Orthopedics and Rheumatology
Open Access Journal
ISSN: 2471-6804

Review Article
Volume 20 issue 2 - June 2022
DOI: 10.19080/OROAJ.2022.556031

Ortho & Rheum Open Access J

Post-Traumatic Osteoarthritis: Complexity & Possible Solutions

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Submission: May 28, 2022; **Published:** June 28, 2022

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Abstract

Post-traumatic osteoarthritis (PTOA) is a common clinic entity in diarthrodial joints representing approximately 12% of all osteoarthritis (OA) in the hip, knee and ankle. Unlike idiopathic OA, PTOA may occur in younger patients, can affect any joint and progresses more quickly. Multiple factors are involved in development of PTOA such as severity of mechanical impact, degree of tissue damage, associated injuries, general condition and co-morbidities. Pathological processes after joint injury can temporally be separated into the acute post-traumatic phase with inflammation of joint tissues, and the chronic phase that slowly progresses through a long, clinically asymptomatic period to a symptomatic phase with joint pain and dysfunction as a result of joint destruction. The pathologic changes can affect articular cartilage, synovium and bone through mechanical, cellular and metabolic changes. Up till now, there are no approved therapies to address the acute PTA and prevent the onset of the chronic disease. Surgical intervention along with technologic advances in fracture fixation and ligament reconstruction will undoubtedly play a role in prevention of PTOA development. However, a significant number of patients still progress to clinical OA even with the best surgical care of joint injuries.

Keywords: Posttraumatic; Osteoarthritis; Joint injury; Articular cartilage; Synovium; Biomarker; Inflammation

Introduction

Post-traumatic osteoarthritis (PTOA) is a common clinic entity in diarthrodial joints due to damage to the articular cartilage, subchondral bone, incongruity of the articular surface or joint instability caused by an acute injury. Intraarticular fractures, meniscal tears, ligamentous injuries and chondral injuries are common causes leading to PTOA [1]. Unlike idiopathic OA which tends to affect older adults in specific joints such as the knee, hip and shoulder, PTOA occurs in younger patients, often develops and progresses more quickly, and in accordance with joint injury [2]. Indeed, it has been reported that patients with disabling OA who had had an articular injury are more than 10 years younger than those who did not have joint trauma. In addition, 13.9% of patients with a history of joint injury during adolescence or young adults developed knee OA, compared with just 6% of those without a history of joint trauma [3]. Other studies reported that ranges from 20% to more than 50% of patients who had had joint trauma develop OA [4].

Posttraumatic OA may present in any joint after trauma, though limited epidemiologic data are available regarding PTOA in joints other than hip, knee, ankle and shoulder. PTOA represents approximately 12% of all OA in the hip, knee and ankle. This translated to an estimate of 5.6 million people in the United States [5]. Posttraumatic OA of the hip, for example, represents approximately 2% of all cases of hip OA [5]. The prevalence of hip PTOA is higher among military personnel, with rates reaching 20% [6]. At the shoulder, PTOA prevalence ranges from 8% to 20% in patients scheduled to undergo a variety of surgical stabilization procedures for anterior glenohumeral instability [7]. Regarding the ankle, for instance, trauma is the most common cause of OA [5].

Generally, PTOA is not clinically diagnosed until the onset of the symptomatic phase, which is highly variable. PTOA may occur early, in less than a year or remain asymptomatic for a long period of time, even 10– 20 years after the trauma. However, in both cases, it is increasingly believed that the OA development in the injured joints initiates during the initial traumatic event by intra-articular pathogenic processes such as apoptosis of articular chondrocytes, subchondral bone remodelling, cellular infiltration and the release of inflammatory mediators in synovial fluid (SF) [8].

An increased understanding of the molecular, mechanobiological and cellular events involved in the pathogenesis of chronic PTA may open interesting perspectives concerning new therapeutic opportunities and thereby offer patients safer and more effective drugs. Preventive measures are thought to be the most effective strategy to limit the degree of acute joint damage and the eventual development of chronic PTA. Thus, The ideal therapy should include early clinical interventions during the first phases after joint injury and address several pathogenic pathways [9].

Factors involved in development of PTOA

The pathogenic mechanisms after joint injury may vary depending on the severity of mechanical impact, degree of tissue damage, associated injuries, general condition and co-morbidities. Low-energy injuries, such as joint contusions, dislocations, and ligamentous and meniscal injuries, commonly cause articular surface damage without displaced bone fracture, although microfractures of calcified cartilage and/or subchondral bone may exist. Higher energy injuries often cause displaced intra-articular fractures [10].

