS) pain	Change in total bone marrow lesion (BML) area on MRI	Significant VAS improvement in the per protocol analysis (no significant difference in intention to treat population).

					Significantly reduced BML size at 6 months but not 12 months
Clodronate 2 mg/week vs intra-articular placebo [70]	4 months	80	Sum of VAS pain on passive movement and digital pressure	N/A	Significant improvement at 2 months but not 4 months
Neridronate (100 mg 4× over 10 days) vs IV placebo [71]	2 months	68	VAS pain	Change in BML size (semi-quantitative scoring)	Significant improvement in pain score and BML size

A sub-study of this 2-year ZOL trial investigated the effects of ZOL 5mg plus intravenous methylprednisolone 10mg in a preparation called VOLT01[72]. One hundred seven patients with symptomatic knee OA were randomized to receive single dose VOLT01, ZOL 5mg monotherapy or placebo. The study's primary outcome measurement was the incidence of the acute phase response following ZA administration (a flu-like or febrile response which can occur following IV bisphosphonate) and secondary outcomes measured BML size, WOMAC and visual analogue scale (VAS) pain and WOMAC function at 6 months. The incidence of acute phase responses was similar between treatment groups. In addition, VOLT01 and ZOL were not superior to placebo in any of the secondary outcome pain measurements.

Conclusions

Thus, so far, the clinical studies on bisphosphonates as a treatment modality in knee OA have been disappointing, contradicting the solid evidence of positive effects demonstrated in preclinical studies. Our findings are however in keeping with 2 previous meta-analyses of bisphosphonate intervention in OA [67, 73]. We note that Deveza et al are currently conducting a review of bisphosphonate intervention data to identify whether certain patient subgroups are more likely to benefit from bisphosphonate therapy than others [74] .

It is likely that many of the studies assessing radiographic progression were underpowered and many did not use modern inclusion criteria that enable detection of a pain response (such as pain >4 on a 10-point scale). Bisphosphonates may also be

more beneficial in early OA when there is increased remodeling, although a general consensus on a definition of early OA which would allow a homogenous patient group selection is still awaited. Moreover, underdosing may be a problem. In this context it is of interest that the positive study by Varenna et al. used quite high doses over a short period of time.

REFERENCES

[1] V.B. Kraus, F.J. Blanco, M. Englund, M.A. Karsdal, L.S. Lohmander, Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 23(8) (2015) 1233-41.

[2] NICE guidelines osteoarthritis, 2014. https://www.nice.org.uk › guidance › resources › osteoarthritis-care-and-management.

[3] E. Yusuf, J. Bijsterbosch, P.E. Slagboom, H.M. Kroon, F.R. Rosendaal, T.W. Huizinga, M. Kloppenburg, Association between several clinical and radiological determinants with long-term clinical progression and good prognosis of lower limb osteoarthritis, PloS one 6(10) (2011) e25426.

[4] Global Burden of Disease Study, C., Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. , Lancet 386 (2015) 743-800.

[5] T. Neogi, Y. Zhang, Epidemiology of osteoarthritis, Rheum Dis Clin North Am 39(1) (2013) 1-19.

[6] J.H. Salmon, A.C. Rat, J. Sellam, M. Michel, J.P. Eschard, F. Guillemin, D. Jolly, B. Fautrel, Economic impact of lower-limb osteoarthritis worldwide: a systematic review of cost-of-illness studies, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 24(9) (2016) 1500-8.

[7] R. Klose-Jensen, L.B. Hartlev, L.W.T. Boel, M.B. Laursen, K. Stengaard-Pedersen, K.K. Keller, E.M. Hauge, Subchondral bone turnover, but not bone volume, is increased in early stage osteoarthritic lesions in the human hip joint, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 23(12) (2015) 2167-2173.

[8] D.B. Burr, M.A. Gallant, Bone remodelling in osteoarthritis, Nature reviews. Rheumatology 8(11) (2012) 665-73.

