Annals of Physical and Rehabilitation Medicine 59 (2016) 149–156

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Update article

Altered joint tribology in osteoarthritis: Reduced lubricin synthesis due to the inflammatory process. New horizons for therapeutic approaches

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ARTICLE INFO

Article history:
Received 8 December 2015
Accepted 9 March 2016

Keywords:
Inflammation
Pro-inflammatory cytokines
Lubricin
Osteoarthritis
Joint injury

ABSTRACT

Osteoarthritis (OA) is the most common form of joint disease. This review aimed to consolidate the current evidence that implicates the inflammatory process in the attenuation of synovial lubrication and joint tissue homeostasis in OA. Moreover, with these findings, we propose some evidence for novel therapeutic strategies for preventing and/or treating this complex disorder. The studies reviewed support that inflammatory mediators participate in the onset and progression of OA after joint injury. The flow of pro-inflammatory cytokines following an acute injury seems to be directly associated with altered lubricating ability in the joint tissue. The latter is associated with reduced level of lubricin, one of the major joint lubricants. Future research should focus on the development of new therapies that attenuate the inflammatory process and restore lubricin synthesis and function. This approach could support joint tribology and synovial lubrication leading to improved joint function and pain relief.

1. Introduction

Osteoarthritis (OA) has long been considered a "wear and tear" disease. Traditionally, the etiology of OA has been linked to increased mechanical overload on weight bearing joints, anatomical joint incongruence, and fragility of articular cartilage [1]. However, this concept is gradually being challenged as evidence accumulates to support an "inflammatory" basis of OA.

The capacity for joint repair gradually diminishes with aging. The articular cartilage component of the joint is often damaged in focal or more extensive areas after joint injury. Cartilage is a connective tissue that is neither vascularized nor innervated and therefore cannot respond to acute injuries with the usual cycle of reparative responses [2]. Chondrocytes, the unique cells that are present in cartilage, are sparsely distributed within the tissue and have a low reparative capacity because they have very low metabolic activity.

OA is a complex disease with a multifactorial etiology that includes aging, synovitis, "low-grade" systemic inflammation, obesity, prior joint injuries, gender, genetic factors and metabolic syndrome among the most prominent risk factors for development and progression [3–5] (Fig. 1). Another fundamental aspect of the OA pathophysiological process is the reduced boundary-lubricating ability of synovial fluid. This aspect is associated with reduced level of lubricin, one of the major joint lubricants [6].

In this review, we discuss the most important findings regarding the inflammatory process and the altered lubricating ability in the joint tissue following acute injury, to highlight a possible cross-link between these 2 pathological aspects of OA, a complex disease. The key observations in this review should provide further motivation for studying the link between these 2 important features of OA, laying the foundation for novel therapeutic approaches and innovative treatments.

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http://dx.doi.org/10.1016/j.rehab.2016.03.005
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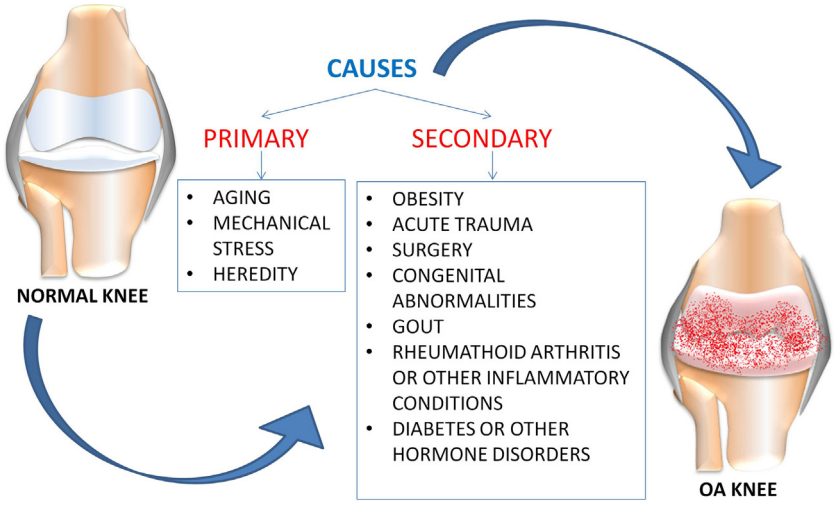

Fig. 1. Several factors responsible for the development of primary or secondary osteoarthritis (OA).

