Drug Metabolism Reviews

ISSN: 0360-2532 (Print) 1097-9883 (Online) Journal homepage: https://www.tandfonline.com/loi/idmr20

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To cite this article: Dragos Apostu, Ondine Lucaciu, Alexandru Mester, Daniel Oltean-Dan, Mihaela Baciut, Grigore Baciut, Simion Bran, Florin Onisor, Andra Piciu, Roxana D Pasca, Andrei Maxim & Horea Benea (2019): Systemic drugs with impact on osteoarthritis, Drug Metabolism Reviews, DOI: 10.1080/03602532.2019.1687511

To link to this article: https://doi.org/10.1080/03602532.2019.1687511

Published online: 15 Nov 2019.

DRUG METABOLISM REVIEWS
https://doi.org/10.1080/03602532.2019.1687511

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REVIEW ARTICLE

Systemic drugs with impact on osteoarthritis

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ABSTRACT

Articular cartilage has a complex structure and metabolism which allow for a proper movement within joints. Nevertheless, several systemically administered pharmacological agents have been proved to improve the anabolic response in the case of cartilage lesions. Alendronate, glucosamine, chondroitin sulfate, hyaluronic acid, collagen hydrolysate, vitamin C, vitamin D, aspirin and strontium ranelate have shown positive results in clinical trials. On the other hand, calcitonin, risedronate, doxycycline, and celecoxib did not slow the progression of cartilage lesions in clinical trials. Other systemic drugs or supplements such as teriparatide, leptin, zoledronic acid, bevacizumab, atorvastatin, omega-3 fatty acid, naringin, MSM, selenium, zinc, magnesium, resveratrol, donepezil, naproxen, etodolac, ursodeoxycholic acid (UDCA), lithium chloride, and rebamipide showed positive results in in vitro and animal studies but clinical trials are needed to confirm the positive impact on cartilage repair. A number of molecules, not currently available on the market, have also shown promising results in cartilage healing, such as licofelone, sclerostin, cyclopamine, cyclodextrin polysulfate, AG-041R, osteoprotegerin, rhMK, β-cryptoxanthine, NF-κb essential modulator binding domain (NBD), TGF-β-neutralizing antibody, osteogenic protein-1 (BMP-7), fibroblast growth factor 2 (FGF2), and RhBMP-2. Currently available systemic drugs that impair cartilage healing are represented by corticosteroids, vitamin A, and fluoroquinolones.

ARTICLE HISTORY
Received 15 September 2019
Accepted 29 October 2019

KEYWORDS
Systemic drugs; articular cartilage; collagen; osteoarthritis; knee

Introduction

Articular cartilage is a specialized type of connective tissue found in diarthrodial joints such as the knee, hip, shoulder, ankle, elbow, and wrist (Sophia et al. 2009). Its unique structure forms a smooth and lubricated surface that allows for a proper joint motion with a low friction coefficient, good shock-absorbing capabilities and minimized peak pressure on the subchondral bone (Bhosale and Richardson 2008; Sophia et al. 2009). Cartilage lesions can occur due to acute trauma, repetitive stress, impaired vascular supply or they can be idiopathic (Bhosale and Richardson 2008). These lesions can progress into debilitating joint pathology called osteoarthritis, characterized by pain, swelling, mechanical symptoms, decreased range of motion and loss of function (Sophia et al. 2009). Osteoarthritis (OA) is a global health priority, affecting more than 50% of patients over 60 years old (Poole et al. 2002). Multiple methods of treatment are currently used, including physiotherapy, drug administration (systemic or intraarticular) and surgical techniques, but each has its limitations. Our review focuses on the systemic drugs which can improve the cartilage repair process and reduce symptoms. The aim of our review is to provide an update of the current and future systemic drugs which can improve the functional status in the case of articular cartilage lesions.

Articular cartilage structure

The articular cartilage has a thickness of 1–5 mm consisting of hyaline-type cartilage (Eckstein et al. 2001; Bhosale and Richardson 2008). It is composed of two main parts: extracellular matrix (ECM) and specialized cells called chondrocytes.

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Extracellular matrix

The ECM represents approximately 95% of the cartilage structure and is made up of type II collagen, as well as other collagen types (VI, IX, X, and XI), proteoglycans, water and non-collagenous proteins (Goldring 2012; Ng et al. 2017).

Collagen represents 10–20% of articular cartilage weight and it is the main component of the fibrillar network, which provides the tensile strength (Bhosale and Richardson 2008). Collagen type II is made up of three identical α chains which form homotrimers, making it more flexible and having an overall smaller bending stiffness compared to other types of collagen (Ricard-Blum 2011; Chang et al. 2012). Collagen type VI is important in attaching chondrocytes to the matrix (Bhosale and Richardson 2008), while collagen types IX, X, and XI have a role in structural support and in cartilage mineralization (Bhosale and Richardson 2008; Blumbach et al. 2009).

Proteoglycans are produced by chondrocytes and represent between 10-20% of cartilage weight, providing the compressive strength of the articular cartilage (Bhosale and Richardson 2008). There are two main classes of proteoglycans: large aggregating proteoglycan monomers such as aggrecans or versican, and smaller proteoglycans such as decorin, biglycan, epiphycan, lumican and fibromodulin (Roughley 2001; Bhosale and Richardson 2008). The most common matrix molecule is the proteoglycan aggrecan, which forms macromolecular aggregates with hyaluronic acid (Poole et al. 2002). Aggrecan has in its structure glycosaminoglycan (GAG) side chains of chondroitin sulfate and keratin sulfate (Bhosale and Richardson 2008; Goldring 2012). The negatively charged chondroitin sulfate and keratin sulfate chains have the ability to bind water, thus creating a structure that provides good resistance for deformation and for compression (Poole et al. 2002; Bhosale and Richardson 2008; Titorencu et al. 2010).

Noncollagenous proteins are represented by structural proteins such as COMP (thrombospondin-5), thrombospondin-1, thrombospondin-3, CMP (matriline-1), CILP, PRELP, tenascin-C, fibronectin, elastin, chondroadherin, matriline-3 and C-type lecithin, while regulatory proteins are represented by chondromodulin-I, chondromodulin-II, growth factors, CD-RAP, pleiotrophin, gp-39/YKL-40 and matrix gla proteins (Roughley 2001). These proteins have a role in the structure and modulation of cartilage metabolism.

Water constitutes between 65% up to 80% of the total cartilage weight, providing the cartilage the possibility of deformation under load (Bhosale and Richardson 2008). In osteoarthritic cartilage, the water content can reach up to 90% due to increased permeability and matrix disruption, causing a decreased modulus of elasticity which further leads to degeneration (Bhosale and Richardson 2008).

Chondrocytes play a central role in cartilage metabolism. They are uninucleate cells derived from mesenchymal stem cells that secrete extracellular matrix (Goldring 2012; Akkiraju and Nohe 2015). Chondrocytes produce collagen, proteoglycans, noncollagenous proteins, which form the extracellular matrix (Akkiraju and Nohe 2015). When located superficially, chondrocytes can produce lubricin (proteoglycan 4), essential for the low friction motion within joints (Coles et al. 2010; Goldring 2012). Chondrocyte differentiation, as well as chondrocyte hypertrophy and apoptosis, are key targets for drugs in the treatment of articular cartilage lesions. Moreover, studies showed that chondrocyte hypertrophy-like changes play an important role in the induction and progression of osteoarthritis (van der Kraan and van den Berg 2012). First, articular chondrocytes change their phenotype and become terminal differentiation chondrocytes (hypertrophic-like), followed by the process of calcium deposition (van der Kraan and van den Berg 2012). Therefore the articular cartilage becomes calcified and the osteoarthritic changes progress (van der Kraan and van den Berg 2012). These changes of chondrocyte phenotype can be due to the pro-inflammatory expression of osteoblasts (Vaysbrot et al. 2018). Current studies focus on the inhibition of hypertrphic-like changes in chondrocytes for decreasing the progression of osteoarthrtis (van der Kraan and van den Berg 2012).

Articular cartilage zones consist of the following: superficial, transitional (middle), radial and calcified cartilage zone (Bhosale and Richardson 2008). Superficial zone is the thinnest and is composed of cells parallel to the joint surface (Bhosale and Richardson 2008). It is covered by a thin film of synovial fluid called *lubricin* (Bhosale and Richardson 2008). Lubricin is encoded in the PRG4 gene and its' importance in the physiopathology is described in multiple studies, as it reduces friction, inhibits overgrowth of the synovial cells and reduces cell adhesion (Coles et al. 2010; Ogawa et al. 2014). Deletion of the PRG4 genes in animal model was shown to promote osteoarthritic degeneration (Coles et al. 2010). Reduced concentration of lubricin are found in anterior cruciate ligament lesions (Coles et al. 2010). In the superficial zone we also find high quantities of collagen types II, as well as low quantities of aggrecans, collagen type IX and XI (Bhosale and Richardson 2008; Akkiraju and Nohe 2015). The parallel

distribution of fibrils aid in achieving the greatest tensile and shear strength in the articular cartilage (Bhosale and Richardson 2008). In the transitional or middle zone, cell density is lower and we find higher concentrations of proteoglycan aggrecan (Bhosale and Richardson 2008). In the transitional zone, in addition to the superficial zone, we find small proteoglycans such as biglycan and decorin (Akkiraju and Nohe 2015). The radial zone is characterized by cells perpendicular to the surface and by collagen fibrils with the largest diameter, highest concentration of proteoglycans and by lowest cell density (Bhosale and Richardson 2008). Calcified cartilage zone is demarcated by a line that marks the interface between the non-mineralized articular cartilage and subchondral bone (Goldring 2012). Calcified cartilage lacks collagen IX and XI but contains collagen type X, hypertrophic phenotype chondrocytes which have low metabolic activity and MMP-13 (Bhosale and Richardson 2008; Akkiraju and Nohe 2015). Collagen type X is important for providing structural integrity and for its shock-absorbing properties (Bhosale and Richardson 2008). Moreover, collagen type X is a marker of chondrocyte hypertrophy (van der Kraan and van den Berg 2012).