[9] E.L. Radin, R.B. Martin, D.B. Burr, B. Caterson, R.D. Boyd, C. Goodwin, Effects of mechanical loading on the tissues of the rabbit knee, Journal of orthopaedic research : official publication of the Orthopaedic Research Society 2(3) (1984) 221-34.

[10] D.B. Burr, E.L. Radin, Microfractures and microcracks in subchondral bone: are they relevant to osteoarthrosis?, Rheum.Dis.Clin.North Am. 29(4) (2003) 675-685.

[11] M. Shabestari, J. Vik, J.E. Reseland, E.F. Eriksen, Bone marrow lesions in hip osteoarthritis are characterized by increased bone turnover and enhanced angiogenesis, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society (2016).

[12] C.S. Carlson, R.F. Loeser, C.B. Purser, J.F. Gardin, C.P. Jerome, Osteoarthritis in cynomolgus macaques. III: Effects of age, gender, and subchondral bone thickness on the severity of disease, Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 11(9) (1996) 1209-17.

[13] D.K. Dedrick, S.A. Goldstein, K.D. Brandt, B.L. O'Connor, R.W. Goulet, M. Albrecht, A longitudinal study of subchondral plate and trabecular bone in cruciate-deficient dogs with osteoarthritis followed up for 54 months, Arthritis and rheumatism 36(10) (1993) 1460-7.

[14] K. Kuroki, C.R. Cook, J.L. Cook, Subchondral bone changes in three different canine models of osteoarthritis, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 19(9) (2011) 1142-9.

[15] P. Lavigne, M. Benderdour, D. Lajeunesse, P. Reboul, Q. Shi, J.P. Pelletier, J. Martel-Pelletier, J.C. Fernandes, Subchondral and trabecular bone metabolism regulation in canine experimental knee osteoarthritis, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 13(4) (2005) 310-7.

[16] J.Y. Yan, F.M. Tian, W.Y. Wang, Y. Cheng, H.F. Xu, H.P. Song, Y.Z. Zhang, L. Zhang, Age dependent changes in cartilage matrix, subchondral bone mass, and estradiol levels in blood serum, in naturally occurring osteoarthritis in Guinea pigs, Int J Mol Sci 15(8) (2014) 13578-95.

[17] T. Hayami, M. Pickarski, Y. Zhuo, G.A. Wesolowski, G.A. Rodan, L.T. Duong, Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis, Bone 38(2) (2006) 234-43.

[18] G. Mohan, E. Perilli, J.S. Kuliwaba, J.M. Humphries, I.H. Parkinson, N.L. Fazzalari, Application of in vivo micro-computed tomography in the temporal characterisation of subchondral bone architecture in a rat model of low-dose monosodium iodoacetate-induced osteoarthritis, Arthritis research & therapy 13(6) (2011) R210.

[19] S.M. Botter, G.J. van Osch, J.H. Waarsing, J.C. van der Linden, J.A. Verhaar, H.A. Pols, J.P. van Leeuwen, H. Weinans, Cartilage damage pattern in relation to subchondral plate thickness in a collagenase-induced model of osteoarthritis, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 16(4) (2008) 506-14.

[20] A. Kadri, T. Funck-Brentano, H. Lin, H.K. Ea, D. Hannouche, C. Marty, F. Liote, V. Geoffroy, M.E. Cohen-Solal, Inhibition of bone resorption blunts osteoarthritis in mice with high bone remodelling, Annals of the rheumatic diseases 69(8) (2010) 1533-8.

[21] G. Zhen, C. Wen, X. Jia, Y. Li, J.L. Crane, S.C. Mears, F.B. Askin, F.J. Frassica, W. Chang, J. Yao, J.A. Carrino, A. Cosgarea, D. Artemov, Q. Chen, Z. Zhao, X. Zhou, L. Riley, P. Sponseller, M. Wan, W.W. Lu, X. Cao, Inhibition of TGF-beta signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis, Nature medicine 19(6) (2013) 704-12.