2. Inflammatory theory of OA

The "inflammatory theory" of OA onset is certainly not a recent concept. Indeed, in a paper published in 1975, George Ehrlich described a cohort of predominantly menopausal females presenting a deforming and inflammatory OA, some of whom showed changes characteristic of rheumatoid arthritis (RA) [7]. This was probably the first paper that emphasized inflammation as a key component of OA. Although the original observations were published more than 40 years ago, the importance of Ehrlich's findings has not been fully appreciated until recently. The major players in OA research have realized the importance of this aspect and proposed a connection between inflammation, synovitis and structural changes in OA. The advent of molecular biology and its introduction to bone and joint research dates back to the 1990s. Numerous soluble mediators of inflammation, such as cytokines and prostaglandins, were discovered and found to be associated with increased production of matrix metalloproteinases (MMPs), primary enzymes responsible for cartilage degradation [8]. More recent data indicate subchondral bone, cartilage and synovium as a source of inflammatory mediators in OA progression and cartilage degeneration [2,9]. These data emphasize the complexity of the disease, implicating the entire joint as an organ and not just cartilage as a joint tissue. Such findings are supported by a recent discovery of the effect of pro-inflammatory cytokines on the reduced production of lubricin and the consequent decreased boundary-lubricating ability of synovial fluid in OA joints, which suggests the important role of lubricin in the development of this complex disease [10].

2.1. Inflammatory cytokines

A primarily destructive impact on cartilage is the effect of inflammatory cytokines associated with biomechanical factors. The latter have a multilevel impact on joint tissues, involving premature aging, chondrocyte apoptosis and decreased synthesis of key components of extracellular matrix. Inflammatory cytokines also contribute to increased synthesis of many proteolytic enzymes, responsible for cartilage degradation and determine the reduced lubricating ability of synovial fluid. Among the inflammatory cytokines determining the loss of metabolic homeostasis of joint tissues by promoting catabolic and destructive processes, those with the greatest effect are interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), IL-6, IL-15, IL-17, and IL-18 (Fig. 2 and Table 1) [11].

2.2. Synovitis

Synovitis is a critical feature of OA and many studies have focused on this condition as a key driver of the disease process. Synovitis is defined as the local inflammation of synovial membrane, usually painful, characterized by joint swelling due to synovial thickening or effusion. Synovial inflammation occurs frequently after traumatic joint injury and is associated with increased pain and dysfunction [12]. It probably occurs as degraded cartilage fragments and extracellular matrix macromolecules are released into the joint and contact the synovium. Synovial cells react to the release of these fragments/molecules and become activated, thereby producing inflammatory mediators [8]. The latter stimulate chondrocytes in the superficial layer of cartilage and the synovium itself to synthesize MMPs and other matrix-degrading enzymes that increase cartilage degradation. These mediators are also responsible for synovial angiogenesis and increased synthesis of inflammatory cytokines and MMPs by synovial cells themselves, for a vicious cycle [13]. Clearly, the described events affect the lubricating ability of the joint as confirmed by Jay et al. in a study of the lubricating ability of aspirated synovial fluid from patients with knee joint synovitis. The study demonstrated the non-lubricating bearing and increased catabolism of collagen II in synovial fluid aspirates of these patients, so collagen II may play a fundamental role in acute cartilage destruction ultimately resulting in post-traumatic OA [14].

2.3. Inflammaging

Age is the most important risk factor for OA onset. The aging process does not necessarily relate to the passage of time but depends also on our lifestyle. Indeed, 2 different types of cellular senescence are replicative and stress-induced. The former is associated with an arrest in cell-cycle progression, resulting from a natural telomere shortening process and found in cells in older adults. The latter is independent of telomere length and is associated with several kinds of stresses, especially oxidative stress and inflammatory processes established during OA onset [15]. "Inflammaging" refers to low-grade inflammation that occurs during physiological aging. According to this concept, the inflammatory process, as well as all events closely linked to it, contributes to chondrocyte senescence, which results in the age-related degradation of cartilage, subchondral bone, and synovium, thereby determining the early development of OA [16]. Interestingly, the link between inflammation and aging appears to be interdependent

