Chapter 3
Osteoarthritis: Trauma vs Disease

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Abstract Osteoarthritis (OA) is the most prevalent joint disease characterized by pain and degenerative lesions of the cartilage, subchondral bone, and other joint tissues. The causes of OA remain incompletely understood. Over the years, it has become recognized that OA is a multifactorial disease. In particular, aging and trauma are the main risk factors identified for the development of OA; however,

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J. M. Oliveira et al. (eds.), *Osteochondral Tissue Engineering*,
Advances in Experimental Medicine and Biology 1059,
https://doi.org/10.1007/978-3-319-76735-2_3

other factors such as genetic predisposition, obesity, inflammation, gender and hormones, or metabolic syndrome contribute to OA development and lead to a more severe outcome. While this disease mainly affects people older than 60 years, OA developed after joint trauma affects all range ages and has a particular impact on young individuals and people who have highest levels of physical activity such as athletes. Traumatic injury to the joint often results in joint instability or intra-articular fractures which lead to posttraumatic osteoarthritis (PTOA). In response to injury, several molecular mechanisms are activated, increasing the production and activation of different factors that contribute to the progression of OA.

In this chapter, we have focused on the interactions and contribution of the multiple factors involved in joint destruction and progression of OA. In addition, we overview the main changes and molecular mechanisms related to OA pathogenesis.

Keywords Osteoarthritis · Posttraumatic osteoarthritis · Risk factors · Joint trauma

Highlights

- OA is a multifactorial disorder and is associated with pathological changes in all joint tissues; thus, OA is considered a whole-joint disease.
- Factors that contribute to the development of OA include joint injury, obesity, aging, inflammation, genetic predisposition, gender and hormones, or metabolic syndrome. Among these factors, collective evidence indicates that aging and trauma are pivotal factors that mark OA progression.
- Comprehensive understanding of the molecular networks regulating articular cartilage homeostasis and OA pathogenesis is needed for the development of novel treatments for preventing cartilage damage and promoting repair.

3.1 Introduction

Osteoarthritis (OA) is the most prevalent joint disease characterized by pain and degenerative lesions in the cartilage and in the tissues within and surrounding the joint involved. OA has a high prevalence in the population, and it is accompanied by significant morbidity and physical disability [67]. It has been estimated that approximately 25% of the population over 18 years old is affected [22]. So far, it is also predicted that 35% of people will eventually suffer disability due to OA by 2030, and this number is expected to further expand [110]. Owing to the high incidence of this disease among population, required therapies have a substantial public health impact [87].

Any joint in the body can suffer from OA, but major joints such as the knee and hip are most commonly affected. Current OA therapies include pain management and surgical intervention for end-stage OA patients, but there are no effective therapies which can effectively prevent or reverse the progression of the disease.

Despite OA has received a lot of attention in clinical research, more studies are needed to increase our understanding of the molecular mechanism, and the etiology of this complex disease, only then the development of effective treatments will be much closer.

OA is characterized by degenerative lesions of the cartilage, but also other tissues of the joint are involved in the complex initiation and progression of the disease; thus, progression of OA also involves subchondral bone remodeling, the formation of osteophytes, the development of bone marrow lesions, and changes in the synovium, joint capsule, and ligaments (Fig. 3.1) [131].

Although OA ultimately ends to a common phenotype consisting of chronic pain, joint instability, stiffness, and loss of function, it results from a number of different etiologies. Among the multiple factors that contribute to the development and progression of OA are joint injury, obesity, aging, inflammation, and genetic risk factors [77]. Moreover, OA risk increases with the presence of other factors including gender and hormones or metabolic syndrome.

While most of the OA is idiopathic and mainly affects people older than 60 years, the risk of OA following a significant joint trauma is especially prevalent in patients at younger age and highly active individuals [6, 58]. Traumatic injury to the joint often leads to joint instability or intra-articular fractures which in the long term end in OA. The OA which is initiated after a joint injury is called posttraumatic

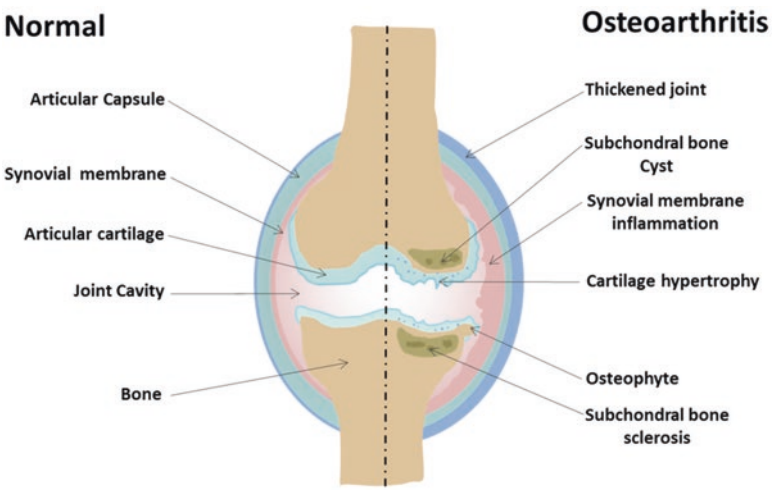

Fig. 3.1 Progression of osteoarthritis. On the left, cross section of the normal articular joint illustrates the main structural elements including the articular cartilage covering the surface of the subchondral bones and enclosed in a connective tissue capsule lined by a synovial membrane. On the right, cross section of the OA articular joint showing advanced osteoarthritic changes characterized by subchondral bone remodeling, subchondral cysts, the formation of osteophytes, cartilage hypertrophy, fissuring and fragmentation of the articular cartilage, inflammation of the synovial membrane, and joint thickening

osteoarthritis (PTOA) [81]. It is estimated that approximately 12% of all OA is a result of an injury insult, such as an articular fracture, chondral injury, or a ligament or meniscal injury [17].

Although joint trauma affects the entire joint to some degree, damage to articular cartilage is commonly the most relevant pathologic feature and primary change after joint injury and prior to joint dysfunction [16, 66]. Damage to articular cartilage leads to an imbalance of articular cartilage homeostasis which leads to the appearance of a sequence of biologic events. The chondrocytes produce and maintain the physical function of cartilage by synthesizing and degrading matrix components. In response to environmental changes, such as mechanical stress or inflammatory stimuli, the stable phenotype of the chondrocytes shift toward a catabolic phenotype increasing the production and activation of different factors that actively participate in the degeneration process [123].

In this chapter, we discuss the multiple factors involved in joint destruction, development, and progression of OA with special interest in the impact of trauma injury on OA. In addition, the identification of the molecular mechanisms related to OA pathogenesis and main changes in composition and structure of joint tissues involved are discussed.

3.2 Changes During Osteoarthritis Progress

Articular cartilage is a unique tissue composed of chondrocytes (the only cell present in cartilage) embedded in a highly hydrated extracellular matrix of collagen fibers and proteoglycans together with other non-collagenous proteins and glycoproteins present in lesser amounts [104]. Under normal conditions, chondrocytes are resting in a nonstressed steady state with low turnover conditions. In response to environmental changes such as changes in biomechanical forces, growth factors, or cytokines, chondrocytes increase its metabolic activities, and the molecular composition and organization of the extracellular matrix are altered. Factors such as age, obesity, genetic predisposition, joint instability, repetitive stress injury, or inflammation are known to disrupt the articular chondrocyte homeostasis [77].