[22] N.L. Fazzalari, R.J. Moore, B.A. Manthey, B. Vernon-Roberts, Comparative study of iliac crest and subchondral femoral bone in osteoarthritic patients, Bone 13(4) (1992) 331-5.

[23] P. Bettica, G. Cline, D.J. Hart, J. Meyer, T.D. Spector, Evidence for increased bone resorption in patients with progressive knee osteoarthritis: longitudinal results from the Chingford study, Arthritis and rheumatism 46(12) (2002) 3178-84.

[24] O. Maas, G.B. Joseph, G. Sommer, D. Wild, M. Kretzschmar, Association between cartilage degeneration and subchondral bone remodeling in patients with knee osteoarthritis comparing MRI and (99m)Tc-DPD-SPECT/CT,

Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 23(10) (2015) 1713-20.
[25] B.J. Davis, J.I. Risinger, G.V. Chandramouli, P.R. Bushel, D.D. Baird, S.D. Peddada, Gene expression in uterine leiomyoma from tumors likely to be growing (from black women over 35) and tumors likely to be non-growing (from white women over 35), PloS one 8(6) (2013) e63909.
[26] D.R. Sagar, S. Ashraf, L. Xu, J.J. Burston, M.R. Menhinick, C.L. Poulter, A.J. Bennett, D.A. Walsh, V. Chapman, Osteoprotegerin reduces the development of pain behaviour and joint pathology in a model of osteoarthritis, Annals of the rheumatic diseases 73(8) (2014) 1558-65.
[27] A. Pilichou, I. Papassotiriou, K. Michalakakou, S. Fessatou, E. Fandridis, G. Papachristou, E. Terpos, High levels of synovial fluid osteoprotegerin (OPG) and increased serum ratio of receptor activator of nuclear factor-kappa B ligand (RANKL) to OPG correlate with disease severity in patients with primary knee osteoarthritis, Clin Biochem 41(9) (2008) 746-9.
[28] S.R. Goldring, Alterations in periarticular bone and cross talk between subchondral bone and articular cartilage in osteoarthritis, Ther Adv Musculoskelet Dis 4(4) (2012) 249-58.
[29] D. Bobinac, J. Spanjol, S. Zoricic, I. Maric, Changes in articular cartilage and subchondral bone histomorphometry in osteoarthritic knee joints in humans, Bone 32(3) (2003) 284-90.
[30] Z.F. Xiao, G.Y. Su, Y. Hou, S.D. Chen, D.K. Lin, Cartilage degradation in osteoarthritis: A process of osteochondral remodeling resembles the endochondral ossification in growth plate?, Medical hypotheses 121 (2018) 183-187.
[31] M.S. Taljanovic, A.R. Graham, J.B. Benjamin, A.F. Gmitro, E.A. Krupinski, S.A. Schwartz, T.B. Hunter, D.L. Resnick, Bone marrow edema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination, radiographic findings, and histopathology, Skeletal radiology 37(5) (2008) 423-31.
[32] F.W. Roemer, F. Eckstein, D. Hayashi, A. Guermazi, The role of imaging in osteoarthritis, Best practice & research. Clinical rheumatology 28(1) (2014) 31-60.
[33] E.F. Eriksen, J.D. Ringe, Bone marrow lesions: a universal bone response to injury?, Rheumatology international 32(3) (2012) 575-84.
[34] T. Alliston, C.J. Hernandez, D.M. Findlay, D.T. Felson, O.D. Kennedy, Bone marrow lesions in osteoarthritis: What lies beneath, Journal of orthopaedic research : official publication of the Orthopaedic Research Society 36(7) (2018) 1818-1825.
[35] D.T. Felson, M.J. Parkes, E.J. Marjanovic, M. Callaghan, A. Gait, T. Cootes, M. Lunt, J. Oldham, C.E. Hutchinson, Bone marrow lesions in knee osteoarthritis change in 6-12 weeks, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 20(12) (2012) 1514-8.
[36] A. Kuttapitiya, L. Assi, K. Laing, C. Hing, P. Mitchell, G. Whitley, A. Harrison, F.A. Howe, V. Ejindu, C. Heron, N. Sofat, Microarray analysis of bone marrow lesions in osteoarthritis demonstrates upregulation of genes implicated in osteochondral turnover, neurogenesis and inflammation, Annals of the rheumatic diseases 76(10) (2017) 1764-1773.