Anabolic metabolism of the articular cartilage

Differentiation of chondrocytes from mesenchymal stem cells is regulated by many molecules including Wnt/β-catenin, TGF-β (transforming growth factor β), FGF (fibroblast growth factor), IGF-1 (insulin-like growth factor 1) and BMPs (bone morphogenetic protein) (Figure 1) (Lucaciu et al. 2015a, 2015b, 2018; Goldring 2017; Apostu et al. 2017). Chondrocytes have a major role in secreting collagen types II, IX and XI, as well as matrix proteins where the most important is aggrecan (Figure 1) (Goldring 2017). The production of extracellular matrix by chondrocytes is regulated by many factors. IGF-1 and TGF-β activate the PI3/Akt pathway, leading to protection against catabolic effects of reactive

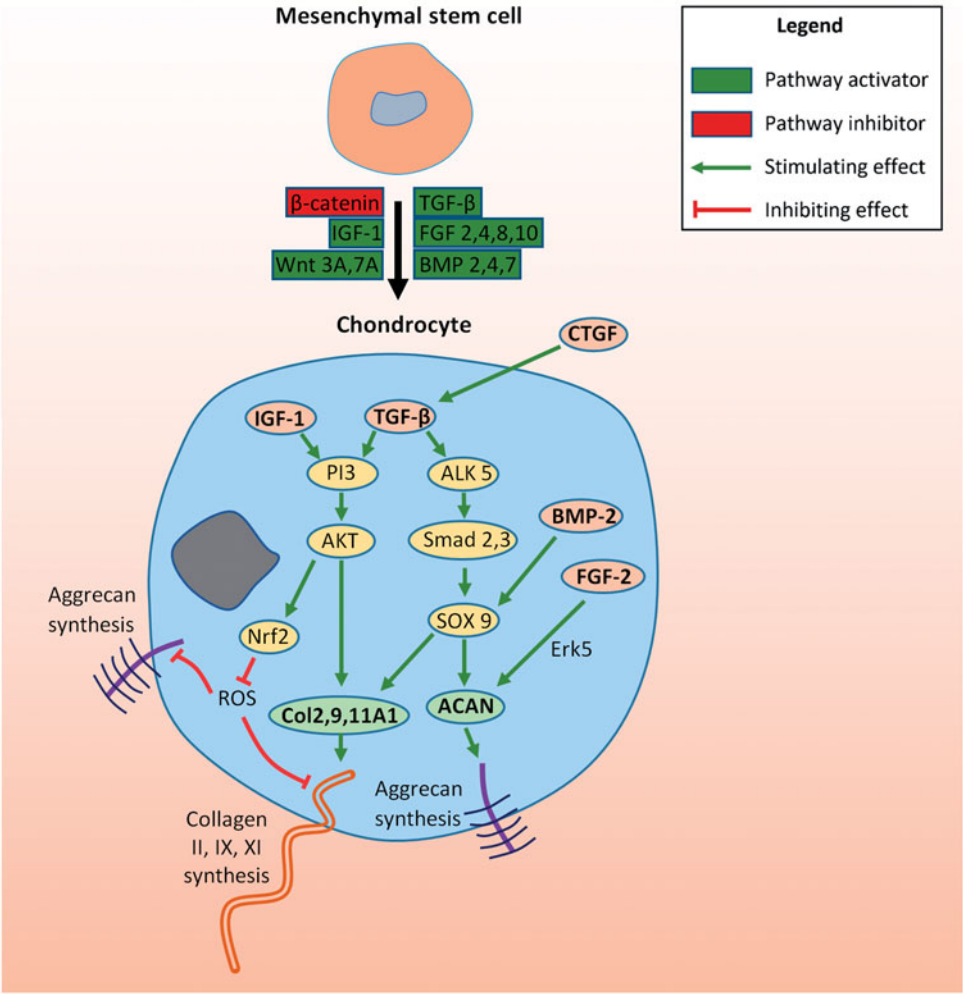

Figure 1. Anabolic metabolism of the articular cartilage (Ashraf et al. 2016; Goldring 2017; Jørgensen et al. 2017; Huang et al. 2018; Tang et al. 2018).

oxygen species (ROS) by Nrf2 (Figure 1; Huang et al. 2018). The PI3/Akt pathway also activates the gene responsible for collagen II, IX or XI synthesis such as Col2A1, Col9A1 or Col11A1 respectively (Figure 1; Ashraf et al. 2016). CTGF (connective tissue growth factor) has a positive effect on TGF-β expression, leading to both an increase in collagen and aggrecan production (Figure 1; Tang et al. 2018).

TGF-β also stimulate the expression of SOX-9 through ALK5 and Smad 2,3 pathway (Figure 1; Ashraf et al. 2016). Another upregulator of SOX 9 is BMP-2 (Ashraf et al. 2016). SOX-9 further stimulates collagen synthesis and the expression of the ACAN gene which is responsible for aggrecan production (Figure 1; Ashraf et al. 2016). ACAN is also stimulated by FGF-2 through the Erk5 pathway (Figure 1; Jørgensen et al. 2017).

Catabolic metabolism of the articular cartilage

Type II collagen cleavage is mediated by collagenases of the matrix metalloproteinase family (MMP) and by cysteine protease (Figure 2). The collagenases are produced by chondrocytes and synoviocytes (Figure 2. The process can be quantified using markers such as the C-terminal telopeptide of type II collagen and collagen type II cleavage (C2C) (Figure 2; Karsdal et al. 2016). MMP13 is considered to be one of the most important enzymes in collagen type II degradation (Figure 2; Poole et al. 2002). Other factors such as Stromelysin 1 (MMP-3), MMP-1, cathepsin B, cathepsin L, and cathepsin K have also been described to be involved in collagen type II cleavage (Figure 2; Poole et al. 2002). MMP1 is described to participate in the degradation of newly formed collagen (Figure 2; Poole et al. 2002). The activity of collagenases is higher in focal cartilage lesions and osteoarthritis (Figure 2; Poole et al. 2002). Following collagen type II degradation, multiple molecular fragments are produced due to an intensive proteolysis process (Poole et al. 2002). These fragments induce the expression of MMPs, IL-1, and TNF-α (Figure 2; Poole et al. 2002). Collagen type II is stable with an estimated half-life of 117 years unless damaged, therefore its preservation is very important for normal joints (Figure 2; Goldring 2012). The main proteoglycan in the articular cartilage, aggrecan, is cleaved by MMPs aggrecanases ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) -4 and -5 (Figure 2; Poole et al. 2002; Goldring 2012; Yang et al. 2017).

IL-1 (interleukin 1) and TNF-α (tumor necrosis factor α) are the main regulators of cartilage catabolism (Figure 2) (Kobayashi et al. 2005; Ulivi et al. 2011; Huh et al. 2015). They both activate the p38 MAPK pathway which increases the expression of NF-κB, which plays a central role in coordinating catabolic events (Figure 2) (Ulivi et al. 2011). NF-κB (nuclear factor κB) stimulates COX-2 (cyclooxygenase 2) and PGE_2 (prostaglandin E_2) resulting in a decreased aggrecan production, increased ADAMTS 4,5 and MMPs (Figure 2) (Kobayashi et al. 2005; Ulivi et al. 2011; Huh et al. 2015; Rasheed et al. 2016; Mester et al. 2019a; Lucaciu et al. 2019). NF-κB activation also leads to an inhibition of SOX-9 (an important positive regulator of aggrecan synthesis) and increase in IL-6 and NO expressions, followed by increased ADAMTS and MMPs (Figure 2) (Legendre et al. 2005; Ulivi et al. 2011; Huh et al. 2015; Jørgensen et al. 2017). ROS has a similar effect to IL-1 and TNF-α (Figure 2) (You et al. 2012). Calcitonin has the potential to limit the catabolic effect of IL-1 and TNF-α. NF-κB upregulates Jagged-1, which further activates Notch-1 pathway (Figure 2) (Wang et al. 2001). This inhibits the expression of NF-kB (Figure 2) (Wang et al. 2001). NF-κB is also downregulated by IL-4 and IL-10 (Figure 2) (Jørgensen et al. 2017).

RUNX2, FGF, TGF-α, VEGF, β-catenin, BMP2, BMP7, PTHrP or IHH, chondrocyte can become hypertrophic chondrocytes which secrete collagen type X, MMP-13, ADAMTS, alkaline phosphatase and osteocalcin (Figure 2) (Poole et al. 2002; Van der Kraan and van den Berg 2012). This results in an enhanced cleavage of the extracellular matrix, as well as calcified cartilage. Under certain factors (e.g. RUNX2), hypertrophic chondrocytes undergo apoptosis (Figure 2) (Zhao et al. 2016).

Treatment of chondral lesions

Repair means the restoration of damaged tissue with neo-cartilage tissue, which resembles the native cartilage but does not necessarily duplicate its structure, composition, and function (Bhosale and Richardson 2008). Regeneration refers to the formation of a tissue indistinguishable from native articular tissue (Bhosale and Richardson 2008).

The ability for cartilage lesions to undergo repair or regeneration is influenced by factors such as vascularity, depth of the defect, size of the defect, repetitive trauma, and age (Bhosale and Richardson 2008). The depth of defect –the repair depends on whether the injury extends to the subchondral vascular bone marrow (Bhosale and Richardson 2008). Extension into subchondral bone allows for migration of bone marrow mesenchymal progenitors migrating into the defect (Bhosale and Richardson 2008). This leads to fibrocartilage type of repair, biomechanically and structurally inferior to hyaline cartilage (Bhosale and Richardson 2008). The size of