Loss of cartilage function and quality can occur due to trauma resulting in focal or diffuse loss of cartilage or as a consequence of aging cartilage involved in the osteoarthritic process [66]. The precise molecular mechanisms of OA initiation and progression are poorly understood. However, there has been an increasing literature describing multiple growth factors and cytokines involved in the destruction of articular cartilage and subchondral bone [65]. Once the microenvironment changes, the alteration in the normal physiologic balance of cartilage tissue leads to abnormal function of chondrocytes. At early changes in cartilage tissue, chondrocytes initiate the release of oxygen free radicals which contribute to initiate progressive

tissue damage [97]. Several studies have also reported the release of fibronectin fragments that induce cell damage and matrix degradation [50]. A large number of proteins and genes show altered expression in OA cartilage compared with that in cartilage from individuals without OA. For example, transforming growth factor-β (TGFβ) has been shown to be involved in OA progression. While it is known that TGFβ is expressed at low levels in mature cartilage, the expression TGFβ and signaling have been seen upregulated in OA [124]. Moreover, OA chondrocytes increase the expression of hypertrophic markers such as Runx2 and ColX [89]. Inflammatory mediators released from the synovium can also contribute to the cartilage pathology in OA [89]. Therefore, the immediate release of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-1 from the synovium or from the traumatized chondrocytes themselves induces a positive feedback loop [65]. This disturbed balance also induces chondrocytes to produce matrix metalloproteinases (MMPs), aggrecanases, and other proteases, which lead to increased cartilage matrix degradation [131].The pivotal proteinase that marks OA progression is MMP-13, the major type II collagen-degrading collagenase, which is regulated by both stress and inflammatory signals [43]. In vivo studies showed that joint injuries increase the levels of metalloproteinases in synovial fluid [88]. Other catabolic enzymes such as ADAMTS5 and MMP-8 are implicated in the degradation of articular cartilage structure by cleaving the aggrecan and collagen II matrix [39].

The release of these degradative enzymes and other collagenases in joints leads to proteoglycan and collagen network breakdown which degrade the structure of articular cartilage and result in functional abnormality of chondrocytes. Consequently, chondrocytes will undergo apoptosis, and cartilage will eventually be completely lost. Numerous studies provide evidence that chondrocyte death by apoptosis is associated with the initiation and severity of articular cartilage degradation [109]. Following degradation and metabolic changes in joint tissues, the disease slowly progresses through a long clinically asymptomatic latency period to a symptomatic phase with joint pain and dysfunction. Advanced OA degeneration is associated with increased damage to cartilage and loss of type II collagen. Loss of cartilage causes friction between bones. The progressive damage of bones will cause pain and limited joint mobility. Bone remodeling and loss/degeneration of cartilage are considered central features of OA [39]. Indeed, subchondral bone has received increasing attention in OA progression, and several studies evidence that abnormalities in subchondral bone can induce joint pain and cartilage degeneration. Moreover, changes in subchondral bone could be observed even preceding cartilage lesions, and clear evidence of an association between subchondral bone mineral density and OA have been described [41]. However, the pathological changes and the role of subchondral bone in OA still require further investigation. Other pathological changes seen in advanced OA include degeneration of ligaments and menisci of the knee and hypertrophy of the joint capsule [24].

3.3 Factors that Contribute to the Development of OA

3.3.1 Joint Trauma

Patients with OA due to a joint trauma normally have a well-defined damage to the structures of the articular joint. When we talk about joint trauma, we refer mainly to those lesions that affect the articular cartilage and/or the associated subchondral bone. Numerous studies have demonstrated that joint trauma is one of the main risk factors for the development of OA. It has been demonstrated that articular fracture is associated with a loss of chondrocyte viability and increased levels of systemic biomarkers [62]. Studies have indicated that focal loss of chondrocyte viability is an initiating pathway for development of PTOA [80]. Moreover, increased intra-articular trauma severity is associated with increased acute joint trauma in a variety of joint tissues, including synovial and bone [6]. Following joint trauma, the acute symptoms include swelling of the affected joint area due to the rupture of the vessels adjacent to the joint that causes hemorrhage in the interstitial space and, consequently, the formation of a hematoma. If the injury also affects the subchondral bone, the bone marrow will be probably involved. An early consequence after the initial injury is chondrocyte death. In addition, certain enzymes are released causing an inflammatory reaction in the affected area and an accumulation of fluids out of the vessels, which result in an increased volume of the knee joint and edema [4]. Hence, acute impact joint injuries initiate a sequence of biologic events that cause the progressive joint degeneration and can lead to the development of OA [6].

The main sign of OA due to joint trauma is the pain which is predominantly related to an unfavorable biomechanical environment at the joint. Diagnosis varies according to the intensity of the trauma and the presence of soft tissue injuries or bone injures. In addition to pain, within the anamnesis, it is important to evaluate signs of inflammation that can be observed in the joint. The right diagnosis and early treatment can slow and prevent further joint damage. The nontreatment or wrong treatment may lead to joint deterioration, poor function, and compromised mobility [63]. For the diagnosis of joint trauma, it is also important to perform imaging tests such as radiography. However, radiography is very limited as it only gives indirect information of the cartilage through the image of the subchondral bone. If another imaging test is needed, computed tomography (CT) is recommended in order to study any possible loss of osteochondral fragments [13].

Acute injuries are common in young, active, and athletic individuals, but diagnosing OA in these populations has become a challenge due to their higher tolerance for pain [5]. In both professional athletes and sports fans, the most frequent cause of OA is joint overload, excessive training, or the use of incorrect techniques that cause damage to the joints. The joints that are most frequently affected are the hip and the knee as they are the ones that carry the greatest weight during the performance of the workouts; however, we should not rule out also injuries to the elbow or foot [8]. It is important to take into account that physical activity cannot be forced and that it is necessary to avoid overloads in the same area of the body.

Typically, the most common injuries that cause PTOA include chondral and osteochondral lesions, articular fracture, ligamentous lesions, or fibrocartilage lesions, among others.

3.3.1.1 Joint Injuries that Cause PTOA

Chondral and Osteochondral Lesions

The hyaline cartilage is supported by the subchondral bone. In this way, we must differentiate two types of acute lesions, hyaline cartilage lesions and lesions produced in subchondral bone [14]. However, loss of hyaline cartilage usually appears in subchondral bone lesions. The extension of the lesion depends on the intensity of the trauma and the affected structures. When a relevant injury without fracture occurs, there is an overload of the subchondral bone tissue, which causes a progressive wear of the joint [63]. Chondral injuries include abrasion, laceration (cut), or fracture. Because cartilage is an avascular and aneural tissue, the articular cartilage has a poor intrinsic healing capacity. After a chondral injury, cartilage is incapable of directly generating pain. Depending on the size and location of the chondral injury, evolution can lead to further degeneration and a great loss of cartilage surface [63].

On the other hand, when an injury to the subchondral bone occurs, the joint is filled with blood arising from the bone marrow leading to an inflammatory process. Consequently, a reparative reaction will occur due to the exposure of the joint to blood and marrow contents, and matrix will be repaired; however, a fibrocartilage tissue without the same characteristics as original articular cartilage and with reduced mechanical properties will be formed [63].

Articular Fracture

Articular fracture is a very common injury due to the high percentage of injuries caused during minor accidents. In vivo models have demonstrated that articular fracture includes physical disruption of the articular surface and underlying subchondral bone with varying degrees of severity depending on the intensity of the impact. Clinically, more complex intra-articular fractures are associated with patients with higher severity of trauma and subsequent degeneration of the articular cartilage; moreover, these injuries are closely linked with worse outcomes for the patients [17]. Articular fracture treatment includes restoration of the articular surface, correction of axial and rotational alignment of the injured limb, and surgical fixation for stabilization to allow early range of motion of the injured joint [80].