The clinical expression of this damage depends on the main underlying pathway and predominant joint tissue involved at a point in time [11]. Subchondral bone injury is the main event, non-specific bone pain due to subchondral ischaemia or oedema, or both, is the prominent manifestation and is expressed as bone marrow lesions on MRI [12]. If the main target tissue is the synovial membrane, an inflammatory phenotype will dominate the clinical presentation. In other cases, soft tissue alterations dominate clinical manifestations of bursitis or tendonitis. All these clinical forms are interchangeable in the early stages of the disease, and sometimes a predominantly damaged mechanism can manifest through different clinical phenotypes in various tissues at the same time. Later on, symptoms become more homogeneous, entering a clinical status that we describe as the common OA syndrome in the advanced stages of the disease (Figure 1) [13].

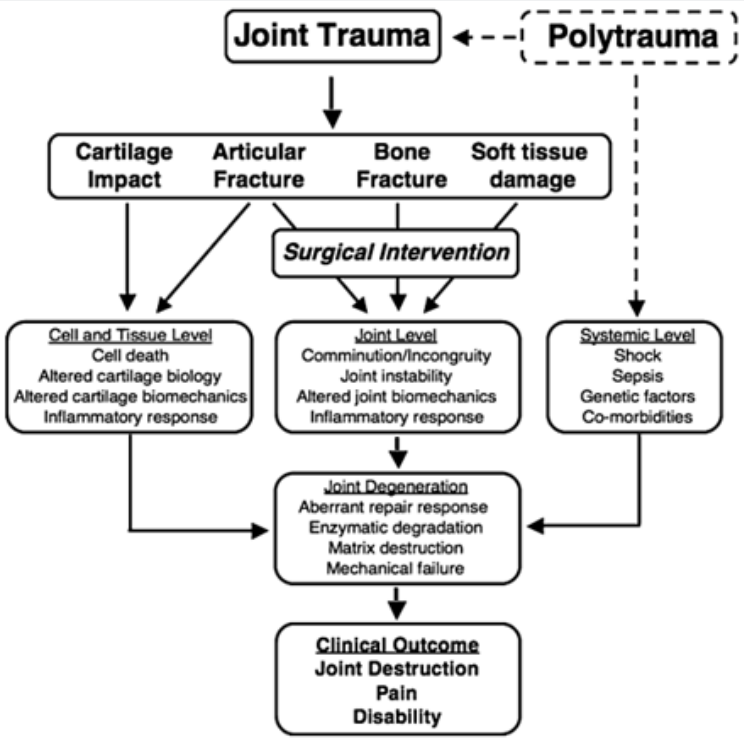

Figure 1: Factors involved in the development of posttraumatic arthritis after injury [14].

Concerning articular fractures, they represent a complex injury state consisting of impact loading to the joint as well as disruption of cartilage, bone, and other soft tissues. These effects result in a multifaceted interaction of mechanical as well as biological effects that may influence the natural history of joint disease [15]. In more challenging cases of highly comminuted fractures, restoration of the biomechanical state and congruity of the joint may, in fact, be impossible [14]. This alteration in the articular surfaces may result in abnormal loading of the cartilage and subchondral bone, and some of the cartilage may be overloaded and other areas where displacement remains may be unloaded. Under normal conditions, mechanical stress plays an important

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role in the health of the joint; however, under abnormal conditions, mechanical stress has been associated with progressive cartilage degeneration (Figure 2) [16]. Inadequate loading, or joint disuse, can also lead to loss of proteoglycans, decreased compressive stiffness, and increased hydration. Furthermore, in vivo as well as in vitro studies have demonstrated that a traumatic impact load may induce mechanical damage to the tissue, including splitting of the extracellular matrix, increased tissue hydration, and decreased stiffness and damage to the subchondral bone [17]. Thus, the effects of articular fracture may represent localized differences in patterns of joint stresses as well as the biological responses of joint tissues to these stresses. Furthermore, recent studies suggest that the effect of mechanical loading on the homeostasis of joint tissues may depend on the degree of joint inflammation [18,19]. The interaction of biomechanical loading and inflammation in the repair process after articular fracture is largely unknown [20].