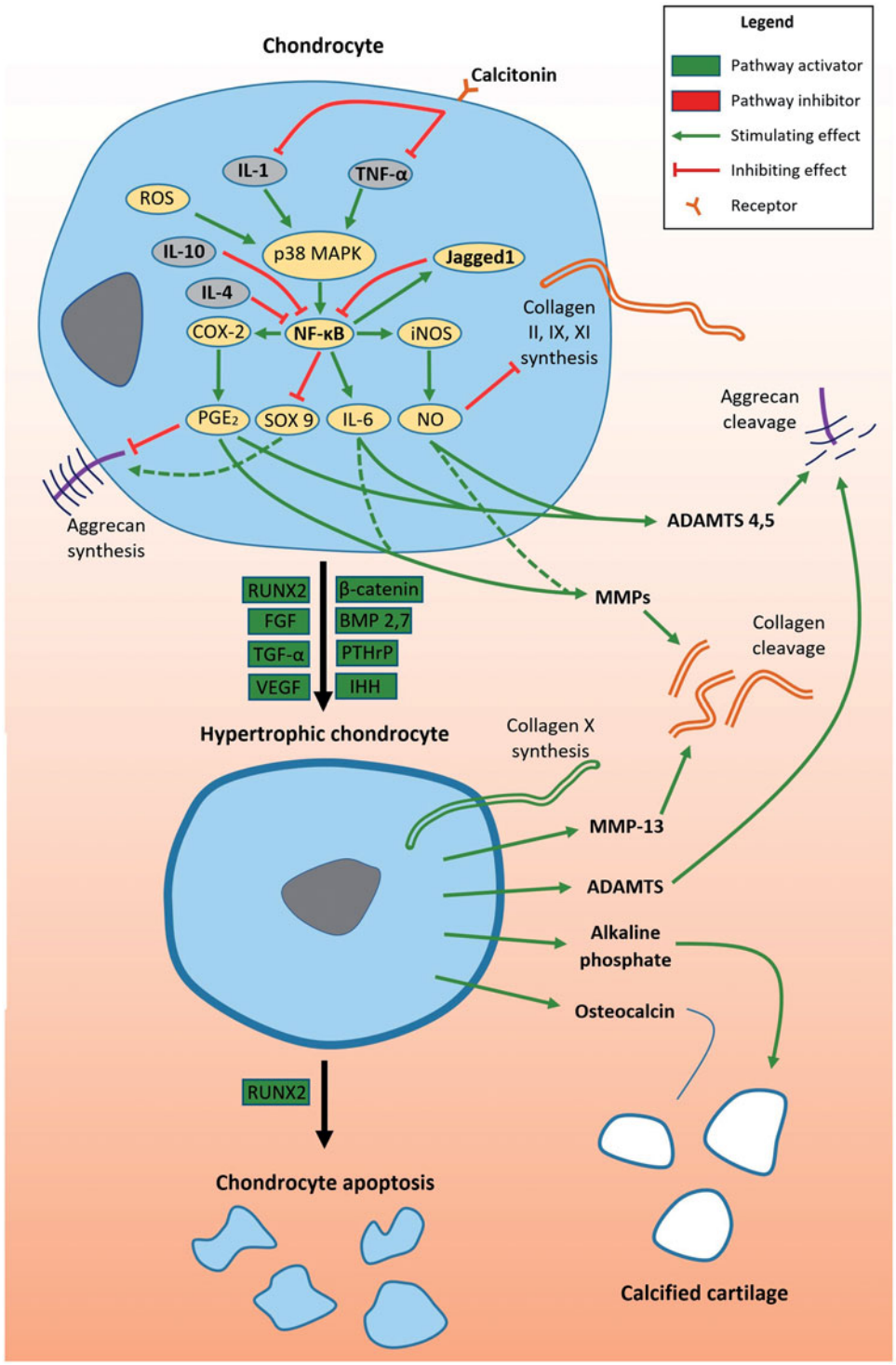

Figure 2. Catabolic metabolism of the articular cartilage (Wang et al. 2001; Poole et al. 2002; Kobayashi et al. 2005; Legendre et al. 2005; Ulivi et al. 2011; You et al. 2012; Van der Kraan and van den Berg 2012; Goldring 2012; Huh et al. 2015; Karsdal et al. 2016; Zhao et al. 2016; Rasheed et al. 2016; Yang et al. 2017; Jørgensen et al. 2017).

the defect is also very important (Bhosale and Richardson 2008). Less than 3 mm defects can lead to complete repair after 9 months (Bhosale and Richardson 2008). Repetitive trauma of the cartilage lesion can damage the chondrocyte and impair production of proteoglycans (Bhosale and Richardson 2008). Age is also very important; as younger ages have a greater chance of cartilage healing (Bhosale and Richardson 2008).

There are two main types of treatment: surgical and non-surgical treatment.

Nonsurgical treatment

The non-surgical approach is the first line of treatment in the high majority of cartilage lesions worldwide and is represented by a large number of techniques (Buttgereit et al. 2015). It consists of two major categories: non-pharmacological and pharmacological treatment (Buttgereit et al. 2015). Non-pharmacological treatment includes weight management, physiotherapy, kinesiotherapy, self-management and education (Buttgereit et al. 2015). Pharmacological agents mostly used in the treatment of cartilage lesions include paracetamol, capsaicin, topical NSAIDs, COX-2 inhibitors, oral NSAIDs and intra-articular injections with corticosteroids and hyaluronic acid (Buttgereit et al. 2015; Laptoiu et al. 2015).

Surgical treatment of articular cartilage lesions

Surgical treatment is the most commonly used approach in cartilage lesions, consisting of a wide variety of surgical techniques. Bone marrow stimulation is still the most frequently used worldwide, consisting of perforation of chondral defect and migration of mesenchymal stem cells, which later develop into chondrocytes. This is represented by joint debridement and drilling, specialization (excision of damaged cartilage along with subchondral bone) and microfractures (Bhosale and Richardson 2008). Mosaicplasty is a method in which osteochondral grafts from the non-weight bearing areas are used to fill the osteochondral cartilage defect (Bhosale and Richardson 2008). Carbon fiber implants, perichondral grafts, periosteal grafts, osteotomies, and autologous chondrocyte implantation are other surgical techniques described to help cartilage repair (Bhosale and Richardson 2008). Complications related to the surgery such as quadriceps femoris strength deficits, gait deviations, wound infections, delayed wound healings or deep vein thrombosis have been observed in approximately 33% of cases (Schmitt et al. 2014; Ding et al. 2016). Moreover, the functional results are not predictable (Schmitt et al. 2014). Therefore, other types of surgical treatment in cartilage lesions are studied (Rau et al. 2016).

Currently available systemic drugs that improve cartilage metabolism or osteoarthritis symptoms

Many currently available drugs have been tested in vitro or in vivo for their effect on articular cartilage with beneficial results. These include hormones (parathyroid hormone, calcitonin, leptin), bisphosphonates (zoledronic acid, risedronate, alendronate), monoclonal antibodies (bevacizumab, adalimumab), statins (atorvastatin), supplements (glucosamine, chondroitin sulfate, high molecular weight hyaluronic acid, collagenase hydrolysate, vitamin C, vitamin D, omega-3 fatty acid, calcium gluconate, naringin, methylsulfonylmethane—MSM, selenium, zinc, magnesium, resveratrol, diacerein, piascledine), reversible acetylcholinesterase inhibitor (donepezil), antibiotics (doxycycline, erythromycin), analgesics (acetaminophen, opioids) nonsteroidal anti-inflammatory drugs (aspirin, naproxen, etodolac, celecoxib), and others (strontium ranelate, ursodeoxycholic acid, duloxetine, anti-NGF, lithium chloride, rebamipide) (see Table 1).

Hormones regulate multiple pathways and the cartilage metabolism is no exception.

Parathyroid hormone (PTH) has been shown to improve the micro and macroscopic quality of cartilage repair in 3 mm cylindrical osteochondral defects in rabbits following six weeks of systemic treatment (Orth et al. 2013). Other studies showed that PTH limits the progression of cartilage damage in animal models and that it enhances cartilage regeneration (Sampson et al. 2011; Yan et al. 2014). These positive effects are explained by multiple mechanisms of action. PTH increases both parathyroid 1 receptor (PTH1R) and JAGGED1 expression in chondrocytes, thus activating the notch pathway which stimulates chondrocytes, collagen type II and proteoglycan content (Sampson et al. 2011; Orth et al. 2013; Yan et al. 2014). Moreover, PTH showed an enhancement of chondral regeneration by increasing the synthesis of matrix components, including PRG4 (Sampson et al. 2011). Other mechanisms involved in the chondroprotective and chondroregenerative effects of parathyroid hormone are down-regulation of type X collagen, RUNX2, MMP-13, and carboxyl-terminal aggrecan involved in extracellular matrix degradation and chondrocyte apoptosis (Sampson et al. 2011; Piciu et al. 2013; Yan et al. 2014). Currently available parathyroid hormone or analogs are parathyroid hormone (Natpara®), teriparatide (Forteo®) and abaloparatide (Tymlos®) (Anderson et al. 2018). A clinical trial is underway in which teriparatide at dose of 20 mcg is administered daily subcutaneously for 24 weeks (Zuscik et al. 2017). Most frequent adverse reactions are dizziness and leg cramps, but cardiovascular and respiratory adverse reactions are also present (Cunha 2017).

Calcitonin administered orally reduces cartilage thickness loss in meniscetomized rats and reduces type II collagen degradation (Sondergaard et al. 2007; Nielsen et al. 2011). Moreover, Bagger et al. showed a decreased cartilage degeneration in women following three months of treatment (Bagger et al. 2005). Calcitonin lowers MMPs

Table 1. Currently available drugs considered to have a positive impact on articular cartilage tissue.

Agent name	Class	Example of brand names	Effect	Mechanism of action	Clinical trial	Dose	Administration	Example of adverse reactions
Parathyroid hormone (PTH)	Hormone	Natpara® Forteo® Tymlos®	↑anabolic effect on cartilage ↓cartilage degeneration	↑ PTH1R ↑ Jagged1 ↑ PRG4 ↓ RUNX2 ↓ MMP-13	Yes (Undergoing)	20 mcg daily	subcutaneously	Dizziness Leg cramps
Calcitonin	Hormone	Tbria® (waiting FDA approval)	↑anabolic effect on cartilage ↓cartilage degeneration	↑ collagen type II ↑ proteoglycans ↓ MMPs	Yes – no clinical impact on cartilage deterioration	0.8 mg twice daily	orally	Gastrointestinal disorders
Leptin	Hormone	Myalept®	↑anabolic effect on cartilage ↓cartilage degeneration	↓ TNF-α ↑ IGF-1 ↑ TGF-β	No	–	subcutaneously	Headache Hypoglycemia Decreased weight
Zoledronic acid	Biphosphonate	Zometa® Reclast® Aclasta®	↓cartilage degeneration	↓ chondrocyte apoptosis ↓ type II collagen cleavage	Yes (Undergoing)	5 mg annually	intravenously	Cold or flu-like symptoms Headache
Risedronate	Biphosphonate	Actonel® Atelvia®	↓cartilage degeneration	↓ type II collagen cleavage	Yes – no clinical impact on cartilage deterioration	5–50 mg/day,	orally	Abdominal pain Osteoalgia Arthralgia
Alendronate	Biphosphonate	Binosto® Fosamax®	↓cartilage degeneration	↓ MMP-13	Yes – positive impact on cartilage deterioration	35–70 mg/week	orally	Abdominal pain Stomach pain
Bevacizumab	Monoclonal antibody	Avastin® Mvasi®	↑anabolic effect on cartilage ↓cartilage degeneration	↑ collagen type II ↑ chondromodulin-1 ↑ aggrecan	No	40 mg/kg	intravenously	Dizziness Fever Chills Chest pain Irregular breathing Irregular heartbeat Nasal congestion
Adalimumab	Monoclonal antibody	Humira® Hadlima® Hyrimoz® Amjevita®		↓ TNF-α	Yes – no clinical impact on cartilage deterioration	40 mg every other week	subcutaneously	Rash Headache Abdmonial pain Hypertension
Atorvastatin	Statin	Lipitor®	↓cartilage degeneration	↓ MMP-13 ↓ TNF-α ↓ IL-1β	Yes (Undergoing)	40 mg daily	orally	Hemorrhagic stroke Arthralgia Diarrhea Nasopharyngitis

(*continued*)

Table 1. Continued.