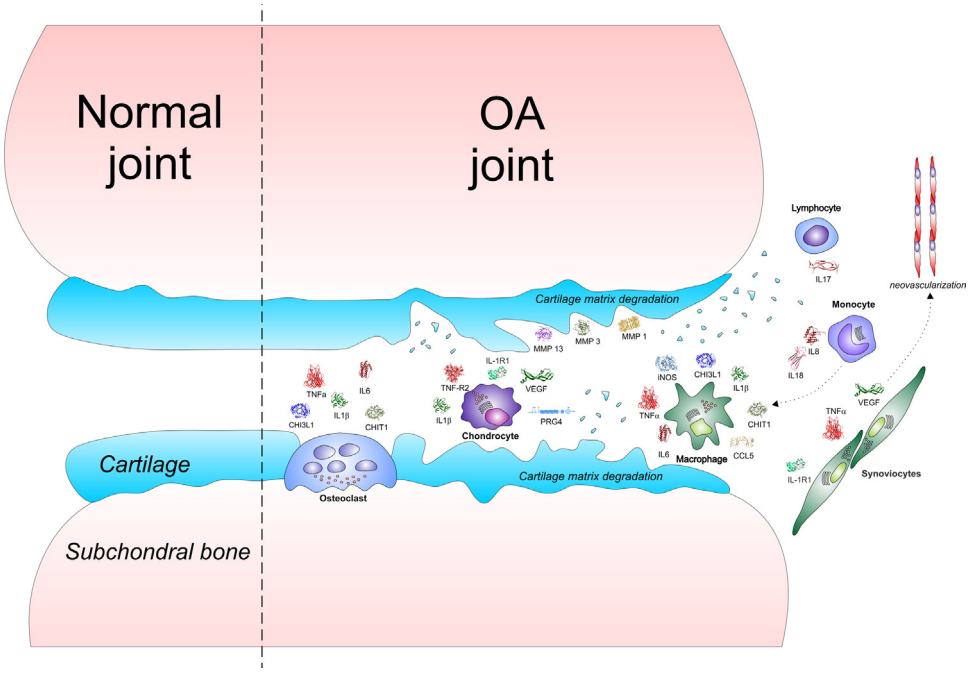

Fig. 2. The pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), interleukin-8 (IL-8), interleukin-18 (IL-18), interleukin-6 (IL-6) and chitinase-3-like protein 1 (CHI3L1) and chitotriosidasi (CHIT1), are upregulated in osteoarthritis (OA). These cytokines contribute to the pathogenesis of OA by mediating the destruction of articular cartilage within the joint. The degenerative processes involve different types of cells including monocytes, macrophages, lymphocytes, osteoclasts, chondrocytes and synoviocytes.

because it determines the early senescence of chondrocytes and also appears to be its direct consequence. Indeed, activity is impaired in senescent chondrocytes as compared with normal chondrocytes, with evidence of the "senescent secretory phenotype", characterized by increased expression of genes encoding for inflammatory cytokines such as IL-6, IL-1β and several members of the MMP family [17]. The increased expression of both advanced glycation end-products (AGEs) and AGE receptors (RAGEs) in OA chondrocytes has been associated with dysregulated signalling pathways, altered synthetic activity and enhanced sensitivity to cytokines and chemokines, which in turn trigger the expression of MMPs and other inflammatory mediators [18]. Interestingly, lubricin production in aged rats appeared to be decreased, so chondrocyte senescence may have an important role in the lubricating properties of cartilage tissue [16]. This observation is probably a direct consequence of the above suggested strict link between aging and inflammation.

2.4. Chitinases

Lately, much interest has been given to some members of the family of chitinases such as chitotriosidase (CHIT1) and chitinase 3-like-1 (CHI3L1) involved in OA pathophysiology. Elevated levels of these proteins have been reported in several chronic inflammatory and degenerative disorders [19]. In our recent study, we observed increased expression of these proteins in a rat model of OA. Their production has been closely related to inflammatory processes and pro-inflammatory cytokines, and their overexpression was suggested to be involved in cartilage remodelling and degradation processes in OA joints [20]. Moreover, in another recent study, we demonstrate an inverse proportional relation of the expression of CHI3L1 and lubricin in normal and osteoarthritic rat articular cartilage. Levels of lubricin increased in normal cartilage and decreased in OA cartilage and levels of CHI3L1 increased in OA cartilage and decreased in normal cartilage. These 2 glycoproteins may be functionally associated with the development of OA, which again underlines the important link between the inflammation and lubricating properties of articular cartilage tissue in OA onset [21].