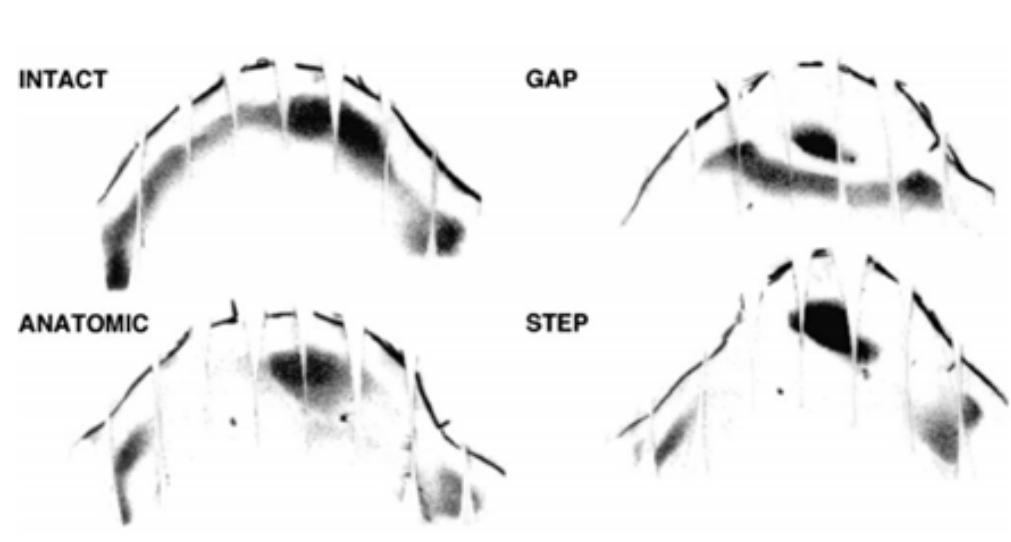

Figure 2: Hip-joint contact patterns as measured by pressure sensitive film interposed in the joint of a cadaver pelvis loaded in simulated single-leg stance. Contact patters are shown for joints with an intact acetabulum (intact), after transverse acetabular fracture that was anatomically reduced (anatomic), or after malreductions that result in steps (step) or gaps (gap) in the articular surface. For example, Step malreduction of the transtectal transverse fracture resulted in significantly increased peak contact pressures (20.5 MPa) in the superior acetabular articular surface as opposed to the intact acetabulum (9.1 MPa) [14].

Timeline of the pathogenic processes following joint injury

Joint injuries, with or without associated disruption of the articular surface, frequently lead to a progressive process of severe debilitating condition known as acute posttraumatic arthritis (PTA) (Figure 3) [8]. The acute symptoms following joint trauma include swelling, synovial effusion, severe pain and sometimes internal bleeding. Usually, PTA recoveries spontaneously in 2–3 months. The persistence of symptoms after this period should deserve attention and after 6 months, in clinical practice, it may be considered pathological and so-called chronic PTA. Chronic PTA can therefore represent an inflammatory condition that persists over time after a joint trauma. The most frequent chronic PTA is post-traumatic osteoarthritis (PTOA). However, a non-negligible number of PTA may lead to chronic inflammatory arthritis (PTIA), in particular psoriatic arthritis (PsA) [10,21].

Pathological Changes in Post-Traumatic OA

Pathological processes after joint injury can temporally be separated into the acute post-traumatic phase with inflammation of joint tissues, and the chronic phase. In the acute posttraumatic phase, effects of joint trauma include structural damage to joint tissues, hemarthrosis, and death of articular chondrocytes [22]. The lubricating properties of the synovial fluid is compromised as a result of the dilution of synovial fluid by intra-articular bleeding and plasma extravasation, leading to lower concentrations of hyaluronic acid and lubricant. Also, Joint trauma may lead to suppression of collagen and proteoglycan synthesis in articular cartilage. Remaining viable cells in joint tissues may respond to the injury with enhanced synthetic activity and overexpression of matrix degrading enzymes and inflammatory mediators. Initial cell necrosis is followed by a subsequent spreading of cell death mediated by apoptotic mechanisms, which occurs beyond the initial area into surrounding unimpacted regions [23,24]. In the chronic phase, metabolic changes in articular cartilage and other joint tissues slowly progress through a long, clinically asymptomatic period to a symptomatic phase with joint pain and dysfunction as a result of joint destruction. The majority of patients with PTOA are not clinically diagnosed with arthritis until the symptomatic phase [25]. For simplicity, pathologic changes occurring in PTOA can be divided into changes in articular cartilage, synovium and bone (Figure 4).

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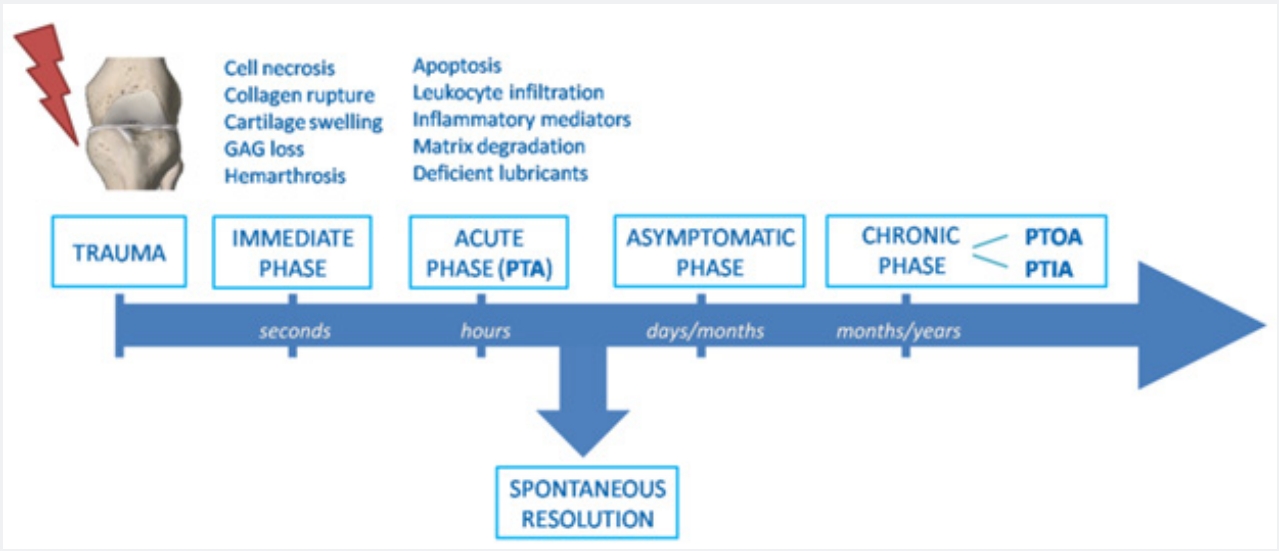