Agent name	Class	Example of brand names	Effect	Mechanism of action	Clinical trial	Dose	Administration	Example of adverse reactions
Glucosamine	Supplement	Genicin® Optiflex-G®	↑anabolic effect on cartilage ↓cartilage degeneration	↓ MMP-13 ↓ chondrocyte apoptosis ↑ TGF-β1 ↑ CTGF	Yes – positive impact on cartilage deterioration	1500 mg/day	orally	Nausea Vomiting Diarrhea Constipation
Chondroitin sulfate	Supplement	Optiflex-C®	↑anabolic effect on cartilage ↓cartilage degeneration	↓ MMP-3 ↓ MMP-13 ↓ IL-1β ↓ ADAMTS-4 and 5 ↓ chondrocyte apoptosis ↑ collagen type II ↑ proteoglycans	Yes – positive impact on cartilage deterioration	800–1200 mg daily	orally	Nausea Diarrhea Constipation Mild stomach pain
Hyaluronic acid	Supplement	Hyabest® Play Again Now®	↑anabolic effect on cartilage ↓cartilage degeneration	↓ MMP-13 ↓ IL-1β ↓ IL-6 ↓ ADAMTS-4 and 5 ↑ proteoglycans	Yes – positive impact on cartilage deterioration	48–240 mg daily	orally	No adverse reactions described
Collagen hydrolysate	Supplement	Numerous products available	↑anabolic effect on cartilage	↑ collagen type II	Yes – positive impact on cartilage deterioration	5–10 grams	orally	No adverse reactions described
Vitamin C	Supplement	Numerous products available	↑anabolic effect on cartilage ↓cartilage degeneration	↑ collagen type II ↑ aggrecan ↓ chondrocyte apoptosis ↓ MMP-3 ↓ Nrf2 ↓ NF-κB	Yes—positive impact on cartilage deterioration	120–898 mg daily	orally	No adverse reactions described
Vitamin D	Supplement	Numerous products available	↓cartilage degeneration	↓ MMP-13 ↓ MMP-9 ↑ TGF-β1	Yes—positive impact on cartilage deterioration	800 IU/daily 50.000 -60.000 IU/month	orally	Weakness Fatigue Sleepiness Headache Loss of appetite
Omega-3 fatty acid	Supplement	Numerous products available	↓cartilage degeneration	↓ NF-κB ↓ IL-1β ↓ ADAMTS-4 ↓ TNF-α ↓ IL-1α	No	0.45–4.5 grams daily	orally	Stomach upset Nausea Uncomfortable taste
Calcium gluconate	Supplement	Numerous products available	↓cartilage degeneration	↓ COX-2	No	50 mg/kg daily	orally	Nausea

(*continued*)

Table 1. Continued.

Agent name	Class	Example of brand names	Effect	Mechanism of action	Clinical trial	Dose	Administration	Example of adverse reactions
Narginin	Supplement	Numerous products available	↑anabolic effect on cartilage ↓cartilage degeneration	↓ NF-κB ↓ chondrocyte apoptosis ↓ MMP-13 ↓ GAG ↓ IL-6 ↓ PGE_2 ↓ NO ↓ TNF-α	No	100 mg/kg daily	orally	No adverse reactions described
MethylSulfonylMethane (MSM)	Supplement	Numerous products available	↓cartilage degeneration	↓ TNF-α ↓ NF-κB ↓ COX-2 ↓ IL-6	Yes (Undergoing)	6 grams daily	orally	Gastrointestinal symptoms Headache
Selenium	Supplement	Numerous products available	↓cartilage degeneration	↓ NO	No	2 mg/kg daily	orally	Diabetes Nausea Vomiting
Zinc	Supplement	Numerous products available	↓cartilage degeneration	↓ IL-10 ↓ IL-1β ↓ MMP-13 ↑ Nrf2	No	1.6 mg/kg daily	orally	Diarrhea Abdominal cramps Vomiting
Magnesium	Supplement	Numerous products available	↑anabolic effect on cartilage	↑ chondrogenesis	No	–	–	Diarrhea Abdominal cramps Depression
Resveratrol	Supplement	Numerous products available	↑anabolic effect on cartilage	↑ collagen type II ↓ chondrocyte apoptosis	Yes (Undergoing)	80 mg daily 1st week followed by 40 mg daily	orally	–
Diacerein	Supplement	Numerous products available	↓cartilage degeneration	↓ IL-1β ↓ MMP-13 ↓ TNF-α	Yes – positive impact on symptoms	50 mg daily for the first 10 days, followed by 100 mg daily for7 weeks		
Piascledine	Supplement	Piascledine®	↓cartilage degeneration	↓ IL-1	Yes – positive impact on symptoms	300 mg daily	orally	Allergic reactions Gastrointestinal disorders
Donepezil	Reversible acetylcholinesterase inhibitor	Aricept®	↓cartilage degeneration	↓ MMP-13	No	–	orally	Diarrhea Nausea Vomiting Loss of appetite
Doxycicline	Antibiotic	Acticlate® Adoxa® Alodox® Avidoxy Doryx® Mondoxyne NL® Mondox® Morgidox® Oracea® Oraxyl® Targadox® Vibramycin®	↑anabolic effect on cartilage ↓cartilage degeneration	↑ chondrogenesis ↓ MMP-13	Yes—no clinical impact on cartilage deterioration	200 mg daily	orally	Headache Sinus headache

(*continued*)

Table 1. Continued.

Agent name	Class	Example of brand names	Effect	Mechanism of action	Clinical trial	Dose	Administration	Example of adverse reactions
Erythromycin	Antibiotic	Ery-Tab® Erythrocin® EryPed® E-Mycin®	↓cartilage degeneration	↓ NF-κB ↓ IL-1β	No	–	orally	Diarrhea Nausea Vomiting Loss of appetite
Acetaminophen (paracetamol)	Analgesics	Panadol® Tylenol® Calopol®	–	–	Yes—positive impact on symptoms	2–4 g daily	orally	Nausea Vomiting Abdominal pain Liver failure Kidney failure
Opioids	Analgesics	Abstral® Actiq® OxyContin® Xtampaza ER® Zohydro ER® Roxanol-T®	↓cartilage degeneration	↓ TNF-α	Yes—positive impact on symptoms	20–400 mg	orally	Constipation Nausea Vomiting Loss of appetite Rash Pruritus Dizziness Headache Somnolence Insomnia Addiction
Aspirin	Nonsteroidal anti-inflammatory drugs (NSAIDs)	Arthritis Pain® Aspir 81® Aspir-Low® Miniprin® and more	↓cartilage degeneration	↓ MMPs ↓ NF-κB ↓ NO ↓ chondrocyte apoptosis	Yes—positive impact on cartilage deterioration	300 mg daily	orally	Dyspepsia
Naproxen	Nonsteroidal anti-inflammatory drugs (NSAIDs)	Aleve® Naprosyn® Aflaxen® Naprelan 750® and others	↑anabolic effect on cartilage	↑ chondrogenesis	No	–	orally	Dyspepsia Heartburn Nausea Constipation
Etodolac	Nonsteroidal anti-inflammatory drugs (NSAIDs)	Lodine® Lodine XL®	↑anabolic effect on cartilage ↓cartilage degeneration	↓ TNF-α ↓ chondrocyte apoptosis	No	–	orally	Dyspepsia Abdominal pain Constipation Diarrhea Nausea

(*continued*)

Table 1. Continued.

Agent name	Class	Example of brand names	Effect	Mechanism of action	Clinical trial	Dose	Administration	Example of adverse reactions
Celecoxib	Nonsteroidal anti-inflammatory drugs (NSAIDs)	Celebrex®	↑anabolic effect on cartilage ↓cartilage degeneration	↓ MMP-1 ↓ TNF-α ↓ IL-1β ↑ proteoglycans	Yes—no clinical impact on cartilage deterioration	200 mg daily	orally	Abdominal pain Diarrhea Dyspepsia Nausea
Strontium ranelate	Anti-osteoporotic	Protelos® Protos® Protaxos® Bivalos® Osseor®	↑anabolic effect on cartilage ↓cartilage degeneration	↓ TNF-α ↓ IL-1β ↓ MMP-1 ↓ MMP-13 ↑ collagen type II ↓ chondrocyte apoptosis ↑ proteoglycans	Yes—positive impact on cartilage deterioration	1–2 g/daily	orally	Nausea Diarrhea
Ursodeoxycholic acid (UDCA)	Bile acid agent	Stonex® Uliv® Ursocol® Ursodil® and others	↓cartilage degeneration	↓ IL-1β ↓ IL-6 ↓ MMP-3 ↓ MMP-13 ↓ ADAMTS-5 ↓ NO	No	–	Orally	Diarrhea
Duloxetine	Selective serotonin and norepinephrine reuptake inhibitor	Cymbalta® Irenka® Drizamla Sprinkle®	–	–	Yes—positive impact on symptoms	30 mg/day at first week, 60 mg/day at the next 6 weeks	Orally	Gastrointestinal disorders
Anti-NGF	Nerve growth factor antibodies	Fluranumab®	–	–	Yes—positive impact on symptoms	1 mg every 4 weeks; 3 mg every 8 weeks; 3 mg every 4 weeks; 6 mg every 8 weeks; 10 mg every 8 weeks	Orally	Arthralgia Exacerbated pain
Lithium chloride	Psychiatric medication	Lithium Chloride Sanalabor® LiDCO Lithiumchlorid®	↓cartilage degeneration	↓ MMP-1 ↓ MMP-13 ↓ NF-κB ↓ IL-6 ↓ IL-1β	No	–	Orally	Lithium poisoning
Rebamipide	Quinilinone	Mucosta® Rebamapide Pfizer® Rebamapide NP® and others	↓cartilage degeneration	↓ MMP-1 ↓ MMP-3 ↓ IL-1β	No	–	Orally	Altered taste Diarrhea

expression and activity while stimulating the synthesis of collagen type II and proteoglycans (Karsdal et al. 2006). These actions are believed to be due to the calcitonin receptor at the level of the chondrocytes (Karsdal et al. 2006). On the other hand, a clinical trial on 2206 patients with painful knee osteoarthritis concluded that 0.8 mg twice daily of calcitonin does not produce clinical benefits after 24 months of treatment (Karsdal et al., CSMC021C2301/2 investigators 2015). The most frequent adverse reaction is gastrointestinal disorders, where nausea, dyspepsia, and diarrhea were the most frequent (Karsdal et al., CSMC021C2301/2 investigators 2015).