3. Inflammation and lubricin synthesis

3.1. Lubricin

The biology of OA has been attributed to changes in lubrication at the surface of articular cartilage. This aspect of the pathophysiological process of OA has not been entirely understood. Lubricin is a surface-active mucin-like glycoprotein, encoded by the *proteoglycan 4* (*PRG4*) gene, specifically synthesized by chondrocytes located at the surface of articular cartilage [22–24]. As a lubricating glycoprotein, lubricin is produced in synovial fluid [25], menisci [25,26], the superficial layer of articular cartilage [27,28], tendons [29], the temporomandibular joint disc [30,31] and the periodontal ligament [32]. Also called superficial zone protein (SZP), lubricin has been reported to be a proteoglycan, specifically PRG4. Lord et al. demonstrated that lubricin in human synovial fluid is a heterogeneous population with both glycoprotein and proteoglycan forms [33]. PRG4 has been identified as megakaryocyte stimulating factor (MSF); the expression of human and mouse *PRG4* genes was found to be similar and was found in cartilage and also liver, heart, lung, and bone [34]. Ludwig et al. [35] demonstrated lower levels of PRG4 and reduced boundary lubrication properties in the synovial fluid of human patients with symptomatic OA. In contrast, and perhaps unexpectedly, Neu et al. [36] found elevated levels of SZP in patients with advanced OA, so SZP may be ineffective in reducing joint friction in the boundary lubrication mode in advanced OA, where other mechanisms may dominate the observed tribological behaviour. Lubricin contains multiple protein domains. The largest central mucin-like domain (high content of proline, serine and threonine) consists of

Table 1
Target genes involved in OA. Molecular analyses involved use of the UCSF Chimera package. Chimera is a graphics software developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco (Petterson et al., 2004).

Chimera image	Gene	PBD code	Name
	*CCL15*	1U4L	Chemokine (C-C motif) ligand 15
	*CH13L1*	4P8U	Chitinase-3-like protein 1
	*CHIT1*	1GUV	Chitotriosidasi
	*IL-1β*	1TWM	Interleukin-1 beta
	*IL-1βR*	1F20H	Interleukin-1 beta receptor
	*IL-6*	1ALU	Interleukin-6
	*IL-18*	1IL8	Interleukin-18
	*iNOS*	1NS1	Nitric oxide synthases
	*MMP1*	3SH1	Matrix metalloproteinase-1
	*MMP3*	1B3D	Matrix metalloproteinase-3
	*MMP13*	1CXV	Matrix metalloproteinase-13
	*TGFB1*	3KFD	Transforming growth factor beta 1
	*TNF-α*	1TNF	Tumor necrosis factor alpha
	*TNFR1*	3ALP	Cluster of differentiation 120a
	*TNFR12*	3ALQ	Cluster of differentiation 120b
	*VEGF*	4KZM	Vascular endothelial growth factor

OA: osteoarthritis.

imperfectly repeated sequences of EPATTPK, which provide the scaffold for O-glycosylation [37]. This domain contains the C-terminal haemopexin domain and 2 somatomedin domains at the N-terminus. The boundary-lubricating ability of lubricin has been attributed to its O-glycans, which affect physical properties such as high viscosity and low friction [37]. Glycomic studies have shown that lubricin presents abundant sialylated and unsialylated core 1 oligosaccharides and several sialylated, fucosylated and sulfated core 2 oligosaccharides [37].