Figure 3: Timeline of the pathogenic processes following joint injury [8].

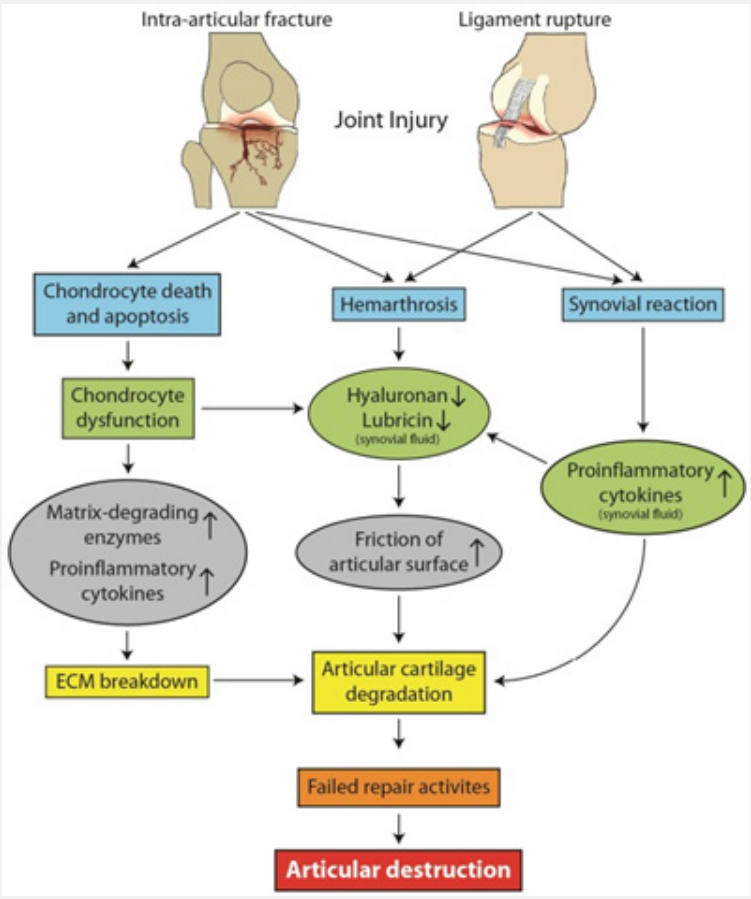

Figure 4: Possible pathogenetic mechanisms underlying the development of PTOA after joint injury [10].

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Pathologic changes in articular cartilage

Mechanobiologic Mechanisms

The mechanical disruption of the extracellular matrix (ECM) may lead to release of glycosylated amino glycans (GAG) and collagen molecules, which are sensed through mechanoreceptors and molecular cell surface receptors by the surrounding chondrocytes [26,27]. This leads to changes in gene expression and cartilage metabolism, which could set up a cascade of events leading to degradation of the articular cartilage [17]. Chondrocytes sense mechanical load through integrin-cytoskeletal interactions as well as ion-stretch activated channels in the membrane [28]. Mechanical stimulations activate α5β1 integrin-dependent intracellular signaling cascade. This triggers Interleukin 4 (IL- 4) release through focal adhesion kinase and kinase C [29]. Repression in gene expression of cell adhesion molecules, intercellular adhesion molecule 3 (ICAM-3), neural cell adhesion molecule (NCAM) and vascular cell adhesion protein are involved in homophilic cell-adhesion. Ezrin, an actin binding protein, is also up regulated. Ezrin works with other actions in mediating cytoskeletal interactions with CD44 regulating hyaluronic acid metabolism. Other signal transduction molecules SP110 nuclear body protein, high-mobility group box 2 (HMGB-2) and neurogranin are also up-regulated [30]. At least a subset of N-methyl-D-aspartic acid (NMDA) receptors also appears to be involved in mechanotransduction in articular chondrocytes [29].