[37] M.D. Crema, D.T. Felson, F.W. Roemer, K. Wang, M.D. Marra, M.C. Nevitt, J.A. Lynch, J. Torner, C.E. Lewis, A. Guermazi, Prevalent cartilage damage and cartilage loss over time are associated with incident bone marrow lesions in the tibiofemoral compartments: the MOST study, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 21(2) (2013) 306-13.
[38] M. Shabestari, J. Vik, J.E. Reseland, E.F. Eriksen, Erratum to "Bone marrow lesions in hip osteoarthritis are characterized by increased bone turnover and enhanced angiogenesis" [Osteoarthritis Cartilage 24 (2016) 1745-1752], Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 25(4) (2017) 611.
[39] P. Carmeliet, M. Tessier-Lavigne, Common mechanisms of nerve and blood vessel wiring, Nature 436(7048) (2005) 193-200.
[40] S.M. Chim, J. Tickner, S.T. Chow, V. Kuek, B. Guo, G. Zhang, V. Rosen, W. Erber, J. Xu, Angiogenic factors in bone local environment, Cytokine & growth factor reviews 24(3) (2013) 297-310.
[41] J. Wood, K. Bonjean, S. Ruetz, A. Bellahcene, L. Devy, J.M. Foidart, V. Castronovo, J.R. Green, Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid, The Journal of pharmacology and experimental therapeutics 302(3) (2002) 1055-61.
[42] D. Pfander, T. Cramer, D. Deuerling, G. Weseloh, B. Swoboda, Expression of thrombospondin-1 and its receptor CD36 in human osteoarthritic cartilage, Annals of the rheumatic diseases 59(6) (2000) 448-54.
[43] Y. Hiraki, C. Shukunami, Chondromodulin-I as a novel cartilage-specific growth-modulating factor, Pediatr Nephrol 14(7) (2000) 602-5.
[44] D.A. Walsh, D.F. McWilliams, M.J. Turley, M.R. Dixon, R.E. Franses, P.I. Mapp, D. Wilson, Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis, Rheumatology 49(10) (2010) 1852-61.
[45] L. Pesesse, C. Sanchez, Y. Henrotin, Osteochondral plate angiogenesis: a new treatment target in osteoarthritis, Joint, bone, spine : revue du rhumatisme 78(2) (2011) 144-9.
[46] M.H. Harrison, F. Schajowicz, J. Trueta, Osteoarthritis of the hip: a study of the nature and evolution of the disease, The Journal of bone and joint surgery. British volume 35-B(4) (1953) 598-626.
[47] K. Ohzono, K. Takaoka, S. Saito, M. Saito, M. Matsui, K. Ono, Intraosseous arterial architecture in nontraumatic avascular necrosis of the femoral head. Microangiographic and histologic study, Clinical orthopaedics and related research (277) (1992) 79-88.
[48] M. Laroche, C. Moineuse, R. Durroux, B. Mazieres, J. Puget, Can ischemic hip disease cause rapidly destructive hip osteoarthritis? A case report, Joint, bone, spine : revue du rhumatisme 69(1) (2002) 76-80.
[49] B.M. Cinar, G. Ozkoc, F. Bolat, O. Karaeminogullari, N. Sezgin, R.N. Tandogan, Intra-articular zoledronic acid in a rat osteoarthritis model: significant reduced synovitis may indicate chondroprotective effect, Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA 23(5) (2015) 1410-8.
[50] A.R. Sharma, S. Jagga, S.S. Lee, J.S. Nam, Interplay between cartilage and subchondral bone contributing to pathogenesis of osteoarthritis, Int J Mol Sci 14(10) (2013) 19805-30.
[51] G. Blumenkrantz, C.T. Lindsey, T.C. Dunn, H. Jin, M.D. Ries, T.M. Link, L.S. Steinbach, S. Majumdar, A pilot, two-year longitudinal study of the