3.2. Lubricin and OA

Lubricin is critical to normal joint function, providing boundary lubrication of congruent articular surfaces under high contact pressure and near-zero sliding speed. Furthermore, it has an important role in preventing chondrocyte apoptosis and in synovial cell adhesion and proliferation [38]. Lubricin-knockout mice show clinical and radiologic signs of joint disease and histologic abnormalities in their articulating joints with increasing age. The most important features are synovial hyperplasia and subintimal fibrosis, proteinaceous deposits on the cartilage surface, irregular cartilage surface and endochondral growth plates, and abnormal calcification in tendon sheaths and osteophytes [39]. Furthermore, decreased synthesis of lubricin has been observed in several studies of both OA joints and post-traumatic OA [26]. In one study [40], joint friction and cellular apoptosis was greater in lubricin-knockout than wild-type mice. The addition of lubricin in the in vitro bovine explant cartilage-on-cartilage bearing system significantly lowered the coefficient of friction and chondrocyte apoptosis in superficial layers of cartilage, thereby confirming its crucial role in preventing cartilage degeneration [40]. Supplementing lubricin by intra-articular injection improved weight bearing in studies measuring hind limb force. Lubricin reduced the severity of post-traumatic OA and level of urinary C-terminal cross-linked telopeptide type II collagen (CTX-II), without affecting Osteoarthritis Research Society International (OARSI) score [41]. Overproduction of lubricin in transgenic mice reduced the severity of both age-related and post-traumatic OA. This reduction was due to lubricin inhibiting the expression of genes involved in cartilage catabolism and chondrocyte hypertrophy by upregulating hypoxia-inducible factor 3α (HIF-3α), a negative regulator of HIF-1α and HIF-2α, responsible for catabolic and anabolic activity that promotes OA [42]. The early stages after anterior cruciate ligament injury are characterized by changes in levels of sulfated glycosaminoglycans (sGAGs). The significantly increased sGAG and aquaporin levels in synovial fluid after joint injury may indicate articular cartilage damage [43]. Proteoglycan turnover may be increased with low lubricin values because decreased levels have been consistently associated with high sGAG concentrations [6]. Lubricin levels then appear to recover within 1 year after injury [6]; even if once cartilage tissue damage is initiated, it appears to persist over time. These findings support that the initial reduction in lubricin synthesis may initiate a cascade of events leading, over time, to the onset of OA. However, this observation needs further studies to support this hypothesis.

3.3. OA-related lubricin reduction mechanisms

The principal mechanism proposed for the reduction of lubricin synthesis is the degradation activity of neutrophil-derived enzymes and inflammatory mediators present in post-traumatic SF [6]. Some cytokines (IL-1β, TNF-α and IL-6) are associated with the upregulation of proteolytic enzymes such as procathepsin-B, neutrophil elastase and MMPs, which degrade lubricin and lead to loss of synovial fluid chondroprotection, especially in the early stages after injury [6] (Fig. 3). The proteolytic activity seems to be an important link between the inflammatory process and the decreased synovial fluid lubricating ability, which suggests an intimate correlation between these two pathological aspects of OA. In the later stages of injury, other factors such as joint utilization and loss of intra-articular surface congruence may contribute to potentiating this damage. This notion may complicate an