Mechanical compression activates pathways involving intracellular calcium release as well as activation of cyclic AMP-activated protein kinase A. C-fos and c-jun mediated transcription factors are significantly up-regulated immediately following cartilage injury. Although much remains to be elucidated about how chondrocytes sense strain and damage to the matrix around them, it is clear that abnormal mechanical stimulations may cause dysfunction of articular chondrocytes and breakdown of cartilage ECM, leading to articular cartilage degradation (Figure 5) [31].

Cellular Mechanisms

Numerous in vitro as well as in vivo studies have identified chondrocyte death following impact to articular cartilage [32,33]. This occurs both through cell necrosis as well as apoptosis [34]. Necrotic cell death can occur at the time of injury in areas of impaction greater than 15-20 MPa. This appears to be isolated to the cells directly under the compressive force. The amount of necrosis increases predictably with the amount of force applied up to 35 MPa. At greater than 40 MPa of impaction, complete cell death is observed [35]. Kurz et al. found that strain rate was also an important determinant of the chondrocyte in response to injury with higher strain rates associated with decreased cell anabolism and viability. Thus, there is substantial evidence that a single traumatic insult with a threshold amount of force can cause chondrocyte necrosis [36,37]. As chondrocytes are the cells responsible for maintaining the function of articular cartilage, it seems logical that chondrocyte death, mostly through apoptotic mechanisms is a central feature to the development of PTOA [38]. Chondrocyte apoptosis may take place soon or more remotely after articular cartilage disruption [39]. This can occur with or without visible damage to the cartilage. Apoptosis has been correlated with damage to the ECM and likely involves damage to the cell membrane [40,41].

In both in vivo and in vitro models of cartilage damage, chondrocytes both in and peripheral to the zone of injury show continued biochemical and biomechanical changes over time [42]. With damage to the cartilage matrix the chondrocytes experience significant changes in expression of proteins involved in both anabolic as well as catabolic pathways. This increases the overall metabolic stress on the cell. There is continued mechanical stress on the cell through alterations in the cell environment caused by the initial trauma and/or continued abnormal loading of the matrix. There is evidence to suggest that some apoptotic chondrocyte death, at least in vitro models, is mediated through oxygen free radicals from the mitochondria [43]. A reduction in chondrocyte death has been shown with the use of antioxidants following cartilage injury [44,45].

The Caspase pathway is likely the main mediator of apoptosis within the cell. Extracellular signals such as tumor necrosis factor (TNF) and Fas can activate the cascade [46]. Intrinsic signals such as damage to DNA and signaling from the endoplasmic reticulum also activate caspases [47]. As DNA damage accumulates, mitochondria are depolarized leading to further amplification of caspase 3 via caspase 9, which may result in continued DNA breakdown. As chondrocytes die, they are no longer able to maintain the ECM around them. This puts greater mechanical and metabolic stress on the remaining chondrocytes. Therefore, it would seem that once a critical number of chondrocytes have undergone apoptosis, more chondrocyte death would continue until degeneration of the entire cartilage surface has occurred [48]. Instability of the joint may result in abnormal loading forces leading to changes in chondrocyte metabolism and cartilage degradation [49]. However, cell necrosis is unlikely to be the initial cause of alterations in chondrocyte metabolism in the animal model of PTOA induced by destabilization of the meniscus and transection of the ACL [50].

Molecular and metabolic mechanisms

Shortly after cartilage injury, articular cartilage displays significant changes in the expression of matrix-degrading enzymes. Matrix metalloproteinase 3 (MMP-3, stromelysin-1), a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5), and tissue inhibitor of metalloproteinases 1 increased dramatically within 4 hours [23]. These enzymes lead to breakdown of the ECM of articular cartilage. ADAMTS-5 knockout showed less degeneration and less changes in their subchondral bone than their wild type littermates after destabilization of the medial meniscus (DMM) [51]. A study by Polur et al. [52]

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showed DMM led to an increased expression of high temperature requirement A 1 (HTRA1) protein in vivo. This enzyme is involved in degradation of the pericellular matrix. Release of collagen-2 and breakdown of proteoglycans occurs after joint injury [53]. Collagen-2 molecules then act on the discoidin domain receptor 2 (Ddr2) through ras/raf/MEK/ ERK and p38 signaling pathways, which induces the expression of MMP-13 [54,55]. Klatt et al. also provide evidence that collagen II induces MMP1, 2, 13, 14 as well as Interleukin 1 beta (IL-1β), Interleukin 6 (IL-6) and Interleukin 8 (IL- 8). This also involves Mitogen-activated protein kinase p38 (MAPKp38) and Nuclear factor kappa B (NFkB) signaling pathways. This sets up positive feedback cycle in which the MMPs breakdown the ECM exposing the chondrocytes to more collagen II breakdown products, causing further production of degradative enzymes leading to continued degradation of the ECM [56].