Ligamentous Lesions

Ligaments are important structures to maintain the stability of the articulation but are at risk to be injured in traumatic injuries. Knee ligamentous injuries increased injury to the patient, especially if they are unrecognized and untreated, and can lead to significant morbidity. Common diagnostic procedure to find out and confirm capsule-ligamentous lesions includes arthroscopy of the knee which is preferred compared with magnetic resonance (MR) imaging due to its ability to probe, distinguish fragile tissue from normal, and perform additional surgical procedures like removal of loose bodies [14]. Most common ligamentous injuries typically include the anterior cruciate ligament (ACL) and medial collateral ligament (MCL) [99]. Patients with these lesions and/or without a concomitant meniscus injury are at high risk for PTOA. Sports injuries are the most frequent cause of anterior cruciate ligament injuries [60].

Meniscal Lesions

Unlike hyaline cartilage, the collagen present at articular fibrocartilage is oriented variably and contains little density of proteoglycans and less presence of water. Consequently, articular fibrocartilage is less compliant and presents less capacity of regeneration. The greater number of fibrocartilage lesions often occurs at menisci of the knee, glenohumeral input, and triangular fibrocartilage of the wrist [126].

Meniscal lesions are the most common knee injuries seen in patients of all ages and especially in young or adolescent patients due to trauma. These lesions are a recognized risk factor for the development of OA. Commonly, the mechanism of injury involves a twisting injury on a semi-flexed limb through a weight-bearing knee. Overpressure on the knee due to overweight, intensive training, incorrect position of the legs such as varus or valgus, or reduced muscle strength is a typical risk factor for meniscus lesions [100]. Advances in the knowledge of meniscal anatomy, biomechanics, and function are essential to understanding meniscal pathology and treatment [2, 100]. Meniscectomy still remains as a common orthopedic procedure; however, meniscal repairs are increasingly performed over meniscectomies in young patients [1].

3.3.2 Aging

Age has been identified as one of the most important risk factors for the development of OA. The incidence and prevalence of OA increase with aging due to the combination of various risk factors, together with biological changes that lead to broke the homeostasis of the joint resulting in less capacity for healing [3, 66]. For instance, ACL injury is a cause of PTOA, and the progression of this PTOA has been seen to increase with patient age [94]. Seon et al. [99] have shown that the 54%

of the patients over 25 years at the time of ACL surgery developed OA, in front of the 26% below 25 years old [99].

The main factors affecting age-related changes include cellular senescence, reduced cell density, and altered secretory profiles [70]. The decrease in cell density is a direct consequence of cellular senescence, which is characterized by the loss of cell division capacity [111]. There are several processes that affect cell senescence such as the shortening of the telomeres [46], mitochondrial and nuclear DNA damage [15, 55], oxidative stress [68], and inflammatory process [44]. Moreover, reduced repair capacity of the cartilage increases with aging, due to the lesser capacity of chondrocytes to respond to growth factor stimulation to proliferative and anabolic process [66, 70]. For example, lower sensitivity to the stimulation with the TGFβ [57], insulin-like growth factor 1 (IGF-1) [64], and bone morphogenetic protein family (BMPs) [12, 24] leads to induced oxidative stress and prevalence of catabolic process over anabolic.

Apart from cellular changes, ECM also experiment age-associated alterations that lead to develop OA, such as the progressive calcification of cartilage that occurs before evidence OA [75]. In addition, it has been demonstrated that with aging there is a marked increase in the formation of advanced glycation end products (AGEs), which are the results of spontaneous nonenzymatic glycation of the proteins. AGE formation increase the cross-linking of collagen molecules which altered the mechanical properties of cartilage, making it more susceptible to mechanically induced damage [32, 116]. Moreover, the interaction of AGEs with cellular receptors, including the receptor for AGEs (RAGE), displayed an increment in inflammation [20] and catabolic process [108, 125].

3.3.3 Obesity

Obesity is a strong risk factor associated with development and progression of OA, especially in knee OA [36]. Moreover, the overweight increases the development of osteoarthritic processes after knee trauma [119], specifically after fixation of acetabular fractures [59, 84].

It is assumed that behind the influence of obesity on OA is mechanical overload because the joint of overweight person endures the transmission from two to five times the body weight during the course of the day, leading to wear, damage, and microtrauma [33, 74]. Apart from the increment of the mechanical loading, obesity contributes to OA through the secretion of adipose tissue-derived cytokines, called adipokines, such as a variety of interleukins (IL-1β, IL-6, IL-8, IL-15, etc.), tumor necrosis factor alpha (TNF-α), leptin, and adiponectin, among others [28]. These inflammatory factors lead to bone resorption and ECM changes through the downregulation of the synthesis of the major components of the matrix (proteoglycans and type II collagen) and the upregulation of catabolic process across the activity of MMPs and a disintegrinlike and metalloproteinase with thrombospondin type 1 motifs (ADAMTS) [28, 53].

It has been established that if obese patients with OA lose weight can reduce pain, improve the function of the joint and might reduce disease progression [23, 61]. Even, there are studies that support the use of specific strategies to weight loss in the treatment of these patients 11,121].

3.3.4 Genetic Factors

An inherited predisposition to develop OA has been established from family-based studies that supports the strong link between the genetic factors and this disease. Studies with twin have estimated a genetic influence ranging from 30% to 65% in OA, with larger influence in hands and hips, and smaller in knees [56, 73, 106]. Moreover, linkage studies with families and sibling have suggested loci linked to hip and knee OA in an area of chromosomes 2q and 11q. Related with the loci in chromosome 2q, the regions 2q 12–22 and 2q 33–35 contain genes that could be involved in the OA, like the gene for the α2 chain of type V collagen (a major component of the bone) and fibronectin, and the receptor of IL-8 (inflammatory process) [71, 122]. In relation with chromosome 11q and the susceptibility to develop OA, it has identified a cluster related with at least seven MMP genes and a locus that is a regulator of bone mass [21]. In addition, studies in families with primary OA have detected loci on chromosomes 4, 6, and 16 [40, 72], and more recently, genome-wide association studies (GWAS) have been established loci on chromosomes 3 [76], 7 [54], 13 [31], and 19 [19] that are strongly associated with hip or knee OA susceptibility.

On the other hand, the role of specific genes involved in OA has been demonstrated by in vitro or in vivo studies. For example, in vitro gene analysis of patients and transgenic mice displayed the impact of an alteration in ECM components, (such as type II collagen and COMP), its regulators (aggrecanases), and how it contributed to the degeneration of knee joint [92, 95, 96]. In addition, development and progression of OA can be induced by alterations in signaling pathways like TGFβ/BMP [98, 131], Wnt/β-catenin [112], Indian hedgehog [18], hypoxia-inducible factor (HIF) 1α/HIF-2α [129], nuclear factor-kappaB (NF-κB) [91], and Notch [51] pathways and its downstream molecules [114] that leads to cartilage destruction. The knowledge of the genetic factors that induce or maintain osteochondral defects is a promising therapeutic strategy for novel treatments.

3.3.5 Inflammation

Over the past decade, inflammation has been established as a critical feature of OA. Many studies are opening the way to consider inflammation a key driver of OA progression after joint injury [7]. According to current research, such involvement in the pathophysiology of OA would occur through the action of

inflammatory mediators [10] released by the cartilage, bone, and synovium. These mediators, such as cytokines (IL-1β, TNF-α, IL-6, etc.) and chemokines (IL-8, CCL5, CCL19, and its receptor CCR7), are produced by a variety of cell types, including macrophages, chondrocytes, and fibroblast-like synoviocytes (FLS), in response to joint trauma or chronic overuse injuries. Another source of these cytokines could be chronical inflammatory process associated to age or derived from previous injuries [7, 22, 103]. In addition to traditional mediators, it has been also found the presence of adipokines such as leptin in inflammation processes [28]. All these soluble signaling factors cause alteration of joint cell homeostasis such as pathological maturation, apoptosis, and catabolic responses by means of metalloproteinases (MMPs), prostaglandin E2 (PGE2), or nitric oxide (NO) synthesis, leading to cartilage degradation and subchondral bone remodeling. Moreover, the release of these inflammatory mediators causes alteration of joint cell homeostasis generating a loopback that would aggravate or accelerate joint degeneration [90, 93, 118].