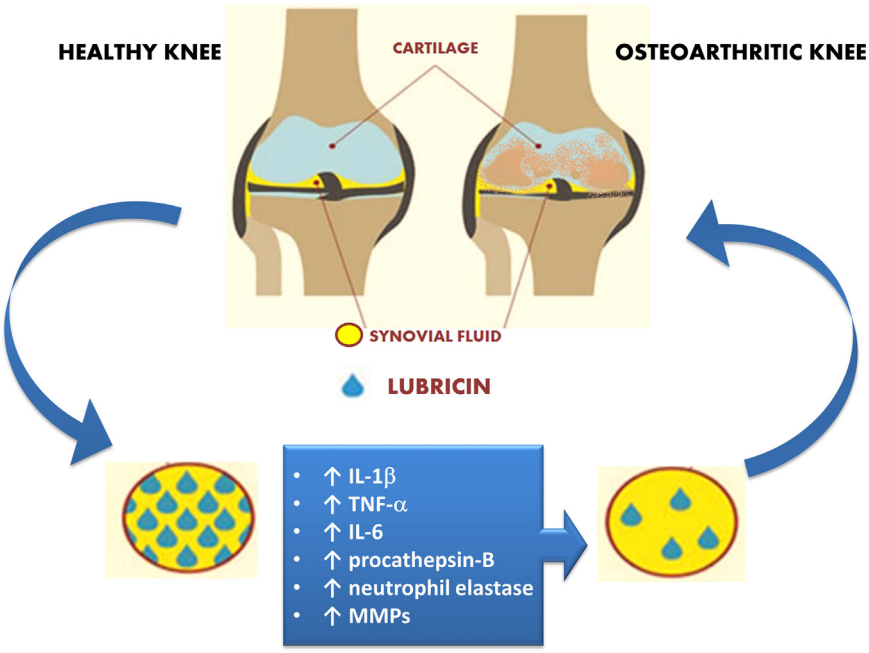

Fig. 3. Schematic representation of the mechanism proposed for reduced lubricin synthesis in knee osteoarthritis (OA). The increased production of pro-inflammatory cytokines (interleukin-1 beta [IL-1β], tumor necrosis factor alpha [TNF-α] and interleukin-6 [IL-6]) is associated with the upregulation of proteolytic enzymes (procathepsin-B, neutrophil elastase and matrix metalloproteinases [MMPs]) that degrade lubricin and lead to loss of synovial fluid chondroprotection and the resulting onset of OA.

understanding of the real sequence of catabolic events that occur during OA onset [42].

The involvement of lubricin in OA disease and inflammation can be identified by its glycosylation. One study [44] reported that lubricin presents an altered glycosylation profile in OA samples, in which decreased sialylation was observed. This phenomenon was associated with decreased lubricating ability, due to the reduced negative charge density on the surface of lubricin, given by the disialylated structures. In fact, more acid residues may enhance the lubricating ability of lubricin via the increased repellent charge forces [45]. Moreover, approximately 50% of lubricin O-glycans contain terminal galactose, a potential ligand for galectins. Galectin-3 level was found increased in OA chondrocytes and may be involved in the cartilage remodelling process [46]. Another attractive glyco-epitope on lubricin is sialyl Lewisx, which indicates the L-selectin binding ability. L-selectin has been found involved in leukocyte trafficking. Lubricin can bind to polymorphonuclear granulocytes (PMNs) or neutrophils, which use L-selectin to roll along the endothelium in the initial phase of the adhesion cascade [47]. Furthermore, PMNs are recruited to the inflamed synovial area, where they probably play an important role in the cartilage degeneration, maintaining a coat of lubricin. These findings imply a role of lubricin in PMN-mediated inflammation in an L-selectin-dependent and independent manner [48].

4. Therapeutic approaches for OA

4.1. Anticytokine therapy

The most evident approach in this field is represented by the anticytokine therapy based on the fact that initiation and progression of articular cartilage destruction primarily involve pro-inflammatory and catabolic cytokines, especially IL-1β and TNF-α [48]. Animal models of OA confirmed that IL-1β inhibition by the IL-1 receptor antagonist (IL-1RA) showed reduced cartilage destruction [49]. Experimental OA was also inhibited by *IL-1RA* gene transfer, which results in the increased expression of IL-1RA in the synovial membrane, thereby diminishing edema, pain and radiological alterations in horses [50]. A human case report described the successful treatment of inflammatory knee OA with adalimumab, a TNF-α inhibitor, with significant reduction in synovitis and synovial effusion and complete resolution of bone marrow oedema [51]. In the study of rats, blocking TNF-α led to increased total lubricin level in the joint, which suggests improved chondroprotective ability. Early inhibition of TNF-α restored lubricin in synovial fluid and on the surface of articular cartilage, lowered the whole joint coefficient of friction and limited cartilage damage [10]. Another approach is the use of antibodies against nerve growth factor (NGF). NGF is a major mediator of inflammatory and neuropathic pain, for a new therapeutic target [52]. In a 2010 study, a phase II trial, tanezumab reduced pain and stiffness in patients with knee OA [53]. Subsequently, a phase III trial studied the efficacy and safety of this monoclonal antibody. Other monoclonal antibodies against NGF have been developed and 2, fulranumab and fasinumab, have been studied in terms of OA. Inhibition of NGF by these antibodies reduced pain and increased the function and well-being of patients with symptomatic OA. All 3 antibody preparations have reported efficacy, although additional studies are required for fulranumab and fasinumab to determine the optimal dose for clinical use and to limit their adverse side effects [54]. Indeed, increasing doses of anti-NGF antibodies has been associated with the syndrome of rapid progression of OA, characterized by chondrolysis and bone destruction [55]. Recently, the anti-inflammatory effect of pituitary adenylate cyclase-activating polypeptide (PACAP), a neuropeptide with trophic effects, was assessed in OA rat models. PACAP levels were decreased in OA cartilage and synovial fluid as compared with controls. Moreover, in vitro, PACAP could prevent IL-1β-induced chondrocyte apoptosis, which suggests its possible therapeutic use in treatment of OA [56].