Studies involving early gene expression after cartilage injury have shown increased transcription of molecules involved in both anabolic as well as catabolic pathways in articular chondrocytes [57]. PTOA cartilage may display loss of proteoglycans, increased water content and decreased stiffness of the ECM [58]. There is also evidence for increases in anabolism, suggesting a reparative reaction to cartilage damage [59]. Lorenz in a study of ACL transection in dogs showed significant and sustained increases in type II and type I collagen production [60]. In a rabbit lateral menisectomy model Hotta et al. [61] showed increased synthesis of type II collagen as OA advances and this was highest in the areas with moderate degeneration. In vitro studies have also shown an increase in type II collagen and aggrecan production after cartilage compression [62].

In adult mice, Runx2 is expressed in the articular cartilage of wild-type mice at the early stage of post-traumatic knee OA, induced by surgical transection of the medial collateral ligament and resection of the medial meniscus. In this mouse model of OA, Runx2 expression in osteoarthritic cartilage parallels collagen-10 expression but arises earlier than MMP13. After induction of post-traumatic knee OA by the same surgical procedure, Runx2+/- mice displayed decreased cartilage destruction and osteophyte formation, along with reduced expression of collagen-10 and MMP13, as compared with wild-type mice [63]. Adult articular cartilage is an avascular tissue. This is important for cartilage function, the environment of the articular chondrocytes and maintenance of the ECM. Vascular endothelial growth factor (VEGF) is induced by damage to articular cartilage [64]. Hayami et al. showed increased expression of VEGF was paralleled by decreased expression of chondromodulin-I, an anti-angiogenetic factor involved in maintaining the avascularity of articular cartilage. Pufe et al. showed that inhibition of VEGF suppressed mechanically induced MMP expression [50,65].

In an ex vivo model at 24 hours after cartilage injury, Dell'accio showed up-regulation of the Wnt-16 pathways and up-regulation of Wnt target genes [66]. Nuclear localization of β-catenin was also seen. These genes were shown to be up regulated in areas of degenerated cartilage but showed normal expression in areas of normal cartilage within the same joint. These results implicate a reactivation of morphogenetic pathways by mechanical forces [67]. Adult mice forced to express β-catenin showed cartilage degeneration and increased expression of aggrecan, MMP-9 and MMP-13 [68]. In contrast to this, mice deficient in β-catenin signaling also show increased chondrocyte apoptosis and cartilage degeneration. These results suggest that both excessive and insufficient β-catenin levels may impair the homeostasis of articular chondrocytes [69].

Inflammatory cytokines have also been shown to be elevated following joint injury [70]. Lee et al. found increases in resistin, a macrophage derived proinflammatory mediator that stimulates inflammatory cytokines after joint injury. IL-I, IL-6 and tumor necrosis factor alpha (TNFα) have all been shown to be increased after joint injury [71]. These inflammatory cytokines further the loss of proteoglycans in the ECM through activation of catabolic pathways and inhibition of anabolic activities [20,72]. IL-1 upregulates production of MMPs by increasing nitric oxide (NO) production in chondrocytes. Inoue et al. showed IL-1 induces expression of MMP-3 and VEGF by chondrocytes and synoviocytes. This may be inhibited by IL-1 receptor antagonist [64].

Inhibition of Nitric oxide synthase 2 (NOS_2) has been shown to mitigate the effects of IL-1β [70]. Yorimitsu et al. showed, in destabilization of rat knees, that inhibition of NO production by IL-4 was protective to cartilage [73]. IL-6 and IL-7 also appear to be involved in degradation of cartilage and IL-1 may work partly through activation of IL-6 [20]. The catabolic effects of TNFα may also be mediated through endogenous IL-6 [74]. Interestingly, Clements showed that IL-1β, IL-1β converting enzyme, stromelysin 1 and iNOS deficient mice all showed an increased progression of arthritic changes as well as increased levels of MMP, aggrecanase and collagenase in a mouse destabilization model. These results suggest that healthy articular cartilage demands a balance between anabolism and catabolism. Completely eliminating a catabolic cytokine will have unintended effects on the regulation of other cytokines and chondrocyte metabolism. This highlights the complex nature of the in vivo interactions of different signaling molecules and the likelihood of multiple regulatory effects on chondrocytes [10].

Pathologic changes in synovium

Regardless of the insult to a particular joint, trauma versus instability, changes in the synovium and synovial fluid are observed [75]. Lubricin, a joint lubricating molecule produced by synoviocytes and superficial chondrocytes, is significantly lower in unstable knees and remains so at 12 months post injury [76]. Lowered levels of lubricin correlated with an increase in TNFα, and inhibition of TNFα resulted in increased lubricin levels [77]. The decreased concentrations of lubricin result in decreased

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boundary lubrication of the articular cartilage and this in turn is correlated with cartilage damage [78]. Concentrations of other joint lubricant, hyaluronan (HA), and proteoglycan 4 (PRG4), are also affected by factors such as TNFα, IL-1β, and TGF-β, known to be elevated after joint trauma [79].