Leptin (Myalept®), a hormone present in normal articular cartilage, decreases TNF-α induced chondrocyte apoptosis via c-jun N-terminal kinase (JNK) (Lee et al. 2015). Leptin stimulates IGF-1 and TGFb-1, two important mediators for the proliferation of chondrocyte and extracellular matrix synthesis (Jerosch 2011). On the other hand, high concentrations of leptin, as found in obsess, have a negative impact on chondrocytes, cartilage and bone (Jerosch 2011). No clinical trial was found regarding treatment with leptin analog and cartilage lesions. The most common adverse reactions of leptin analog are headache, hypoglycemia and decreased weight (Paz-Filho et al. 2015).

Bisphosphonates are currently used for improving bone metabolism where they limit osteoclasts' bone-resorption activity, but the effect of bisphosphonates on limiting the cartilage lesions have also been described. This can be mostly due to its positive effect on the subchondral bone which is an important element in the induction and progression of osteoarthritis (Vaysbrot et al. 2018). On the other hand, a meta-analysis showed no effect on the symptoms or progression of knee osteoarthritis (Vaysbrot et al. 2018). Nevertheless, positive results of bisphosphonates can occur in those subsets of osteoarthritis where subchondral bone turnover is high (Vaysbrot et al. 2018).

Zoledronic acid has the potential to reduce chondrocyte apoptosis in rats following corticosteroid administration (Ozenci 2013; Herrak et al. 2004). In a cruciate ligament transection animal model, subcutaneous injections every 3 months resulted in reduced collagenase cleavage of type II collagen (Dearmin et al. 2014). The favorable action is also due to an inhibition of chondrocyte apoptosis (Uysal et al. 2016). A clinical trial on osteoarthritis is underway where 5 mg of zoledronic acid is administered annually intravenously (Aitken et al. 2018). Laslett et al. (2012) showed a beneficial effect following 5 mg of intravenous zoledronic acid in osteoarthritis patients in terms of pain. The most common adverse reactions are represented by cold or flu-like symptoms, as well as headaches (Laslett et al. 2012). Zometa®, Reclast®, and Aclasta® are drugs containing zoledronic acid currently available on the market (Anderson et al. 2018).

Risedronate if administered orally can result in a lower extent of cartilage fibrillation in rabbit knee osteoarthritis compared to glucosamine (Permuy et al. 2014). A clinical trial involving risedronate concluded that 5 mg/day, 15 mg/day, 35 mg/week and 50 mg/week after 2 years did not improve the symptoms of knee osteoarthritis, nor did it reduce progression of osteoarthritis, but it reduced the level of C-terminal cross-linking telopeptide of type II collagen (Bingham et al. 2006). Currently, available risedronate products are Actonel® and Atelvia® (Anderson et al. 2018). The more common adverse reactions of risedronate are abdominal pain, ostealgia and arthralgia (Anderson et al. 2018).

Alendronate enhances the preservation of articular cartilage following anterior cruciate ligament transection in mice, but no significant differences could be found between the control and treatment group after 56 days (Khorasani et al. 2015). Another study showed that alendronate prevents cartilage lesions in OVX rats and reduces MMP-13 (Zhu et al. 2013). A clinical trial on hip osteoarthritis showed that 35 mg/week of alendronate showed pain improvement and lower CTX-II levels (Nishii et al. 2013). A clinical trial on knee osteoarthritis concluded that 70 mg/week of alendronate improves stiffness and function (Arti and Azemi 2012). Available products containing alendronate are represented by Binosto® and Fosamax® (Anderson et al. 2018). Most common adverse effects are represented by abdominal and stomach pain (Anderson et al. 2018).

Monoclonal antibodies are an antibody secreted from a unique clonal cell and are used predominantly in cancer therapy, but effects on articular cartilage have also been found in the literature.

Bevacizumab, represented by Avastin® and Mvasi®, is currently used in the treatment of different tumors such as gastrointestinal, breast, renal or lung cancer (Anderson et al. 2018). It has an antiangiogenic effect by inhibiting vascular endothelial growth factor (VEGF) (Nagai et al. 2014). Bevacizumab has a similar antiangiogenic effect to chondromodulin-1, promoting chondromodulin-1 expression, proteoglycan aggrecan content and cartilage regeneration in an animal model (Nagai et al. 2014; Lee et al. 2016). Another study showed that intravenous administration of bevacizumab has been shown to increase collagen type II content and limit knee articular cartilage degeneration after anterior cruciate ligament transection in animal model (Nagai et al.

2014). Bevacizumab has multiple adverse reactions including dizziness, fever, chills, chest pain, irregular breathing, and heartbeat, as well as nasal congestion (Anderson et al. 2018).

Adalimumab decreases histological scores of cartilage lesions in preclinical studies by blocking the function of TNF-α (Zhu et al. 2018). Nevertheless, a randomized controlled trial showed that subcutaneous adalimumab had no effect on pain, synovitis and bone marrow lesions in patients with erosive osteoarthritis of the hand (Aitken et al. 2018). Available brand names of adalimumab are Humira®, Hadlima®, Hyrimoz®, Amjevita®. Some of the common adverse effects are represented by rash, headache, abdominal pain and hypertension.

Statins are lipid-lowering agents that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, but the effect on bone and cartilage metabolism have also been found (Wolozin et al. 2007).

Atorvastatin—the majority of epidemiological studies showed that 40 mg daily of a statin reduces the risk and progression of hip and knee osteoarthritis (Wang et al. 2015). Atorvastatin reduces cartilage degradation by decreasing MMP-13, TNF-α and IL-1β-induced GAG release in vitro (Simopoulou et al. 2010; Pathak et al. 2015). Lipitor® is the current atorvastatin containing product available on the market (Anderson et al. 2018). More common adverse reactions of atorvastatin are hemorrhagic stroke, arthralgia, diarrhea and nasopharyngitis (Anderson et al. 2018).

Supplements are the most commonly used in the non-surgical treatment of cartilage lesions. They contain elements similar to the ones found at the cartilage level and are intended to supplement them.

Glucosamine is predominantly found at the level of connective tissue and cartilage (Jerosch 2011). At the articular level, it is an important precursor for glycosaminoglycan, in the production of hyaluronic acid, keratin sulfate, chondroitin sulfate, aggrecan and collagen type II, which are key components of cartilage matrix (Jerosch 2011). Glucosamine inhibits the synthesis of the key cleavage enzymes in the cartilage, MMP, resulting in a decreased proteoglycan degradation. Glucosamine also inhibits the inflammatory process. A clinical trial has shown that glucosamine (1500 mg daily) reduces the incidence of total knee replacement in knee osteoarthritis (from 14.5 to 6.3%) and stops the progression of joint space loss (Jerosch 2011). Other clinical trials also support the chondroprotective properties of glucosamine (Ali et al. 2011; Gallagher et al. 2015). This effect is explained by a decrease in MMP-3, decrease in chondrocyte apoptosis, increase in both TGF-β1 and connective tissue growth factor (CTGF) (Ali et al. 2011; Taniguchi et al. 2012). On the other hand, a clinical trial showed no structural benefits in MRI appearance and CTX-II urinary excretion in patients taking 1500 mg/day of glucosamine for 24 weeks in chronic knee pain (Kwoh et al. 2014). The same results were obtained in an ACL transection animal model where oral glucosamine did not prevent fibrillations and erosions of the articular cartilage (Tiraloche et al. 2005). Available glucosamine supplements approved by FDA are Genicin® and Opriflex-G® and their adverse reactions are represented by nausea, vomiting, diarrhea or constipation (Anderson et al. 2018).

Chondroitin sulfate is an essential component of the extracellular matrix, being the most frequent glycosaminoglycan in the aggrecan molecule within the cartilage (Jerosch 2011). Multiple clinical trials have shown the significant structure-modifying effect in chondroitin sulfate treated patients at doses of 800-1200 mg daily (Jerosch 2011; Gallagher et al. 2015). Two meta-analyses showed the importance of chondroitin in delaying the progression of knee osteoarthritis (Jerosch 2011; Knapik et al. 2019). Chondroitin sulfate has multiple mechanisms of action at cartilage level. It lowers MMP-3, MMP-13 levels, IL-1β expression, ADAMTS-4, ADAMS-5, chondrocyte apoptosis and increases hyaluronic acid production, chondrocyte metabolism, as well as type II collagen, proteoglycan synthesis (Henrotin et al. 2010; Jerosch 2011; Taniguchi et al. 2012). European League Against Rheumatism (EULAR) gave chondroitin sulfate the highest recommendation and it is considered a structure-modifying drug in osteoarthritis (SMOAD), especially in larger doses (1200 mg daily) (Jerosch 2011; Knapik et al. 2019). Chondroitin sulfate has a good safety profile, most common side effects being nausea, diarrhea and constipation (Henrotin et al. 2010; Anderson et al. 2018).

Hyaluronic acid injected intraarticular is frequently used in the treatment of cartilage lesions worldwide, but less data exists regarding orally administered hyaluronic acid. This agent is a mucopolysaccharide present in the synovial fluid, being responsible for its viscosity and the low friction movement of synovial articulations (Tashiro et al. 2012; Oe et al. 2015). Orally high molecular weight hyaluronic acid was found to reach the joint and provide pain reduction and an increase in physical function (Jerosch 2011). Multiple clinical trials showed that 60–240 mg of hyaluronic acid (Hyabest®) daily significantly improves the symptoms of knee osteoarthritis (Tashiro et al. 2012; Oe et al. 2015). Hyaluronic acid reduces MMP-13, ADAMTS-4, ADAMS-5, IL-1β, IL-6 and increases proteoglycan as well as glycosaminoglycan

production (Altman et al. 2015; Pohlig et al. 2016). The clinical trials did not show any adverse reaction of oral hyaluronic acid (Oe et al. 2015).

Collagen hydrolysate has been reported to have a significant increase in collagen type II a proteoglycan synthesis in cell cultures (Bello and Oesser 2006). The positive effect was also confirmed in a clinical trial using MRI mapping of the knee articular cartilage (DGEMRIC score) after 48 weeks of treatment with 10 grams daily of collagen hydrolysate (Fortigel®) (McAlindon et al. 2011). A study performed on athletes with joint pain showed an improvement of joint pain after 24 weeks of collagen hydrolysate (Clark et al. 2008). The adverse effects are very limited, consisting of gastrointestinal symptoms like fullness and unpleasant taste (Moskowitz 2000).

Vitamin C (ascorbic acid) has a chondroprotective effect on articular cartilage (Jerosch 2011). This effect can be due to the stimulation of collagen and aggrecan synthesis, decrease in chondrocyte apoptosis, as well as the antioxidant capacity of vitamin C (Jerosch 2011; Chang et al. 2015; Marks 2018). Vitamin C also lowers Nrf2 activity, Nf-κB and MMP-3 levels (Chang et al. 2015). On the other hand, there are studies that show that vitamin C can increase apoptosis of chondrocytes due to DNA fragmentation, with a negative impact on cartilage metabolism (Marks 2018). Framingham Osteoarthritis Cohort Study showed that 120–200 mg of vitamin C lowers osteoarthritis progression by three times (Wang et al. 2004). A clinical trial on patients with hip or knee osteoarthritis receiving 898 mg of vitamin C resulted in pain reduction (Wang et al. 2004).