4.2. Recombinant lubricin

Intra-articular recombinant lubricin supplementation has been advocated as a potential new therapeutic modality for this pathology [57,58]. In a rat model of OA, intra-articular injection of a novel recombinant lubricin protein construct resulted in effective binding to cartilage surfaces and facilitation of both cartilage boundary lubrication and inhibition of synovial cell adhesion, for significant chondroprotective effects during the progression of OA [59]. The positive results of intra-articular injection of recombinant lubricin have been confirmed by a rat study of anterior cruciate ligament injury, showing reduced cartilage damage and collagen type II degradation after treatment [60,61]. In a recent study of ovariectomized rats, both early and late recombinant lubricin treatment attenuated the onset of OA by balancing the interplay between articular cartilage and subchondral bone. The best results were shown with early treatment. Specifically, recombinant lubricin treatment protected articular cartilage against degeneration, as demonstrated by reduced proteoglycan loss and OARSI score, less calcification cartilage zone and reduced immunostaining for collagen X and MMP-13 but increased expression of lubricin. Chondroprotective effects of lubricin normalized bone remodelling in subchondral bone underneath, which in turn attenuated the articular cartilage erosion [62]. However, this therapeutic approach is often limited by its short half-life. To remedy this problem and to ensure long-term expression of PRG4 and chondroprotection in OA, the use of intra-articular, *helper-dependent adenoviral virus* (*HDV*) gene transfer delivering PRG4 was proposed recently [41]. The latter showed protection against both post-traumatic and age-related OA, without significant adverse effects on cartilage development. Recently, a study evaluated the binding of recombinant human PRG4 (rhPRG4) to CD44 receptor and its consequences on cytokine-induced synoviocyte proliferation. PRG4 (lubricin) was found a novel putative ligand for CD44 and may control synoviocyte overgrowth in inflammatory arthropathies via a CD44-mediated mechanism [63].

4.3. Physical activity

Physical activity covers not just sports but also simple everyday movements such as housework, walking and playing. Regular exercise has a great importance in maintaining good health, balance, and posture; indeed, inactivity is a risk factor for different chronic diseases [64,65]. Regular physical exercise is normally suggested with non-communicable chronic disease (NCD) for its specific effects in reducing cardiovascular risk factors and in anti-inflammation, the principal component of many chronic diseases [66]. In our recent study, we investigated a possible preventive treatment for OA involving a combination of the Mediterranean diet, based on consumption of olive oil, and mild physical activity. The beneficial effects of extra-virgin olive oil have been widely studied owing to its anti-inflammatory properties. Therefore, we studied the role of a diet based on extra-virgin olive oil coupled with moderate physical activity on inflammation and the expression of lubricin in rat articular cartilage after induced OA. The effects of injury greatly decreased the expression of lubricin and increased that of IL-1 in rats; after the diet with extra-virgin olive oil supplementation and physical activity, the levels returned to normal as compared to controls [11]. Therefore, mild physical activity may improve lubrication by promoting lubricin synthesis and preventing cartilage degeneration in rats. These findings are supported by our 2 previous studies showing that physical activity increased joint mobility and lubricin expression, for enhanced lubrication of articular surfaces in aged rats [67] and beneficial effects of physical activity on the articular cartilage of rats with glucocorticoid-induced osteoporosis [38]. In both studies, the expression of lubricin was increased after moderate physical activity. These findings are also supported by several other studies. Ogawa et al. demonstrated that running induced maximal expression of lubricin in the superficial zone of articular cartilage in a COX-2-dependent manner, which underlies a positive effect of mechanical motion on lubricin expression [68]. Furthermore, the effect of mechanical factors on lubricin metabolism in vivo was also reported by Ni et al. in aiming to understand alterations in cartilage lubricin expression and immunolocalisation after treadmill treatment with different intensities in a rat model. The authors observed a marked intensity-specific effect of running on lubricin immunolocalisation and gene expression in cartilage, which was inversely proportional to the Mankin score [69]. Elsaid et al. evaluated the impact of forced joint exercise after acute joint injury on lubricin metabolism, which decreased lubricin expression and increased cartilage degeneration. The same study also aimed to assess a single-dose of purified human lubricin injection in exercised injured joints, which resulted in chondroprotection and preserved superficial zone chondrocyte viability [70]. All these results suggest that mechanical stimulation in the articular cartilage could induce the expression of lubricin, which can prevent cartilage degeneration and might be used to slow the development of OA in joint tissues [71–73].