In this way, having an inflammation either attributed to previous injuries, obesity, or age would have an increased risk to develop, aggravate, or accelerate OA progression, after tissue damage. Results from image studies using MRI and ultrasonography have evidenced a positive correlation between inflammation and the risk for structural progression of OA [37, 47, 83]. Similarly, in vivo studies have reported the association between increased serum levels of adipokines and greater cartilage loss with a higher incidence of knee joint replacement [61].

The knowledge of inflammation role in OA development and mechanisms by which it acts has provided a window of opportunities to develop disease-modifying interventions targeting inflammatory processes for the prevention and treatment of OA. In vivo and clinical studies performed so far have mainly focused on TNF and IL-1 inhibitor showing clinical symptom relief but did not achieve to stop the disease progression [69]. Then, is necessary to take into account other factors that contribute to OA development, and also the heterogeneity of the OA patients, since their phenotypes may have different pathophysiology.

3.3.6 Metabolic Syndrome

Metabolic syndrome (MetS) is a common phenotype comprised of a cluster of metabolic disorders, such as hypertension, insulin resistance, visceral obesity, and dyslipidemia, that occur together, increasing the risk of developing serious chronic disease [132]. Researchers have suggested a positive association between OA and the four central components of MetS, since epidemiological and clinical data revealed a high prevalence in patients with OA, regarding the population without OA [86, 102, 105, 115, 127]. In addition, people with MetS develop OA at an earlier age, and have more generalized pathology with higher inflammation and pain, in comparison with patients with OA in the absence of MetS [34, 86]. Thus, all these disorders have led to consider metabolic syndrome an important risk factor for OA.

During these last years, investigators are assessing how all these components that make up MetS are involved in OA. Studies have shown that all these conditions end up causing cellular damage and subsequent inflammation that, as explained in the previous section, leads to the OA development [52, 132]. Hypertension contributes to OA through subchondral ischemia that results from blood flow reduction related to narrowing of blood vessels [38]. Association between dyslipidemia and OA has also been reported, thus, the disturbance of lipid metabolism increase the risk of OA [42]. Moreover, obese people could display elevated levels of systemic oxidative stress that can be caused by insulin resistance, through hyperglycemia [29, 48, 49, 78]. This condition of local high glucose concentration can also contribute to OA by reduction of chondrocyte differentiation, therefore, decreasing the potential cartilage regeneration [30, 113]. Hence, diseases that derive from insulin resistance state such as type 2 diabetes have been robustly associated with OA in epidemiological studies [9, 29]. Concordant results from clinical studies have also reported a higher rate of knee OA progression in type 2 diabetes patients than nondiabetics on a 3-year follow-up [35]. Otherwise, visceral obesity associated to MetS, contributes directly to inflammation state due to an increase in adipokine concentration that leads to the OA development [85, 132].

So, the link of MetS to OA suggests that control or prevention of MetS conditions would modulate OA progression in humans, for example, by promoting reduction of adipose tissue in obese patients [27, 128].

3.3.7 Gender

Besides excess weight, obesity, and previous knee injury, the onset of knee OA has also been associated with female gender. Unfortunately, it represents a nonmodifiable risk factor that leads to increased susceptibility and predisposition to develop OA. Numerous clinical, pathological, and epidemiological studies of OA suggest relevant difference between sexes. Women not only have higher prevalence than men, but they also have greater severity of OA [107]. In addition, the definite increase in OA in women around the time of menopause has led investigators to hypothesize that hormonal factors, in particular estrogens, may play a role in the development of OA [101]. Further support for a hormonal effect on OA comes from some, but not all, studies which have shown a higher prevalence and incidence of OA in women with hysterectomy than without it [26].

Although a lot of studies are addressing the relation between estrogens and OA, it is still not clearly defined, appearing to be concentration dependent. Despite the controversial results, the overall effect predominantly leads to inhibition of the expression and secretion of proinflammatory cytokines into the joint. It has been evidenced both in vitro and in vivo studies [90]. However, results from observational studies and clinical trials have been conflicting regarding this effect, especially about estrogen therapy [45, 79, 120].

Moreover, the disparities between sexes may be also due to the differences in the anatomical structure of joint elements, in height, weight, or just a thinner and more reduced volume of knee cartilage in women compared with that of men. Therefore, more studies are needed to evidence the role of hormones in OA and resolve these issues.

3.4 Treatment of Osteoarthritis

Currently, no available treatments are able to cure or substantially modify disease progression. In the case of joint trauma, interventions should be addressed as soon as possible to limit the degree of acute joint damage and to reduce the severity of OA [69]. The selection of the treatment depends on the intensity of the affectation. There are several methods to treat traumatic joints that include the following treatments:

Non-operative Management

- Symptomatic medical treatment: control the pain and inflammation by using cryotherapy, analgesics, and anti-inflammatories.
- Decrease early loading of injured articular surfaces after injury.
- Protect from the load to avoid detachment by shearing forces of possible fragments of cartilage detached after the trauma.
- Avoid prolonged rigid immobilization.
- Intra-articular viscosupplementation injections.
- Weight loss and exercise in obese and overweight individuals.

- **Surgical Treatment**

– Surgical management aims to reestablish the joint surface, maximizing the osteochondral biologic environment, achieve rigid fixation, and ensure early motion. The surgical techniques could be either procedures that only address cartilage repair or osteochondral procedures to treat both cartilage and subchondral bone.

- *Chondral and osteochondral defects*: For partial defects simple arthroscopic debridement with or without marrow stimulation (microfracture) is used. In the case of full-thickness defects, microfracture and autologous grafts or allografts are recommended [16]. Autologous grafts involve the extraction of healthy cartilage of the patient and its transplantation to the site of the defect. However, this technique presents several drawbacks such as the graft size limitation and donor site morbidity. In order to prevent greater damage, the cartilage is removed from areas that do not withstand heavy loads, such as the lateral margin of the femoral trochlea and notch of the knee [25].
- *Tissue engineering:* A number of promising cell sources, biocompatible tissue-engineered scaffolds, scaffoldless techniques, biological factors, and mechanical stimuli are currently being investigated in the field of articular cartilage tissue

engineering, which aims to repair, regenerate, and/or improve injured or diseased articular cartilage functionality [130]. For example, autologous chondrocyte implantation (ACI) is the first generation of cell transplantation techniques for cartilage repair and is used widely for patients who have cartilage lesions between 1 cm^2 and 12 cm^2 or had previously failed restoration treatments of the knee such as microfracture surgeries [82].

- *Total and partial joint replacements:* For severe joint injuries as well as for advanced OA, articular cartilage cannot be recovered by any of the above-discussed treatments. In these cases, the damaged osteochondral tissue is partially or totally removed, and total or partial joint replacements are performed to help patients restore normal function. However, joint replacement therapies are not recommended in younger patients due to relatively short life spans of current implants, and revision surgery offers less favorable outcomes [117].

3.5 Conclusions

OA is a complex process without a full understood etiology. Changes observer during progression of OA not only target cartilage tissue, also affect to subchondral bone and synovial tissue. There is a crosstalk between cartilage and bone cells in the course of the disease that play a major role in the joint homeostasis.

Among the risk factors that result in structural and functional failure of joints are joint trauma, obesity, aging, inflammation, genetic predisposition, gender and hormones, or metabolic syndrome. Despite cartilage senescence could be considered part of "normal" chronological age, and represent an important individual risk factor for the development of OA, all risk factors of OA are inter-related, not inter-dependent. In addition to aging, another pivotal factor that marks OA is damage due to trauma.