Cytokines such as IL-1β, IL-6, and TNFα as well as MMP levels are significantly elevated in synovial fluid following injury such as ACL transection [80]. In a human study looking at synovial samples from patients with ACL and meniscal injuries, inflammatory patterns in the synovium were similar to those with clinical OA. Upstream factors such as Wnt signaling pathways are also up-regulated in synovial tissue [81]. Morisugi et al. isolated healthy synoviocytes and subjected them to mechanical stretch. Significant elevation of gene expression of COX-2, iNOS, NFKappaβ, and poly (ADP-ribose) (PAR) synthesis occurred. The PAR synthesis is thought to be representative of oxidative damage to the DNA. This study highlights that the synovium is independently capable of up-regulating cytokines. It is therefore possible that in some pathways the synovium is the primary tissue up-regulating destructive molecular pathways after trauma. For instance, in instability models, it could be that the increased stretch on the synovium is a primary event leading to up-regulation of inflammatory cytokines and ultimately OA development. Yang et al. found that synovial fluid taken from injured human knees could decrease GAG content and collagen II production in cultivated healthy cartilage. This highlights how the synovial fluid can directly affect chondrocyte function [82].

Pathologic changes in bone

As development of OA progresses, subchondral sclerosis and osteophyte formation are diagnostic markers of the disease [20]. In the case of an impact injury to a joint, such as an intraarticular fracture, there is obvious injury to the subchondral bone [83]. Most traumatic ligament injuries are also likely to have injury to the subchondral bone in form of bone bruises and microfractures [84,85]. Histologic changes are seen in the subchondral bone of animal models of OA created by joint instability through ACL transection or DMM even though no direct injury to the subchondral bone has occurred. Boyd et al. showed early architectural changes to the cancellous bone after surgical ACL transection in dogs. The structure and function of the subchondral bone thus appears to be intimately connected with the health of the articular cartilage [86].

The early bone changes that were observed before visible damage to the articular cartilage could be appreciated. Kawaguchi et al., using mechanical stress and induction of Runx2 in mice, suggested that endochondral ossification signals are likely important in the pathogenesis of OA [87]. Kamekura et al. also showed Runx+/- mice to have less osteophyte formation after surgical destabilization of the knee joint, which correlated with articular cartilage destruction [63]. These instability models highlight interplay between the subchondral bone and articular cartilage, demonstrating that subchondral bone changes are not simply later findings seen after cartilage destruction. Numerous and complex communication pathways exist between synovium, articular cartilage and bone. A greater understanding of the interactions of all joint tissues is needed [10].

Opportunities for early intervention and Treatment

At present, there are no approved therapies to address the acute PTA and prevent the onset of the chronic disease. The primary goals of treating patients with PTA are to minimize the symptoms and loss of function and reduce pain. Currently, treatment for PTA includes anti-inflammatory drugs (non-steroidal anti-inflammatory drugs or intra-articular injections of cortisone), low impact exercise and lifestyle changes, for example, losing weight if necessary. However, not all patients benefit from the agent usually used and chronic arthritis can develop in the damaged region. Once the chronic disease has developed, the therapy is the same for the idiopathic forms. If none of these measures are effective, then surgery is the next option. However, any medical or surgical treatment can have severe side effects or risks [8].

Surgical therapies remain the only means of correcting the structural and mechanical abnormalities caused by joint injury. Early surgical intervention includes anatomic reduction and fixation of intra-articular fractures, repair or removal of torn menisci, repair or reconstruction of ruptured ligaments, and treatment of hemarthrosis if necessary. Surgical intervention along with technologic advances in fracture fixation and ligament reconstruction will undoubtedly play a role in improved treatment of joint injuries. However, a significant number of patients still progress to clinical OA even with the best surgical care of joint injuries [38]. It appears that greatest breakthroughs will likely be in early biologic therapies which could effectively block chondrocyte apoptosis and ECM destruction after appropriate surgical treatment (Figure 6). It has been recognized that chondrocyte apoptosis may be a common pathway in PTOA. Caspase inhibitors have been used in rabbits to reduce the severity of articular injury [88]. Antioxidants including N-acetylcysteine, vitamin E, and superoxide dismutase have also shown promise to reduce chondrocyte apoptosis [89,90].

Altering the destruction of the ECM after injury appears to be a promising place for new therapies. However, inhibitors of MMPs have failed up to this point because of adverse events and/ or lack of efficacy [91]. Other targets involved in ECM breakdown such as Ddr2 receptor, ADAMTS-5, and MAPKp38 and NFkB signaling pathways may provide targets for intervention. Cytokine inhibitors have been shown to be effective in altering the PTOA in animal models. TNFα and IL-1β inhibition have shown promise in animal models. IL-10 administration may also alter metabolism, favoring more anabolism and have chondro-protective effects [92]. BMPs may up-regulate chondrocyte metabolism, with BMP-7 showing significant changes in anabolism of chondrocytes [93]. Calcitonin

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and parathyroid hormone 1-34 have also been used in animals to alter cartilage destruction after injury [94]. Numerous attempts at disease modifying drugs for OA have failed. Most candidate drugs have focused on inhibition of a specific enzyme or inflammatory mediator at the later stage of OA. In PTOA, the clear precipitating event presents a unique window of opportunity to intervene early in the acute post-traumatic period.