Vitamin D in the diet significantly reduces cartilage erosion in an ovariectomized animal model. MMP-9 and MMP-13 were decreased by vitamin D intake while increasing TGF-B1 expression. Vitamin D counteracted CTX-II increase by TNF-α stimulation (Li et al. 2016). Some clinical trials showed that vitamin D had no significant effect on the joint structure and knee pain in patients with osteoarthritis (McAlindon et al. 2013; Gallagher et al. 2015; Jin et al. 2016; Arden et al. 2016). On the contrary, other clinical trials showed small or modest benefits on knee pain and physical function under vitamin D supplementation (Sanghi et al. 2013; Ding et al. 2016). Although vitamin D is considered a safe supplement, side effects like nausea, constipation or headache can occur (Sanaei et al. 2016).

Omega-3 fatty acid reduces NF-κB induced inflammation, decreases IL-1 induced aggrecanase and collagenase activity (Jerosch 2011). It also reduces the expression of ADAMSTS-4, COX-2, IL-1α, and TNF-α, all of them representing catabolic factors of cartilage metabolism (Jerosch 2011). Although this supplement is frequently prescribed in osteoarthritic patients, there is a lack of clinical trials to prove any benefits over placebo (Boe and Vangsness 2015; Hill et al. 2016). There is no difference in effect between 0.45 g and 4.5 g of omega-3 fatty acid (Hill et al. 2016). The known adverse effects are nausea, stomach upset and uncomfortable taste (Schachter et al. 2005).

Calcium gluconate at a dose of 50 mg/kg orally daily lowers articular cartilage loss compared to control in anterior cruciate ligament transection animal model (Kang et al. 2014). It is probably linked to an inhibition of COX-2 (Kang et al. 2014). Although no clinical trials on systemic administration of calcium gluconate exist, an intra-articular injection clinical trial showed a good impact on symptoms (Caamaño et al. 2017). The most common adverse reaction of calcium gluconate administered orally is nausea (Anderson et al. 2018).

Naringin is a flavanone glycoside found in citrus fruits (Chen et al. 2016). Its oral administration protects against surgically induced osteoarthritis animal models by suppressing NF-κB, chondrocyte apoptosis, and signaling pathway, resulting in a lower degradation of cartilage matrix (Zhao et al. 2016). Another animal study showed that 5 mg/kg of naringin has the ability to reduce PGE_2, nitric oxide, IL-6 and TNF-α (Qiang Xu et al. 2017). Naringin ability to suppress MMP-13 and GAG release has also been shown in vitro (Crasci and Panico 2013). We could find no common adverse reactions associated with oral naringin.

MethylSulfonylMethane (MSM) is an organosulfur compound popularly used as an anti-inflammatory agent (Butawan et al. 2017). Serum concentrations of MSM rise in surgically induced osteoarthritis animal model (Butawan et al. 2017). Multiple studies have shown a limitation of cartilage degeneration following MSM administration, and it is mostly explained by the reduction of TNF-α expression, IL-6, NF-κB, COX-2 (Butawan et al. 2017). Early results of a clinical trial on knee osteoarthritis showed an improvement of pain and physical function after 3 g twice a day (Kim et al. 2006). Other clinical trials are still under study (Kim et al. 2006; Pagonis 2013). Possible adverse reactions of MSM are gastrointestinal symptoms and headaches (Kim et al. 2006).

Selenium diet of 2 mg/kg daily limits cartilage lesion degeneration when associated with vitamins (A, C, E, B6, B2) in an induced various deformity animal model, possibly by limiting free oxygen radicals (Kurz et al. 2002). We found no clinical trial on selenium's effect on cartilage. At a higher dose, selenium can produce diarrhea, nausea, and vomiting (Anderson et al. 2018).

Zinc can limit the progression of osteoarthritis due to its antioxidant capacity and promotion of

chondrocyte proliferation (Huang et al. 2018). Studies showed that it prevents IL-1β and MMP-13 increases in pathological situations (Huang et al. 2018). Zinc also stimulates the action of Nrf2 and phosphorylated (p)-Akt which protect against cartilage loss (Huang et al. 2018). A dose of 1.6 mg/kg/day is considered sufficient to protect against OA progression in animal models (Kurz et al. 2002). No clinical trial was found regarding zinc supplementation in cartilage lesions. Side effects linked to zinc administration are diarrhea, abdominal cramps and vomiting (Anderson et al. 2018).

Magnesium promotes cartilage formation by enhancing the adhesion of mesenchymal stem cells to collagen, upregulating chondrogenesis and by stimulating the production of cartilage matrix (Shimaya et al. 2010). We found no clinical trials on magnesium treatment of cartilage lesions. Adverse reactions of magnesium supplementation can be diarrhea, abdominal cramps and depression (Anderson et al. 2018).

Resveratrol presents anti-OA effects in an animal model of a high-fat diet after 12 weeks of oral treatment (Gu et al. 2016). It partially recovered the articular cartilage by decreasing chondrocyte apoptosis and preventing collagen type II degradation into CTX-II (Wang et al. 2012; Gu et al. 2016). One clinical trial is underway where patients with knee osteoarthritis receive 80 mg daily for a week, followed by 40 mg daily for 6 months (Nguyen et al. 2017). No adverse reactions of resveratrol have been described so far (Anderson et al. 2018).

Diacerein is an anthraquinone derivate that suppresses IL-1β, MMP-13, and TNF-α, also reducing osteoclast formation (Zhu et al. 2018). Randomized controlled trials showed a positive effect on hip and knee osteoarthritis, but no effects were observed in hand osteoarthritis (Zhu et al. 2018). Although experts concluded a similar effect of diacerein to NSAIDs, due its adverse reactions (diarrhea, hepatobiliary reactions, and skin reactions) its use is restricted in Europe and USA. Products containing diacerein include Bicerin-M®, Cartidin®, Cedia®, Dashing®.

Piascledine, or avocado-soybean unsaponifiable, inhibits IL-1 and also stimulates the synthesis of collagen in cultures (Pavelka et al. 2010). A randomized clinical trial showed that 300 mg of piascledine administration for 3 years reduced the joint space narrowing changes compared to the control group (Maheu et al. 2014). Another clinical trial comparing 300 mg daily of piascledine with chondroitin sulfate for 6 months revealed a similar favorable effect in case of WOMAC score, represented by a 50% decrease (Pavelka et al. 2010). Piascledine is considered to have a good safety profile, but allergic reactions or gastrointestinal reactions could be related to its administration (Pavelka et al. 2010).

Other supplements with a proven potential of reducing or physical function are *Boswellia serrata* extract, pine bark extract, curcumin, willow bark extract, *Artemisia annua* extract, lipid extract of Green-lipped mussel, rosehip, undenatured type II collagen, passion fruit peel extract, cynantine FLX, *Curcuma longa* extract, L-carnitine and bromelain (Liu et al. 2018).

Reversible acetylcholinesterase inhibitors are involved in impulse transmission and used in the treatment of Alzheimer's disease (Čolović et al. 2013; Zhang and Zhou 2014).

Donepezil (Aricept®) inhibits the transcriptional activity of interferon response factor-1 (IRF-1) and therefore limits the expression of MMP-13, resulting in a potentially favorable effect in osteoarthritis (Zhang and Zhou 2014). No clinical trials regarding the donepezil effect on cartilage lesions exist. More common adverse reactions are diarrhea, nausea, vomiting, and loss of appetite (Anderson et al. 2018).

Antibiotics have also been found to positively influence cartilage lesions.

Doxycycline increases human bone marrow-derived mesenchymal stem cells (hMSC) which are important in chondrogenesis and decreases the cleavage protein MMP-13 in osteochondritis dissecans rats (Lee et al. 2013). A clinical trial on more than 400 patients with knee osteoarthritis showed that 100 mg of doxycycline twice a day reduces joint space narrowing and pain (Brandt et al. 2005). On the other hand, another clinical trial didn't show any benefits of doxycycline in terms of symptoms reduction (Snijders et al. 2011). A review by Bruno R da Costa et al. concluded that doxycycline has minimal to non-existent benefits in the treatment of osteoarthritis (da Costa et al. 2012). Available products containing doxycycline are Acticlate®, Adoxa®, Alodox®, Avidoxy®, Doryx®, Mondoxyne NL®, Mondox®, Morgidox®, Oracea®, Oraxyl®, Targadox® and Vibramycin® (Anderson et al. 2018). Side effects are represented by headache and sinus headache (Anderson et al. 2018).

Erythromycin is a well-known macrolide antibiotic that acts by inhibiting the 23 s ribosomal RNA. A recent study showed that erythromycin inhibits the IL-1β-induced catabolic gene expression and the NF-κB expression in human chondrocytes with the help of ghrelin receptor (GHSR) (Uchimura et al. 2019). As a result, it reduces articular inflammation and cartilage destruction (Uchimura et al. 2019). No clinical trials regarding the erythromycin's effect on cartilage lesions were found. Available products containing systemic erythromycin are Ery-Tab®, Erythrocin®, Ery-Ped®, E-

Mycin®. More common adverse reactions are diarrhea, nausea, vomiting, and loss of appetite.

Analgesics

Acetaminophen (paracetamol) is often regarded as the first-line drug used in osteoarthritis pain management. Although its long-time use, the mechanism of action has not been fully understood (Sharma and Mehta 2013). Studies showed an influence of acetaminophen on prostaglandin inhibition, serotoninergic pathway activation, endocannabinoid enhancement, as well as on opioid and nitric oxide pathways (Sharma and Mehta 2013). Multiple clinical trials have demonstrated the positive effect of 2–4 g daily of acetaminophen on pain relief compared to placebo, but when compared to NSAIDs, acetaminophen was less effective (Towheed et al. 2006). Although considered a safe drug, it can produce renal failure, liver failure, nausea, vomiting, abdominal pain or hypotension (Sharma and Mehta 2013). Common brand names include Tylenol®, Calpol® or Panadol®.