interrelationship between trabecular bone and articular cartilage in the osteoarthritic knee, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 12(12) (2004) 997-1005.
[52] R.L. Karvonen, P.R. Miller, D.A. Nelson, J.L. Granda, F. Fernandez-Madrid, Periarticular osteoporosis in osteoarthritis of the knee, The Journal of rheumatology 25(11) (1998) 2187-94.
[53] M. Moreau, P. Rialland, J.P. Pelletier, J. Martel-Pelletier, D. Lajeunesse, C. Boileau, J. Caron, D. Frank, B. Lussier, J.R. del Castillo, G. Beauchamp, D. Gauvin, T. Bertaim, D. Thibaud, E. Troncy, Tiludronate treatment improves structural changes and symptoms of osteoarthritis in the canine anterior cruciate ligament model, Arthritis research & therapy 13(3) (2011) R98.
[54] M.S. Khorasani, S. Diko, A.W. Hsia, M.J. Anderson, D.C. Genetos, D.R. Haudenschild, B.A. Christiansen, Effect of alendronate on post-traumatic osteoarthritis induced by anterior cruciate ligament rupture in mice, Arthritis research & therapy 17 (2015) 30.
[55] S. Zhu, K. Chen, Y. Lan, N. Zhang, R. Jiang, J. Hu, Alendronate protects against articular cartilage erosion by inhibiting subchondral bone loss in ovariectomized rats, Bone 53(2) (2013) 340-9.
[56] D.G. Yu, B. Yu, Y.Q. Mao, X. Zhao, X.Q. Wang, H.F. Ding, L. Cao, G.W. Liu, S.B. Nie, S. Liu, Z.A. Zhu, Efficacy of zoledronic acid in treatment of teoarthritis is dependent on the disease progression stage in rat medial meniscal tear model, Acta pharmacologica Sinica 33(7) (2012) 924-34.
[57] M.G. Dearmin, T.N. Trumble, A. Garcia, J.N. Chambers, S.C. Budsberg, Chondroprotective effects of zoledronic acid on articular cartilage in dogs with experimentally induced osteoarthritis, American journal of veterinary research 75(4) (2014) 329-37.
[58] R.G. Rosa, K. Collavino, A. Lakhani, E. Delve, J.F. Weber, A.K. Rosenthal, S.D. Waldman, Clodronate exerts an anabolic effect on articular chondrocytes mediated through the purinergic receptor pathway, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 22(9) (2014) 1327-36.
[59] T. Hayami, M. Pickarski, G.A. Wesolowski, J. McLane, A. Bone, J. Destefano, G.A. Rodan, L.T. Duong, The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model, Arthritis and rheumatism 50(4) (2004) 1193-206.
[60] C.M. Bagi, E. Berryman, D.E. Zakur, D. Wilkie, C.J. Andresen, Effect of antiresorptive and anabolic bone therapy on development of osteoarthritis in a posttraumatic rat model of OA, Arthritis research & therapy 17 (2015) 315.
[61] S. Castaneda, J.A. Roman-Blas, R. Largo, G. Herrero-Beaumont, Subchondral bone as a key target for osteoarthritis treatment, Biochem Pharmacol 83(3) (2012) 315-23.
[62] D.T. Felson, C.E. Chaisson, C.L. Hill, S.M. Totterman, M.E. Gale, K.M. Skinner, L. Kazis, D.R. Gale, The association of bone marrow lesions with pain in knee osteoarthritis, Annals of internal medicine 134(7) (2001) 541-9.
[63] D.T. Felson, S. McLaughlin, J. Goggins, M.P. LaValley, M.E. Gale, S. Totterman, W. Li, C. Hill, D. Gale, Bone marrow edema and its relation to progression of knee osteoarthritis, Annals of internal medicine 139(5 Pt 1) (2003) 330-6.