The majority of individuals with a significant traumatic joint injury develop PTOA. In the young patient, the pathogenesis of knee OA is predominantly related to joint trauma and an unfavorable biomechanical environment at the joint. Once the damage occurs, a sequence of events is initiated at the joint tissues and leads to progressive articular surface damage.

Future treatments must take into account all the specific characteristic of individuals and clinically relevant factors associated like severity of joint injury. Therefore, a multi-varied therapy which includes the knowledge of the OA risk factors of a specific patient could be used to make the clinical diagnosis.

Therapies focused on joint injuries with a clear trauma origin should address the earliest symptoms such as inflammation, stiffness, joint dysfunction, or pain. This is especially important in the young individual since changes in these patients could still be reversible, and therefore, early treatment could prevent further progression of the disease. A need also exists for therapies that stimulate intrinsic repair of the damage tissue and inhibiting catabolic pathways that lead to chondrocyte death and matrix loss.

Acknowledgments This work was supported by Fundación Progreso y Salud (Junta de Andalucía, project number PIN-0379-2016) and by the Ministerio de Economía, Industria y Competitividad (FEDER funds, project RTC-2016-5451-1). G.J. acknowledges the Junta de Andalucía for providing a postdoctoral fellowship. C.A. acknowledges the predoctoral fellowship from the Spanish Ministry of Education, Culture and Sports (BOE-A-2014-13539). Also, E.L-R. acknowledges the MINECO for providing a postdoctoral fellowship through the project RTC-2016-5451-1.

References

1. Abrams GD et al (2013) Trends in meniscus repair and meniscectomy in the United States, 2005-2011. Am J Sports Med 41(10):2333–2339. https://doi.org/10.1177/0363546513495641
2. Ahmad J, Maltenfort M (2017) Arthroscopic treatment of osteochondral lesions of the talus with allograft cartilage matrix. Foot Ankle Int 38(8):855–862. https://doi.org/10.1177/1071100717709571
3. Aigner T, Richter W (2012) OA in 2011: Age-related OA? A concept emerging from infancy? Nat Rev Rheumatol 8(2):70. https://doi.org/10.1038/nrrheum.2011.206
4. Altman R et al (1991) The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 34(5):505–514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2025304 (Accessed: 12 July 2017)
5. Amoako AO, Pujalte GGA (2014) Osteoarthritis in young, active, and athletic individuals. Clinical medicine insights. Arthritis Musculoskeletal Dis 7:27–32. https://doi.org/10.4137/CMAMD.S14386
6. Anderson DD et al (2011a) Post-traumatic osteoarthritis: improved understanding and opportunities for early intervention. J Orthop Res 29(6):802–809. https://doi.org/10.1002/jor.21359
7. Badalà F, Nouri-mahdavi K, Raoof DA (2008) The role of synovitis in osteoarthritis pathogenesis. Bone 144(5):724–732. https://doi.org/10.1038/jid.2014.371
8. Bauer KL, Polousky JD (2017) Management of Osteochondritis Dissecans Lesions of the knee, elbow and ankle. Clin Sports Med 36(3):469–487. https://doi.org/10.1016/j.csm.2017.02.005
9. Berenbaum F (2012) Diabetes-induced osteoarthritis: from a new paradigm to a new phenotype. Postgrad Med J 88(1038):240–242. https://doi.org/10.1136/pgmj.2010.146399rep
10. Berenbaum F (2013) Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthr Cartil 21(1):16–21. https://doi.org/10.1016/j.joca.2012.11.012
11. Bliddal H, Christensen R (2006) The management of osteoarthritis in the obese patient: practical considerations and guidelines for therapy. Obes Rev 7(4):323–331. https://doi.org/10.1111/j.1467-789X.2006.00252.x
12. Bobacz K et al (2003) Expression of bone morphogenetic protein 6 in healthy and osteoarthritic human articular chondrocytes and stimulation of matrix synthesis in vitro. Arthritis Rheum 48(9):2501–2508. https://doi.org/10.1002/art.11248
13. Boesen M et al (2017) Osteoarthritis year in review 2016: imaging. Osteoarthr Cartil 25(2):216–226. https://doi.org/10.1016/j.joca.2016.12.009
14. Borgohain B et al (2014) Risks of concomitant trauma to the knee in lower limb long bone shaft fractures: a retrospective analysis from a prospective study population. Adv Biomed Res 3(1):49. https://doi.org/10.4103/2277-9175.125764
15. Botter SM et al (2011) Analysis of osteoarthritis in a mouse model of the progeroid human DNA repair syndrome trichothiodystrophy. Age 33(3):247–260. https://doi.org/10.1007/s11357-010-9175-3

16. Brittberg M et al (2016a) Cartilage repair in the degenerative ageing knee. Acta Orthop 87(sup363):26–38. https://doi.org/10.1080/17453674.2016.1265877
17. Brown TD et al (2006) Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and burden of disease. J Orthop Trauma 20(10):739–744. https://doi.org/10.1097/01.bot.0000246468.80635.ef
18. Buckland J (2010) Osteoarthritis: blocking hedgehog signaling might have therapeutic potential in OA. Nat Rev Rheumatol 6(2):61–61. https://doi.org/10.1038/nrrheum.2009.270
19. Castaño Betancourt MC et al (2012) Genome-wide association and functional studies identify the DOT1L gene to be involved in cartilage thickness and hip osteoarthritis. Proc Nat Acad Sci USA 109(21):8218–8223. https://doi.org/10.1073/pnas.1119899109
20. Cecil DL et al (2005) Inflammation-induced chondrocyte hypertrophy is driven by receptor for advanced glycation end products. J Immunol (Baltimore, Md: 1950) 175(12):8296–8302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16339570 (Accessed: 25 June 2017)
21. Chapman K et al (1999) Osteoarthritis-susceptibility locus on chromosome 11q, detected by linkage. Am J Hum Genet 65:167–174. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1378087/pdf/10364529.pdf (Accessed: 28 June 2017)
22. Chen D et al (2017a) Osteoarthritis: toward a comprehensive understanding of pathological mechanism. Bone Res 5(august 2016):16044. https://doi.org/10.1038/boneres.2016.44
23. Christensen R et al (2007) Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheumatic Dis BMJ Pub Group 66(4):433–439. https://doi.org/10.1136/ard.2006.065904
24. Chubinskaya S et al (2002) Age-related changes in cartilage endogenous osteogenic protein-1 (OP-1). Biochim Biophys Acta (BBA) - Mol Basis Dis 1588(2):126–134. https://doi.org/10.1016/S0925-4439(02)00158-8
25. Chubinskaya S et al (2015) Articular Cartilage Injury and Potential Remedies. J Orthopaed Trauma 29(Suppl 12):S47–S52. https://doi.org/10.1097/BOT.0000000000000462
26. Cicuttini FM, Spector T, Baker J (1997) Risk factors for osteoarthritis in the tibiofemoral and patellofemoral joints of the knee. J Rheumatol 24(6):1164–1167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9195526 (Accessed: 16 July 2017)
27. Clockaerts S et al (2012) Statin use is associated with reduced incidence and progression of knee osteoarthritis in the Rotterdam study. Ann Rheum Dis 71(5):642–647. https://doi.org/10.1136/annrheumdis-2011-200092
28. Conde J et al (2011a) Adipokines and osteoarthritis: novel molecules involved in the pathogenesis and progression of disease. Arthritis 2011(2090–1992 (electronic)):203901. https://doi.org/10.1155/2011/203901
29. Courties A, Sellam J (2016) Osteoarthritis and type 2 diabetes mellitus: what are the links? Diabetes Res Clin Pract 122:198–206. https://doi.org/10.1016/j.diabres.2016.10.021
30. Cramer C et al (2010) Persistent high glucose concentrations Alter the regenerative potential of mesenchymal stem cells. Stem Cells Dev 19(12):1875–1884. https://doi.org/10.1089/scd.2010.0009
31. Day-Williams A et al (2011) A variant in MCF2L is associated with osteoarthritis. Am J Hum Genet 89(3):446–450. https://doi.org/10.1016/j.ajhg.2011.08.001
32. DeGroot J et al (2004) Accumulation of advanced glycation end products as a molecular mechanism for aging as a risk factor in osteoarthritis. Arthritis Rheum 50(4):1207–1215. https://doi.org/10.1002/art.20170
33. Ding C et al (2012) Body fat is associated with increased and lean mass with decreased knee cartilage loss in older adults: a prospective cohort study. Int J Obes 37:822–827. https://doi.org/10.1038/ijo.2012.136
34. Engstrm G et al (2008) 325 C-reactive protein metabolic syndrome and incidence of severe hip and knee osteoarthritis. A population-based cohort study. Osteoarthr Cartil 16:S143–S144. https://doi.org/10.1016/S1063-4584(08)60369-6
35. Eymard F et al (2015) Diabetes is a risk factor for knee osteoarthritis progression. Osteoarthr Cartil 23(6):851–859. https://doi.org/10.1016/j.joca.2015.01.013