Opioids have been recommended for pain relief in osteoarthritis for a long time, but due to the high number of safety and tolerability issues reported in the last years, some guidelines recommend against its use in hip or knee osteoarthritis, with one exception, *tramadol* (Fuggle et al. 2019; Apostu et al. 2019). There is no sufficient data regarding the chondroprotective effect of opioids, but recent research found that kappa-opioid receptor signaling can protect against posttraumatic cartilage degeneration by inhibiting TNF-α mediated cartilage degradation (Wu et al. 2017). Side effects of opioids include gastrointestinal disorders (constipation), nausea, vomiting, loss of appetite, rash, pruritus, dizziness, headache, somnolence, insomnia and addiction (Fuggle et al. 2019). Opioids include fentanyl (e.g. Abstral®, Actiq®) tramadol, oxycodone (e.g. OxyContin®, Xtampaza ER®), hydrocodone (e.g. Zohydro ER®), codeine, morphine (e.g. Roxanol-T®) and others.

Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease pain, swelling and functional impairment by inhibiting cyclooxygenase-1 and cyclooxygenase-2, a key enzyme in the inflammation process. NSAIDs are intensively used in order to reduce symptoms of osteoarthritis, therefore we will focus on the chondroprotective effect of these drugs.

Aspirin at a dose of 300 mg/day has the potential to reduce medial tibial plateau cartilage loss in knee osteoarthritis (Wluka et al. 2015). Aspirin has the potential to suppress MMPs, nitric oxide and NF-Κb, thus explaining a possible mechanism of action (Zhang et al. 2017; Yoon et al. 2003). It was also shown to inhibit chondrocyte apoptosis (Yoon et al. 2003). More clinical trials are needed in order to demonstrate the disease-modifying property of aspirin in cartilage lesions. Aspirin brands currently available are numerous (e.g. Arthritis Pain®, Aspir 81®, Aspir-Low®, Miniprin® and more) (Anderson et al. 2018). The most commonly reported side effect of aspirin is dyspepsia (Anderson et al. 2018).

Naproxen upregulates chondrogenic differentiation of human mesenchymal stem cells by both Indian hedgehog and parathyroid hormone/parathyroid hormone-related protein signaling pathways (Antoniou et al. 2015). No clinical trials have been found that study the effect of naproxen on cartilage lesions progression. Naproxen has multiple brand names including Aleve®, Naprosyn®, Aflaxen®, Naprelan 750® and more (Anderson et al. 2018). More frequent adverse effects of naproxen are represented by dyspepsia, heartburn, headache and constipation (Anderson et al. 2018).

Etodolac (Lodine®, Lodine XL®) is a COX-2 selective blocker that inhibits TNF-α induced apoptosis in articular chondrocytes cultures (Anderson et al. 2018; Kumagai et al. 2013). Currently, there are no clinical trials focused on the etodolac effect on cartilage tissue. More common adverse reactions of etodolac are represented by dyspepsia, abdominal pain, constipation, diarrhea and nausea (Anderson et al. 2018).

Celecoxib (Celebrex®), also a COX-2 selective blocker, showed to decrease MMP-1, MMP-13, IL-1β, TNF-α, PGE_2 and increase proteoglycan synthesis after 4 weeks of treatment with 200 mg/daily (Brizuela et al. 2007; de Boer et al. 2009; Zweers et al. 2011). Celecoxib also reduces the cartilage catabolism by inhibiting the expression of prostaglandin E_2 (PGE_2), therefore the levels of IL-1β and TNF-α are decreased (Zweers et al. 2011). Progression of knee osteoarthritis is less successful than chondroitin in reducing knee osteoarthritis progression (Pelletier et al. 2016). A clinical trial has concluded that there is no effect of 4 weeks of 200 mg celecoxib on the progression of cartilage lesions (van Helvoort et al. 2017). A 2-year clinical trial has proved that chondroitin sulfate has a significantly lowered the cartilage volume loss compared to celecoxib (Pelletier et al. 2016). Abdominal pain, diarrhea, dyspepsia, and nausea are the most common side effect of celecoxib (Anderson et al. 2018; Mester et al. 2019a).

Other substances from various classes have also been reported to have an impact on cartilage metabolism.

Strontium ranelate (Protelos®, Protos®, Protaxos®, Bivalos®, Osseor®) is a drug currently used in the treatment of osteoporosis (Turgeman et al. 2002). It reduces TNF-α, IL-1β levels, caspase-3, MMP1, MMP13, CTX-II, and cathepsin K levels, meaning a decreased collagen

cleavage and chondrocyte apoptosis (Turgeman et al. 2002; Pelletier et al. 2013). Strontium ranelate also increases proteoglycan synthesis, improving the properties of the extracellular matrix (Turgeman et al. 2002; Pelletier et al. 2013). A dose of 3000 mg/kg/day improved quality of cartilage matrix in ovarectomized rats due to an increase in proteoglycan synthesis and a reduction in caspase-3 levels (which is related to cellular apoptosis) (Turgeman et al. 2002). Another study showed that strontium ranelate significantly reduces OA cartilage erosions at all doses of treatment (25, 50 or 75 mg/kg daily) after 4 weeks in the ACL transection animal model (Pelletier et al. 2013). An important clinical trial on 1683 patients showed that 1 or 2 g daily of strontium ranelate significantly reduces knee osteoarthritis progression after 3 years (Reginster et al. 2013). Nausea and diarrhea are the most common side effects of strontium ranelate (Anderson et al. 2018).

Ursodeoxycholic acid (Ursodiol or UDCA) is used for the treatment of liver disease for reduction gallstone formation and for treatment of primary biliary cholangitis (Moon et al. 2014). Oral administration of UDCA inhibits cartilage degeneration in rat OA (Moon et al. 2014). UDCA reduces expression of IL-1β, IL-6, MMP3, MMP13, ADAMTS-5, nitrotyrosine and oxidative stress in articulation (Moon et al. 2014). No clinical trial was identified regarding the UDCA effect on cartilage defects. Stonex®, Uliv®, Ursocol®, Ursodil® are brands containing ursodeoxycholic acid (Anderson et al. 2018). Diarrhea is the most common adverse effect of ursodeoxycholic acid, which is generally well tolerated (Hempfling et al. 2003).

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor currently used in the treatment of osteoarthritis. We found no protective effect of duloxetine against cartilage deterioration. It was shown to reduce pain during clinical trials, while gastrointestinal adverse reactions are three to four times more likely to occur compared to placebo (Osani and Bannuru 2019). Available products include Cymbalta®, Irenka®, and Drizamla Sprinkle®.

Anti-NGF (Fulranumab®) are antibodies that block the nerve growth factor (NGF) (Miller et al. 2017). Although it improves pain and function, some of the preclinical studies showed increase damage of the knee joint when using anti-NGF (Miller et al. 2017). A clinical study on 423 patients concluded that long-term administration is well-tolerated and efficient in pain reduction (Sanga et al. 2017). Arthralgia and pain exacerbation was the most common adverse reactions (Sanga et al. 2017).

Lithium chloride limits the progression of cartilage lesions by decreasing MMP-1 and MMP-13 in human chondrocytes (Hui et al. 2010). The action is due to the inhibition of the p38 mitogen-activated protein kinase pathway (Hui et al. 2010). Another study showed that lithium chloride decreased the catabolic factors such as NF-kb, IL-1β, PGE_2, IL-6 and stimulates chondrocyte differentiation from mesenchymal stem cells in human articular cartilage (Minashima et al. 2014; Thompson et al. 2015; Tanthaisong 2016). Examples of products available on the market are Lithium Chloride Sanolabor® and LiDCO Lithiumchlorid® (Anderson et al. 2018). No clinical trial was identified regarding lithium chloride and cartilage lesions. Lithium poisoning is the most frequent complication (Giltin 2016).

Rebamipide, a quinolinone representative used for mucosal protection, limits cartilage degeneration in an osteoarthritic rat model by restoring extracellular matrix homeostasis (Moon et al. 2012). This effect is explained by a decrease of IL-1β, MMP-1 and MMP-3 levels (Moon et al. 2012). We found no human studies on the rebamipide effect on cartilage lesions. Rebamipide tablets are available on the market under numerous brand names (e.g. Mucosta®, Rebamapide Pfizer®, Rebamapide NP® and more) (Anderson et al. 2018). More common side effects of rebamipide are constipation, bloating, diarrhea, nausea and vomiting (Kudur and Hulmani 2013).

Pharmacological factors under development or waiting for approval which can influence articular cartilage metabolism

Licofelone is a LOX/COX inhibitor that decreases leukotrienes and prostaglandins (Cicero and Laghi 2007). Preclinical data showed that licofelone reduces cartilage lesion in surgically removed anterior cruciate ligament animal model (Cicero and Laghi 2007). This result is explained by a reduction in IL-1β and PGE_2 (Cicero and Laghi 2007). A multicenter study on 355 patients with knee osteoarthritis showed that 200 mg twice a day reduces symptoms similar to naproxen, but cartilage volume loss is significantly reduced (Raynauld et al 2009).

Sclerostin (Romosozumab®—not yet approved by FDA) is a monoclonal antibody that can increase cartilage area, cartilage thickness and proteoglycan levels in human tumor necrosis factor transgenic mice (Chen et al. 2013). We found no clinical trials on the sclerostin effect on articular cartilage.

Cyclopamine is a steroidal alkaloid hedgehog inhibitor utilized in tumor treatments. It improves histological appearance for articular cartilage lesion and limits chondrocyte apoptosis in an adjuvant-induced arthritis animal model at doses of 1.5, 5 and 10 mg/kg intraperitoneally (Li et al. 2015). The effects are explained by the reduction of TNF-α, IL-1β, and IL-6 (Li et al. 2015). We did not find

clinical studies on cyclopamine effects on cartilage lesions. Potential adverse reactions to cyclopamine are weight loss and dehydration (Kimura et al. 2008).

Cyclodextrin polysulfate downregulates IL-1α and IL-1β while increasing aggrecan, collagen type II and fibronectin in human chondrocytes (Groeneboer et al. 2008). Subcutaneous injections of cyclodextrin polysulfate produce a protective effect on articular cartilage at concentrations of 1 mg/kg in rabbits with anterior cruciate ligament transection (Groeneboer et al. 2008). No clinical trial could be identified regarding the cyclodextrin polysulfate effect on cartilage lesions.

AMG 108 is a human monoclonal antibody of the IL-1R1, thus inhibiting IL-1α and IL-1β (Cohen et al. 2011). A randomized controlled trial was made in patients with knee osteoarthritis (Cohen et al. 2011). They received 300 mg subcutaneously once every 4 weeks for 3 months (Cohen et al. 2011). AMG 108 showed an improvement in WOMAC pain scores compared to placebo but the result was statistically insignificant (Cohen et al. 2011).

ABT-981 is an immunoglobulin that impairs the activity of IL-1α and IL-1β (Wang et al. 2017). Subcutaneous injection of ABT-981 in patients with mild and moderate knee osteoarthritis showed a reduction in MMP-derived type I collagen and inflammatory response Wang et al. 2017). The most frequent adverse reaction was represented by injection site erythema Wang et al. 2017).