Recent studies have revealed that inhibition of a single catabolic molecule may not be sufficient for the treatment of OA because multiple catabolic factors are involved in its pathogenesis. Furthermore, matrix turnover is a normal part of cartilage function and damaged ECM must be broken down before new matrix can take its place. Therefore, it is likely that potential therapeutic targets will need to be more upstream regulators that may regulate the expression of multiple cytokines, enzymes, and anabolic molecules, thereby maintaining the balance between anabolic and catabolic activity of articular chondrocytes and other joint tissue cells such as synoviocytes [91].

Recent studies have revealed that biological and mechanical abnormalities may affect transcriptional activity of specific transcription factors in articular chondrocytes. Transcription factor Sox9 is critical for the formation of cartilage, including articular cartilage, but its role in the maintenance of adult articular chondrocyte function remains to be elucidated. Transcription factor Nfat1 plays an important role in maintaining the physiological function of adult articular chondrocytes. Transcription factor Runx2 [63] and β-catenin transcriptional signaling may also be involved in the pathogenesis of OA via regulating the expression of anabolic and catabolic molecules in articular chondrocytes. These specific transcriptional signaling molecules that regulate the expression of multiple catabolic and/or anabolic factors in articular chondrocytes may be potential upstream targets for the prevention and treatment of PTOA [68,69].

Despite the use of all these agents has proven effective in reducing the progression of chronic PTA in animal models, only one small, randomized pilot clinical trial has been conducted. Currently, IL-1Ra is the only agent that has been used as an anticytokine approach in patients with acute PTA. In this study, it has been observed that IL-1Ra injected intra-articularly within 30 days of ACL injury (n=6) reduced pain and improved function at 2 weeks compared to placebo (n=5). Although this strategy has proved to be efficacious in the early postinjury phase, the results obtained have not been confirmed in larger studies [95]. A large number of molecules have been explored as potential targets for treatment in preclinical studies. Among these MMPs or caspase inhibitors, growth factors, antioxidants and even mesenchymal stem cells have shown an interesting effect as potential disease modifying drugs in PTA animal models [96,97]. Since activation of inflammatory mechanisms is considered to be critical to development of chronic disease, anti-inflammatory interventions may represent the best available opportunity to intervene early in the acute post-traumatic period. A study carried out by Lewis et al supports this hypothesis using an animal model of the tibial plateau fracture. They observed that MRL/MpJ mice, which are known to have enhanced regenerative abilities in response to injury, exhibited lower levels of inflammation than wild-type mice, were protected from the progression of PTA [98]. In particular, anticytokine therapy has demonstrated a marked efficacy as preventative agents of the long-term onset of chronic PTA. IL-1 inhibition, through knockout of IL-1β, intra-articular injection or adenoviral transfer of IL-1Ra and retroviral transduction to overexpress IL-1Ra, is resulted therapeutically effective in animal models of surgically induced PTA [99].

Blocking of TNF increased the production of lubricin and decreased the release of GAG, resulting in a chondroprotective effect in a rat model of PTA [77]. Recently, the use of lentiviral-mediated RNA interference silencing of IL-1b and TNF to treat PTA in rabbits displayed reduced cartilage damage and speed of degeneration [100]. However, although both cytokines play a role in the post-traumatic acute phase, different studies performed in mouse models assert that intra-articular inhibition of IL-1, rather than TNF, may reduce the development of chronic PTA [101,102].

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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How to cite this article: Ahmed Z, Mohamed E. Post-Traumatic Osteoarthritis: Complexity & Possible Solutions. Ortho & Rheum Open Access J. 2022; 20(2): 556030. DOI: 10.19080/OROAJ.2022.20.556031

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How to cite this article: Ahmed Z, Mohamed E. Post-Traumatic Osteoarthritis: Complexity & Possible Solutions. Ortho & Rheum Open Access J. 2022; 20(2): 556030. DOI: 10.19080/OROAJ.2022.20.556031

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How to cite this article: Ahmed Z, Mohamed E. Post-Traumatic Osteoarthritis: Complexity & Possible Solutions. Ortho & Rheum Open Access J. 2022; 20(2): 556030. DOI: 10.19080/OROAJ.2022.20.556031

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How to cite this article: Ahmed Z, Mohamed E. Post-Traumatic Osteoarthritis: Complexity & Possible Solutions. Ortho & Rheum Open Access J. 2022; 20(2): 556030. DOI: 10.19080/OROAJ.2022.20.556031

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