36. Felson DT et al (2000) Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 133(8):635. https://doi.org/10.7326/0003-4819-133-8-200010170-00016
37. Felson DT et al (2016) Synovitis and the risk of knee osteoarthritis: the most study HHS public access. Osteoarthr Cartil 24(3):458–464. https://doi.org/10.1016/j.joca.2015.09.013
38. Findlay DM (2007) Vascular pathology and osteoarthritis. Rheumatology 46(12):1763–1768. https://doi.org/10.1093/rheumatology/kem191
39. Findlay DM, Kuliwaba JS (2016) Bone-cartilage crosstalk: a conversation for understanding osteoarthritis. Bone Res 4:16028. https://doi.org/10.1038/boneres.2016.28
40. Forster T et al (2004) Finer linkage mapping of primary osteoarthritis susceptibility loci on chromosomes 4 and 16 in families with affected women. Arthri Rheumat 50(1):98–102. https://doi.org/10.1002/art.11427
41. Funck-Brentano T, Cohen-Solal M (2015) Subchondral bone and osteoarthritis. Curr Opin Rheumatol 27(4):420–426. https://doi.org/10.1097/BOR.0000000000000181
42. Gkretsi V, Simopoulou T, Tsezou A (2011) Lipid metabolism and osteoarthritis: lessons from atherosclerosis. Prog Lipid Res 50(2):133–140. https://doi.org/10.1016/j.plipres.2010.11.001
43. Goldring MB et al. (2011) Roles of inflammatory and anabolic cytokines in cartilage metabolism: signals and multiple effectors converge upon MMP-13 regulation in osteoarthritis. Eur Cells Mat 21: 202–20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21351054 (Accessed: 11 July 2017)
44. Greene MA, Loeser RF (2015) Aging-related inflammation in osteoarthritis. Osteoarthr Cartil 23(11):1966–1971. https://doi.org/10.1016/j.joca.2015.01.008
45. Hannan MT et al (1990) Estrogen use and radiographic osteoarthritis of the knee in women. Arthritis Rheum 33(4):525–532. https://doi.org/10.1002/art.1780330410
46. Harbo M et al (2012) The distribution pattern of critically short telomeres in human osteoarthritic knees. Arthrit Res Therapy 14(1):R12. https://doi.org/10.1186/ar3687
47. Hasson CJ, Caldwell GE, Van Emmerik REA (2009) NIH public access. Mot Control 27(4):590–609. https://doi.org/10.1016/j.humov.2008.02.015.Changes
48. Henrotin YE, Bruckner P, Pujol JPL (2003) The role of reactive oxygen species in homeostasis and degradation of cartilage. Osteoarthr Cartil 11(10):747–755. https://doi.org/10.1016/S1063-4584(03)00150-X
49. Hiraiwa H et al (2011) Inflammatory effect of advanced glycation end products on human meniscal cells from osteoarthritic knees. Inflamm Res 60(11):1039–1048. https://doi.org/10.1007/s00011-011-0365-y
50. Homandberg GA (2001) Cartilage damage by matrix degradation products: fibronectin fragments. Clin Orthopaed Relat Res (391 Suppl): S100–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11603694 (Accessed: 16 July 2017)
51. Hosaka Y et al (2013) Notch signaling in chondrocytes modulates endochondral ossification and osteoarthritis development. Proc Natl Acad Sci U S A 110(5):1875–1880. https://doi.org/10.1073/pnas.1207458110
52. Hotamisligil GS (2006) Inflammation and metabolic disorders. Nature 444(7121):860–867. https://doi.org/10.1038/nature05485
53. Kapoor M et al (2011) Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol 7(1):33–42. https://doi.org/10.1038/nrrheum.2010.196
54. Kerkhof HJM et al (2010) A genome-wide association study identifies a locus on chromosome 7q22 to influence susceptibility for osteoarthritis. Arthritis Rheum 62(2):NA. https://doi.org/10.1002/art.27184
55. Kim J et al (2010) Mitochondrial DNA damage is involved in apoptosis caused by pro-inflammatory cytokines in human OA chondrocytes. Osteoarthr Cartil 18(3):424–432. https://doi.org/10.1016/j.joca.2009.09.008
56. Kirk KM et al (2002) The validity and heritability of self-report osteoarthritis in an Australian older twin sample. Twin Res 5(2):98–106. https://doi.org/10.1375/1369052022965
57. van der Kraan PM, Blaney Davidson EN, van den Berg WB (2010) A role for age-related changes in TGF? Signaling in aberrant chondrocyte differentiation and osteoarthritis. Arthritis Res Therapy 12(1):201. https://doi.org/10.1186/ar2896