AG-041R is an indolin-2-one derivate that accelerates proteoglycan synthesis, gene expression of type II collagen and aggrecan (Okazaki et al. 2003). On the other hand, it suppresses ALP activity, expression of type X collagen and Runx2, thus preventing chondrocyte terminal differentiation (Okazaki et al. 2003). In addition, it also prevents chondrocyte terminal differentiation by activating MEK/Erk pathway (Okazaki et al. 2003).

Osteoprotegerin is an osteoclastogenesis inhibitory factor (OCIF) that prevented cartilage destruction in meniscectomized rats (Kadri et al. 2008).

Recombinant human midkine (rhMK) enhances the proliferation of chondrocytes in vitro, by activating ERK and PI3K pathway (Zhang et al. 2010). The same results were obtained in vivo in mice (Zhang et al. 2010).

β-cryptoxanthin significantly prevents osteoarthritic degeneration by down-regulating gene expression of aggrecanase 1 (ADAMTS-4), aggrecanase 2 (ADAMTS-5) and MMP-13 in human chondrocytes (Imada et al. 2016; Park et al. 2017). It also prevents the increase of inflammatory markers TNFα, IL-6 and IL-1β (Park et al. 2017).

Other molecules that have shown a potential to protect articular cartilage are NF-κb essential modulator binding domain (NBD), ADAMTS inhibitors (CRB0017, GSK2394002AGG-523), TGF-β-neutralizing antibody, bone osteogenic protein-1 (BMP-7), fibroblast growth factor 2 (FGF2, FGF18—sprifermin, transforming growth factor-β TGF-β (GEC-TGF-β1), Cathepsin-K inhibitors (MIV-117), RhBMP-2, selective COX-2 inhibitors (VA6940), IL-1 inhibitors, discoidin domain receptors (DDRs) inhibitors and IκB kinase (IKK) inhibitors (Turgeman et al. 2002; Okazaki et al. 2003; Chubinskaya et al. 2007; Liu et al. 2016; Zhu et al. 2018).

Systemic drugs that favor cartilage degeneration

Corticosteroids injected intramuscularly have the potential to reduce the regeneration potential of the articular cartilage (Ozbey et al. 2010). It decreases markers of differentiation, apoptosis, and regeneration including Notch-1, Delta, CD105 and CD166 (Ozbey et al. 2010). An explanation is that systemic corticosteroid administration decreases the volume of rough endoplasmic reticulum and Golgi apparatus, which leads to impaired synthesis of proteoglycan and proteins by chondrocytes (Higuchi et al. 1980).

Vitamin A in the case of long administration can lead to atrophy of articular cartilage (Kubo et al. 2002).

Fluoroquinolones are a class of antibiotics (e.g. ciprofloxacin, ofloxacin, norfloxacin) which form stable complexes with magnesium ions, resulting in decreased concentrations of this essential ion in cartilage (Polachek et al. 2011).

Current recommendations and guidelines for the pharmacological treatment of hip and knee osteoarthritis

We have searched for the latest guidelines in the treatment of hip and knee osteoarthritis and these were: Royal Australian College of General Practitioners (RACGP)—2018, United Rheumatology—2018, The College of Family Physicians of Canada (CFPC)—2017, American Academy of Orthopedic Surgeons (AAOS)—2013 (knee)/2017 (hip), National Institute for Health and Care Excellence (NICE)—2014, Osteoarthritis Research Society (OARSI)—2014 (knee)/2008 (hip), American College of Rheumatology (ACR)—2012 and American Family Physician (AFP)—2012. The current recommendations are found in Table 2.

Conclusions

Articular cartilage lesions represent an important issue nowadays and its complex treatment undergoes many debates. Apart from currently used pharmacological

Table 2. Current recommendations of pharmacological treatment in hip and knee osteoarthritis.

	Royal Australian College of General Practitioners (RACGP) — 2018	United Rheumatology 2018	The College of Family Physicians of Canada (CFPC) 2017	American Academy of Orthopedic Surgeons (AAOS)–2013 (knee)/ 2017 (hip)	National Institute for Health and Care Excellence (NICE)—2014	Osteoarthritis Research Society (OARSI)—2014 (knee) / 2008 (hip)	American College of Rheumatology (ACR)—2012	American Family Physician (AFP)—2012	Overall recommendation
Systemic									
Acetaminophen	Conditional neutral	Recommended (Knee)	Recommended	Inconclusive (Knee)	Recommended	Appropriate	Conditional for	Recommended	Recommended
NSAIDs	Conditional for	Recommended (Knee)	Recommended	Strong recommendation	Recommended	Appropriate	Conditional for	Recommended	Recommended
Opioids	Strong against	–	–	Inconclusive (Knee)	Recommended	Uncertain (Knee) /Appropriate (Hip)	Against	–	Not recommended
Tramadol	–	Recommended	Recommended (Knee)	Strong recommendation (Knee)	–	Appropriate (Hip)	Conditional for	–	Recommended
Bisphosphonates	Conditional against	–	–	–	–	Not appropriate (Knee)	–	–	Not recommended
Strontium ranelate	Strong against	–	–	–	–	–	–	–	Not recommended
Calcitonin	Conditional against	–	–	–	–	–	–	–	Not recommended
Duloxetine	Conditional for	Recommended (Knee)	Recommended	–	–	Appropriate (Knee)	Against	–	Recommended
Methotrexate	Conditional against	–	–	–	–	–	–	–	Not recommended
Colchicine	Conditional against	–	–	–	–	–	–	–	Not recommended
Doxycycline	Strong against	–	–	–	–	–	–	–	Not recommended
Anti-NGF	Conditional against	–	–	–	–	–	–	–	Not recommended
IL-1 inhibitors	Strong against	–	–	–	–	–	–	–	Not recommended
FGF	Strong against	–	–	–	–	–	–	–	Not recommended
Chondroitin sulfate	Conditional against (Knee) Strong against (Hip)	–	Not recommended	Strong recommendation (Knee) /Not recommended (Hip)	–	Uncertain (Knee symptom relief) /Appropriate (Hip)	Conditional against	Inconclusive (Knee)	Not recommended
Glucosamine	Conditional against	–	Not recommended	Strong recommendation (Knee) / Not recommended (Hip)	–	Uncertain (Knee symptom relief) /Appropriate (Hip)	Conditional against	Inconclusive (Knee)	Not recommended
Pine bark extract	Conditional neutral	–	Inconclusive	–	–	–	–	–	Inconclusive
Collagen	Conditional neutral	–	Inconclusive	–	–	–	–	–	Inconclusive
MSM	Conditional neutral	–	Inconclusive	–	–	–	–	–	Inconclusive
Vitamin D	Conditional against	–	–	–	–	–	–	–	Not recommended
Diacerein	Conditional against	–	–	–	–	Uncertain (Knee)	–	–	Inconclusive
Omega-3	Conditional against	–	–	–	–	–	–	–	Not recommended
Rosehip	–	–	–	–	–	Uncertain (Knee)	–	–	Inconclusive
Avocado-soybean unsaponifiable (ASU)	Conditional neutral	–	Inconclusive	–	–	Uncertain (Knee)	–	–	Inconclusive
Boswellia serrata	Conditional neutral	–	Inconclusive	–	–	–	–	–	Inconclusive
Curcuma	Conditional neutral	–	Inconclusive	–	–	–	–	–	Inconclusive
Topical									
NSAIDs	Conditional neutral	Recommended (Knee)	Recommended (Knee) /Inoclusive (Hip)	Strong recommendation (Knee)	Recommended	Appropriate	Conditional for (Knee) /Against (Hip)	–	Recommended

(*continued*)

Table 2. Continued.

	Royal Australian College of General Practitioners (RACGP) — 2018	United Rheumatology 2018	The College of Family Physicians of Canada (CFPC) 2017	American Academy of Orthopedic Surgeons (AAOS)–2013 (knee)/ 2017 (hip)	National Institute for Health and Care Excellence (NICE)—2014	Osteoarthritis Research Society (OARSI)—2014 (knee) / 2008 (hip)	American College of Rheumatology (ACR)—2012	American Family Physician (AFP)—2012	Overall recommendation
Capsaicin	Conditional against/ neutral (Hip)	–	Not recommended	–	Recommended	Appropriate	Conditional against (Knee)	–	Inconclusive
Opioids	Strong against	–	Not recommended (Knee)	–	–	Uncertain (Knee)	–	–	Not recommended
Intraarticular									
Corticosteroid	Conditional for	Recommended (Knee)	Recommended	Inconclusive (Knee) /Strong recommendation (Hip)	Recommended	Appropriate	Conditional for	Recommended (Knee)	Recommended
Viscosupplementation (Hialuronic acid)	Conditional against	Recommended (Knee)	Inconclusive	Strong against	Not recommended	Uncertain	Against	Recommended (Knee)	Inconclusive (Knee) / Not recommended (Hip)
Stem cell therapy	Strong against	–	Inconclusive	–	–	–	–	–	Not recommended
Growth factors	–	–	–	Inconclusive (Knee)	–	–	–	–	Inconclusive
Platelet-rich plasma (PRP)	Conditional neutral	–	Inconclusive	Inconclusive (Knee)	–	–	–	–	Inconclusive

and surgical treatments, systemic drugs that enhance articular cartilage metabolism are increasing in importance. Clinical trials have shown positive results in the case of alendronate, glucosamine, chondroitin sulfate, hyaluronic acid, collagen hydrolysate, vitamin C, vitamin D, aspirin and strontium ranelate. In vitro and animal studies showed promising effects in the case of teriparatide, leptin, zoledronic acid, bevacizumab, atorvastatin, omega-3 fatty acid, naringin, MSM, selenium, zinc, magnesium, resveratrol, donepezil, naproxen, etodolac, ursodeoxycholic acid (UDCA), lithium chloride and rebamipide. Other agents still under development or approval such as licofelone, sclerostin, cyclopamine, cyclodextrin polysulfate, AG-041R, osteoprotegerin, rhMK, β-cryptoxanthine, NF-κb essential modulator binding domain (NBD), TGF-β-neutralizing antibody, osteogenic protein-1 (BMP-7), fibroblast growth factor 2 (FGF2) and RhBMP-2 show beneficial results. Pain-reducing drugs such as acetaminophen, opioids, diacerein, piascledine, duloxetine, and anti-NCF are also options for pharmacological management of osteoarthritis. Corticosteroids, vitamin A and fluoroquinolones should be avoided in case of articular cartilage lesions.

Acknowledgements

Horea Benea, Alexandru Mester, Simion Bran, and Florin Onisor have equally contributed to the current manuscript as the first author.

Disclosure statement

The authors report no declarations of interest.

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