To conclude and to further underline the importance of physical activity in the treatment of OA, we report some of the numerous on-going clinical studies regarding this practice. Murphy et al. [74] are examining the effectiveness of a tailored activity-pacing intervention on fatigue, pain, and physical function in people with knee and hip OA. The activity-pacing intervention was designed to help people modulate their activity levels and reduce OA symptoms associated with too much or too little physical activity. This trial will determine whether activity-pacing is more effective than usual care and whether fatigue and pain is ameliorated more with an individually tailored than general activity-pacing approach. Another recent on-going pilot randomized controlled trail of physical activity is being carried out by Linda Li at the University of British Columbia. The primary goal is to assess the feasibility and preliminary efficacy of a multi-component intervention/model of care involving a group education session, use of the Fitbit Flex (a wireless physical activity tracking device), and weekly telephone counselling by a physiotherapist to improve physical activity and reduce sedentary time in patients with knee OA (ClinicalTrials.gov, NCT02313506).

5. Conclusions

Recent research has uncovered the multiplicity, complexity, and multilevel nature of the inflammatory and degradative processes that occur in OA. Increasingly, inflammatory mediators are considered to participate in the onset and progression of OA. As outlined in this paper, the studies reviewed support that the development of this disease is closely related to inflammatory processes, reduced levels of lubricin, and impaired lubricating ability of synovial fluid. Several therapeutic approaches [75] aim to solve, slow down or improve the joint condition after acute injury, including anticytokine therapy, intra-articular supplementation of recombinant lubricin and physical activity, which suggest new horizons for the treatment of this complex disease. Future research in this field should focus on the development of new therapies that attenuate inflammation and stimulate lubricin production. This approach may support joint tribology and synovial lubrication leading to improved joint function and pain relief.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

This study was supported by grants provided by FIR 2014-2016 (grant No. 314509), University of Catania, Italy. The authors thank Professor Iain Halliday for commenting and making corrections to the paper. A.M. is the co-ordinator of the D-BOARD Consortium funded by European Commission Framework 7 programme (EU FP7; HEALTH.2012.2.4.5-2, project number 305815, Novel Diagnostics and Biomarkers for Early Identification of Chronic Inflammatory Joint Diseases). A.M. is a member of the Applied Public-Private Research enabling OsteoArthritis Clinical Headway (APPROACH) consortium, a 5-year project funded by the European Commission's Innovative Medicines Initiative (IMI). APPROACH is a public-private partnership directed towards osteoarthritis biomarker development through the establishment of a heavily phenotyped and comprehensively analyzed longitudinal cohort. The research leading to these results received partial support from the Innovative Medicines Initiative (IMI) Joint Undertaking (grant No. 115770), with financial contribution from the European Union's Seventh Framework programme (FP7/2007-2013) and EFPIA companies in kind contribution. A.M. is also a member of the Arthritis Research UK Centre for Sport, Exercise, and Osteoarthritis, funded by Arthritis Research UK (grant No. 20194). A.M. has received funding from the Deanship of Scientific Research (DSR), King AbdulAziz University (grant No. 1-141/1434 HiCi). The decision to submit this paper for publication was not influenced by any of the funding bodies. Furthermore, the funders had no role in study design, data collection and analysis.

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