58. Kuijt M-TK et al (2012) Knee and ankle osteoarthritis in former elite soccer players: a systematic review of the recent literature. J Sci Med Sport 15(6):480–487. https://doi.org/10.1016/j.jsams.2012.02.008
59. Lawyer TJ et al (2014) Prevalence of post-traumatic osteoarthritis in morbidly obese patients after acetabular fracture fixation. J Long-Term Eff Med Implants 24(2–3):225–231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25272222 (Accessed: 1 July 2017)
60. Lee HH, Chu CR (2012) Clinical and basic science of cartilage injury and arthritis in the Football (Soccer) Athlete. Cartilage 3(1 Suppl):63S–68S. https://doi.org/10.1177/1947603511426882
61. Lee R, Kean WF (2012) Obesity and knee osteoarthritis. InflammoPharmacology 20(2):53–58. https://doi.org/10.1007/s10787-011-0118-0
62. Lewis JS et al (2011) Acute joint pathology and synovial inflammation is associated with increased intra-articular fracture severity in the mouse knee. Osteoarthr Cartil 19(7):864–873. https://doi.org/10.1016/j.joca.2011.04.011
63. Li H et al (2017) Treatment of talus osteochondral defects in chronic lateral unstable ankles: small-sized lateral chondral lesions had good clinical outcomes. Knee Surg Sports Traumatol Arthrosc. https://doi.org/10.1007/s00167-017-4591-x
64. Loeser RF et al (2000) Reduction in the chondrocyte response to insulin?Like growth factor 1 in aging and osteoarthritis: studies in a non?Human primate model of naturally occurring disease. Arthritis Rheum 43(9):2110–2120. https://doi.org/10.1002/1529-0131(200009)43:9<2110::AID-ANR23>3.0.CO;2-U
65. Loeser RF (2006) Molecular mechanisms of cartilage destruction: mechanics, inflammatory mediators, and aging collide. Arthritis Rheum 54(5):1357–1360. https://doi.org/10.1002/art.21813
66. Loeser RF (2011) Aging and osteoarthritis. Current Opinion Rheum 23(5):492–496. https://doi.org/10.1097/BOR.0b013e3283494005
67. Loeser RF et al (2012) Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 64(6):1697–1707. https://doi.org/10.1002/art.34453
68. Loeser RF et al (2014) Aging and oxidative stress reduce the response of human articular chondrocytes to insulin-like growth factor 1 and osteogenic protein 1. Arthritis Rheum 66(8):2201–2209. https://doi.org/10.1002/art.38641
69. Lotz MK (2010a) New developments in osteoarthritis. Posttraumatic osteoarthritis: pathogenesis and pharmacological treatment options. Arthritis Res Therapy 12(3):211. https://doi.org/10.1186/ar3046
70. Lotz M, Loeser RF (2012) Effects of aging on articular cartilage homeostasis. Bone 51(2):241–248. https://doi.org/10.1016/j.bone.2012.03.023
71. Loughlin J et al (2000) Linkage analysis of chromosome 2q in osteoarthritis. Rheumatology 39:377–381. Available at: https://oup.silverchair-cdn.com/oup/backfile/Content_public/Journal/rheumatology/39/4/10.1093_rheumatology_39.4.377/3/390377.pdf?Expires=1498762747&Signature=TLcBIZF13-QNxl0d-uQ0aLbOke6TiUBveOt~oJDDuLFsU7fy5cxleS-SelEKgm-7N-GMLPbnGeh17Bkc3rssk3G4OxIVM8Heg0 (Accessed: 28 June 2017)
72. Loughlin J et al (2002) Finer linkage mapping of a primary hip osteoarthritis susceptibility locus on chromosome 6. Eur J Hum Genet 10(9):562–568. https://doi.org/10.1038/sj.ejhg.5200848
73. MacGregor AJ et al (2000) The genetic contribution to radiographic hip osteoarthritis in women: results of a classic twin study. Arthritis Rheum 43(11):2410–2416. https://doi.org/10.1002/1529-0131(200011)43:11<2410::AID-ANR6>3.0.CO;2-E
74. Maquet PG, Pelzer GA (1977) Evolution of the maximum stress in osteo-arthritis of the knee. J Biomech 10(2):107–117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/858709 (Accessed: 26 June 2017)
75. Mitsuyama H et al (2007) Calcification of human articular knee cartilage is primarily an effect of aging rather than osteoarthritis. Osteoarthr Cartil 15(5):559–565. https://doi.org/10.1016/j.joca.2006.10.017

76. Miyamoto Y et al (2008) Common variants in DVWA on chromosome 3p24.3 are associated with susceptibility to knee osteoarthritis. Nat Genet 40(8):994–998. https://doi.org/10.1038/ng.176
77. Moskowitz RW (2009) The burden of osteoarthritis: clinical and quality-of-life issues. Am J Manag Care 15(8 Suppl):S223–S229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19817508 (Accessed: 10 July 2017)
78. Nah SS et al (2008) Effects of advanced glycation end products on the expression of COX-2, PGE2 and NO in human osteoarthritic chondrocytes. Rheumatology 47(4):425–431. https://doi.org/10.1093/rheumatology/kem376
79. Nevitt MC et al. (1996) Association of estrogen replacement therapy with the risk of osteoarthritis of the hip in elderly white women. Study of Osteoporotic Fractures Research Group. Arch Intern Med 156(18):2073-80. Avalaible at: https://www.ncbi.nlm.nih.gov/pubmed/8862099
80. Olson SA et al (2015) Therapeutic opportunities to prevent post-traumatic arthritis: lessons from the natural history of arthritis after articular fracture. J Orthop Res 33(9):1266–1277. https://doi.org/10.1002/jor.22940
81. Onur TS et al (2014) Joint instability and cartilage compression in a mouse model of post-traumatic osteoarthritis. J Orthopaed Res: Off Pub Orthopaed Res Soc 32(2):318–323. https://doi.org/10.1002/jor.22509
82. Pascual-Garrido C, McNickle AG, Cole BJ (2009) Surgical treatment options for osteochondritis dissecans of the knee. Sports Health 1(4):326–334. https://doi.org/10.1177/1941738109334216
83. Pelletier JP et al (2008) A new non-invasive method to assess synovitis severity in relation to symptoms and cartilage volume loss in knee osteoarthritis patients using MRI. Osteoarthr Cartil 16(SUPPL. 3):8–13. https://doi.org/10.1016/S1063-4584(08)60004-7
84. Porter SE et al (2008) Complications of acetabular fracture surgery in morbidly obese patients. J Orthop Trauma 22(9):589–594. https://doi.org/10.1097/BOT.0b013e318188d6c3
85. Pottie P et al (2006) Obesity and osteoarthritis: more complex than predicted! Ann Rheum Dis 65(11):1403–1405. https://doi.org/10.1136/ard.2006.061994
86. Puenpatom RA, Victor TW (2009) Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgrad Med 121(6):9–20. https://doi.org/10.3810/pgm.2009.11.2073
87. Puig-Junoy J, Ruiz Zamora A (2015) Socio-economic costs of osteoarthritis: a systematic review of cost-of-illness studies. Semin Arthritis Rheum 44(5):531–541. https://doi.org/10.1016/j.semarthrit.2014.10.012
88. Qi C, Changlin H, Zefeng H (2007) Matrix metalloproteinases and inhibitor in knee synovial fluid as cartilage biomarkers in rabbits: the effect of high-intensity jumping exercise. J Surg Res 140(1):149–157. https://doi.org/10.1016/j.jss.2006.12.556
89. Reynard LN, Loughlin J (2013) The genetics and functional analysis of primary osteoarthritis susceptibility. Expert Rev Mol Med 15:e2. https://doi.org/10.1017/erm.2013.4
90. Richette P et al (2007) Oestrogens inhibit interleukin 1beta-mediated nitric oxide synthase expression in articular chondrocytes through nuclear factor-kappa B impairment. Ann Rheum Dis 66(3):345–350. https://doi.org/10.1136/ard.2006.059550
91. Rigoglou S, Papavassiliou AG (2013) The NF-κB signalling pathway in osteoarthritis. Int J Biochem Cell Biol 45(11):2580–2584. https://doi.org/10.1016/j.biocel.2013.08.018
92. Rodriguez-Lopez J et al (2008) Genetic variation including nonsynonymous polymorphisms of a major aggrecanase, ADAMTS-5, in susceptibility to osteoarthritis. Arthritis Rheum 58(2):435–441. https://doi.org/10.1002/art.23201
93. Roos EM, Arden NK (2015) Strategies for the prevention of knee osteoarthritis. Nat Rev Rheumatol 12(2):92–101. https://doi.org/10.1038/nrrheum.2015.135
94. Roos H et al (1995) Osteoarthritis of the knee after injury to the anterior cruciate ligament or meniscus: the influence of time and age. Osteoarthr Cartil 3(4):261–267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8689461 (Accessed: 1 July 2017)