[64] G. Zhai, J. Stankovich, F. Cicuttini, C. Ding, G. Jones, Familial, structural, and environmental correlates of MRI-defined bone marrow lesions: a sibpair study, Arthritis research & therapy 8(4) (2006) R137.

[65] L.L. Laslett, D.A. Dore, S.J. Quinn, P. Boon, E. Ryan, T.M. Winzenberg, G. Jones, Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial, Annals of the rheumatic diseases 71(8) (2012) 1322-8.

[66] G. Cai , D. Aitken, L. Laslett, . OP0016 A multicentre randomised controlled trial of zoledronic acid for osteoarthritis of the knee with bone marrow lesions, Annals of the rheumatic diseases, 2018, p. 57.

[67] E.E. Vaysbrot, M.C. Osani, M.C. Musetti, T.E. McAlindon, R.R. Bannuru, Are bisphosphonates efficacious in knee osteoarthritis? A meta-analysis of randomized controlled trials, Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 26(2) (2018) 154-164.

[68] T.D. Spector, P.G. Conaghan, J.C. Buckland-Wright, P. Garnero, G.A. Cline, J.F. Beary, D.J. Valent, J.M. Meyer, Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomized, controlled trial [ISRCTN01928173], Arthritis research & therapy 7(3) (2005) R625-33.

[69] C.O. Bingham, 3rd, J.C. Buckland-Wright, P. Garnero, S.B. Cohen, M. Dougados, S. Adami, D.J. Clauw, T.D. Spector, J.P. Pelletier, J.P. Raynauld, V. Strand, L.S. Simon, J.M. Meyer, G.A. Cline, J.F. Beary, Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study, Arthritis and rheumatism 54(11) (2006) 3494-507.

[70] M. Rossini, S. Adami, E. Fracassi, O. Viapiana, G. Orsolini, M.R. Povino, L. Idolazzi, D. Gatti, Effects of intra-articular clodronate in the treatment of knee osteoarthritis: results of a double-blind, randomized placebo-controlled trial, Rheumatology international 35(2) (2015) 255-63.

[71] M. Varenna, F. Zucchi, S. Failoni, A. Becciolini, M. Berruto, Intravenous neridronate in the treatment of acute painful knee osteoarthritis: a randomized controlled study, Rheumatology 54(10) (2015) 1826-32.

[72] G. Cai, L.L. Laslett, D. Aitken, F. Cicuttini, L. March, C. Hill, T. Winzenberg, G. Jones, Zoledronic acid plus methylprednisolone versus zoledronic acid or placebo in symptomatic knee osteoarthritis: a randomized controlled trial, Ther Adv Musculoskelet Dis 11 (2019) 1759720X19880054.

[73] A.J. Davis, T.O. Smith, C.B. Hing, N. Sofat, Are bisphosphonates effective in the treatment of osteoarthritis pain? A meta-analysis and systematic review, PloS one 8(9) (2013) e72714.

[74] L.A. Deveza, S.M.A. Bierma-Zeinstra, W.E. van Spil, W.M. Oo, B.T. Saragiotto, T. Neogi, M. van Middelkoop, D.J. Hunter, Efficacy of bisphosphonates in specific knee osteoarthritis subpopulations: protocol for an OA Trial Bank systematic review and individual patient data meta-analysis, BMJ Open 8(12) (2018) e023889.