95. Säämänen A-M et al (2000) Osteoarthritis-like lesions in transgenic mice harboring a small deletion mutation in type II collagen gene. Osteoarthr Cartil 8(4):248–257. https://doi.org/10.1053/joca.2000.0298
96. Salminen H et al (2000) Up-regulation of cartilage oligomeric matrix protein at the onset of articular cartilage degeneration in a transgenic mouse model of osteoarthritis. Arthritis Rheum 43(8):1742–1748. https://doi.org/10.1002/1529-0131(200008)43:8<1742::AID-ANR10>3.0.CO;2-U
97. Sauter E et al (2012) Cytoskeletal dissolution blocks oxidant release and cell death in injured cartilage. J Orthop Res 30(4):593–598. https://doi.org/10.1002/jor.21552
98. Schmal H et al (2012) Expression of BMP-receptor type 1A correlates with progress of osteoarthritis in human knee joints with focal cartilage lesions. Cytotherapy 14(7):868–876. https://doi.org/10.3109/14653249.2012.681039
99. Seon JK, Song EK, Park SJ (2006) Osteoarthritis after anterior cruciate ligament reconstruction using a patellar tendon autograft. Int Orthop 30(2): 94–8. https://doi.org/10.1007/s00264-005-0036-0
100. Sigurdsson U et al. (2016) Delayed gadolinium-enhanced MRI of meniscus (dGEMRIM) and cartilage (dGEMRIC) in healthy knees and in knees with different stages of meniscus pathology. BMC Musculoskeletal Dis 17(1): 406. https://doi.org/10.1186/s12891-016-1244-z
101. Silman AJ, Newman J (1996) Obstetric and gynaecological factors in susceptibility to peripheral joint osteoarthritis. Ann Rheum Dis 55(9):671–673. Available at: http://ard.bmj.com/content/55/9/671.full.pdf
102. Singh G et al (2002) Prevalence of cardiovascular disease risk factors among US adults with self reported osteoarthritis. Am J Manag Care 8(15):383–391
103. Sokolove J, Lepus CM (2013) Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Therapeutic Advances in Musculoskeletal Disease 5(2):77–94. https://doi.org/10.1177/1759720X12467868
104. Sophia Fox AJ, Bedi A, Rodeo SA (2009) The basic science of articular cartilage: structure, composition, and function. Sports health 1(6):461–468. https://doi.org/10.1177/1941738109350438
105. Sowers M et al (2009) Knee osteoarthritis in obese women with cardiometabolic clustering. Arthritis Care Res 61(10):1328–1336. https://doi.org/10.1002/art.24739
106. Spector TD et al (1996) Genetic influences on osteoarthritis in women: a twin study. BMJ 312(7036):940–943. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8616305 (Accessed: 27 June 2017)
107. Srikanth VK et al (2005) A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthr Cartil 13(9):769–781. https://doi.org/10.1016/j.joca.2005.04.014
108. Steenvoorden MMC et al (2006) Activation of receptor for advanced glycation end products in osteoarthritis leads to increased stimulation of chondrocytes and synoviocytes. Arthritis Rheum 54(1):253–263. https://doi.org/10.1002/art.21523
109. Thomas CM et al (2011) Chondrocyte death by apoptosis is associated with the initiation and severity of articular cartilage degradation. Int J Rheum Dis 14(2):191–198. https://doi.org/10.1111/j.1756-185X.2010.01578.x
110. Thomas E, Peat G, Croft P (2014) Defining and mapping the person with osteoarthritis for population studies and public health. Rheumatology (Oxford) 53(2):338–345. https://doi.org/10.1093/rheumatology/ket346
111. Toh WS et al (2016) Cellular senescence in aging and osteoarthritis. Acta Orthopaed 87(sup363):6–14. https://doi.org/10.1080/17453674.2016.1235087
112. Tornero-Esteban P et al (2015) Altered expression of Wnt signaling pathway components in osteogenesis of mesenchymal stem cells in osteoarthritis patients. PLoS One 10(9):e0137170. https://doi.org/10.1371/journal.pone.0137170
113. Tsai TL, Manner PA, Li WJ (2013) Regulation of mesenchymal stem cell chondrogenesis by glucose through protein kinase C/transforming growth factor signaling. Osteoarthr Cartil 21(2):368–376. https://doi.org/10.1016/j.joca.2012.11.001

114. Valdes AM et al (2010) Genetic variation in the SMAD3 gene is associated with hip and knee osteoarthritis. Arthritis Rheum 62(8):2347–2352. https://doi.org/10.1002/art.27530
115. Velasquez MT, Katz JD (2010) Osteoarthritis: another component of metabolic syndrome? Metab Syndr Relat Disord 8(4):295–305. https://doi.org/10.1089/met.2009.0110
116. Verzijl N et al (2003) AGEing and osteoarthritis: a different perspective. Curr Opin Rheumatol 15(5):616–622. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12960490 (Accessed: 25 June 2017)
117. Wainwright C et al (2011) Age at hip or knee joint replacement surgery predicts likelihood of revision surgery. Bone Joint J 93–B(10):1411–1415. https://doi.org/10.1302/0301-620X.93B10.27100
118. Wei Y, Bai L (2016) Recent advances in the understanding of molecular mechanisms of cartilage degeneration, synovitis and subchondral bone changes in osteoarthritis. Connect Tissue Res 57(4):245–261. https://doi.org/10.1080/03008207.2016.1177036
119. Whittaker JL et al (2015) Outcomes associated with early post-traumatic osteoarthritis and other negative health consequences 3?10 years following knee joint injury in youth sport. Osteoarthr Cartil 23(7):1122–1129. https://doi.org/10.1016/j.joca.2015.02.021
120. Wluka AE, Cicuttini FM, Spector TD (2000) Menopause, oestrogens and arthritis. Maturitas 35(3):183–199. https://doi.org/10.1016/S0378-5122(00)00118-3
121. Wluka AE, Lombard CB, Cicuttini FM (2012) Tackling obesity in knee osteoarthritis. Nat Rev Rheumatol 9(4):225–235. https://doi.org/10.1038/nrrheum.2012.224
122. Wright GD et al (1996) Association of two loci on chromosome 2q with nodal osteoarthritis. Ann Rheum Dis 55(5):317–319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8660106 (Accessed: 28 June 2017)
123. Xia B et al (2014) Osteoarthritis pathogenesis: a review of molecular mechanisms. Calcif Tissue Int 95(6):495–505. https://doi.org/10.1007/s00223-014-9917-9
124. Xu L et al (2014) Induction of high temperature requirement A1, a serine protease, by TGF-beta1 in articular chondrocytes of mouse models of OA. Histol Histopathol 29(5):609–618. https://doi.org/10.14670/HH-29.10.609
125. Yammani RR et al (2006) Increase in production of matrix metalloproteinase 13 by human articular chondrocytes due to stimulation with S100A4: role of the receptor for advanced glycation end products. Arthritis Rheum 54(9):2901–2911. https://doi.org/10.1002/art.22042
126. Yoon KH, Park KH (2014) Meniscal repair. Knee Surg Relat Res 26(2):68–76. https://doi.org/10.5792/ksrr.2014.26.2.68
127. Yoshimura N et al (2012) 'Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. Osteoarthr Cartil 20(11):1217–1226. https://doi.org/10.1016/j.joca.2012.06.006
128. Yudoh K, Karasawa R (2010) Statin prevents chondrocyte aging and degeneration of articular cartilage in osteoarthritis (OA). Aging 2(12):990–998. https://doi.org/10.18632/aging.100213
129. Zhang F-J, Luo W, Lei G-H (2015) Role of HIF-1? And HIF-2? In osteoarthritis. Joint Bone Spine 82(3):144–147. https://doi.org/10.1016/j.jbspin.2014.10.003
130. Zhang L, Hu J, Athanasiou KA (2009) The role of tissue engineering in articular cartilage repair and regeneration. Crit Rev Biomed Eng 37(1–2):1–57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20201770 (Accessed: 16 July 2017)
131. Zhao W et al (2016) Cartilage degeneration and excessive subchondral bone formation in spontaneous osteoarthritis involves altered TGF-β signaling. Journal of orthopaedic research : official publication of the Orthopaedic Research Society 34(5):763–770. https://doi.org/10.1002/jor.23079
132. Zhuo Q et al (2012) Metabolic syndrome meets osteoarthritis. Nature Rev Rheum 8(12):729–737. https://doi.org/10.1038/nrrheum.2012.135