

"PLAY" (Preventing Long-Term Arthritis in Youth) Program a Review of the Literature of the Etiology of Post-traumatic Osteoarthritis and Potential Preventative Treatments

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Abstract

Osteoarthritis (OA) is the most common form of arthritis, and it is one of the leading causes of disability around the world. Post-traumatic osteoarthritis (PTOA) can be triggered by athletic injury, falls, motor vehicle accidents, and surgeries. One of the most common joints injured is the knee, when supporting structures are not able to handle the forces delivered through the joint. Traumatic injuries are one of the leading causes of joint hemarthrosis and can result in damage of the periarticular structures. These insults accelerate a deleterious cytokine cascade which risks future cartilage degeneration ultimately leading to significant degenerative arthritis and functional decline. There is a potential role for joint aspiration in conjunction with targeted proteomics to slow down and hopefully arrest the inflammatory cytokine mediated cascade. Our hope is that early detection, treatment interventions and monitoring can prevent long term sequelae of arthritis following acute injury in youth.

Keywords: Post-traumatic osteoarthritis • Youth • Cytokines • Orthobiologics

Introduction

Incidence and risk of developing oa after sports injuries

Osteoarthritis (OA) is the most common form of arthritis, and one of the leading causes of disability in the United States (US) and worldwide [1]. OA is also a major cause of pain and contributes to a significant economic burden; posing challenges to healthcare systems globally [2]. This issue not only affects adults, but also affects adolescents and youth. Interestingly, the prevalence of OA in those of ages 25-74 was found to be 12.1% in the US with increasing percentages of patients suffering from osteoarthritis over the age of 65 [1].

In this paper, we discuss osteoarthritis in the scope of post-traumatic arthritis (PTOA). PTOA can be triggered by athletic injury, falls, motor vehicle accidents, and surgeries. It is estimated that 12% of OA is caused by trauma. The Center for Disease Control reports that 5.6 million people in the US are affected by PTOA [3]. In addition, the lifetime risk of knee PTOA is 57% in persons with a history of prior knee injury. This is attributed to the long term sequelae of ACL and meniscal tears.

The volume of young athletes that are prone to traumatic injury of lower extremity joints has been increasing over the years. There are (7.9 million) high school athletes according to the 2016-2017 National Federation of State High School Association Athletics Participation Survey. This number has significantly increased from the beginning of recording athletic participation in 1971-1972 (3.9 million) and over the past decade 2006-2007 (7.3 million). Another significant trend in this survey

is the decreased male-to-female ratio in participation. Currently, female participation in sports has risen to 75% of the total number in males in high school athletics [4].

In youth sports, injury is a common occurrence. According to the "Research Report: Changing The Culture Of Youth Sports" performed by the Safe Kids Worldwide organization, among children mostly between the ages of 13 to 15, 90% had suffered a sports injury, of which 36% were joint soreness, 33% were sprained ankles and 13% were fractures [5]. Among high school athletes in the US, football had the highest injury rate (26.5 per 100,000 athlete-exposures), followed by gymnastics (18.6) and wrestling (17.9), with the most commonly injured body site being the knee (33.7%) [6]. In a study that evaluated 25 NCAA sports 2009-2010 through 2014-2015 academic years, a total of 3183 severe injuries were reported. The most common injured body parts were the knee (32.9%, n=1047), lower leg/ankle/foot (22.5%, n=715), and head/face/neck (11.2%, n=358), with diagnoses including sprains (32.9%, n=1048), strains (16.9%, n=538), and fractures (14.4%, n=458) [7]. European descriptive epidemiology study that looked at soccer injuries for players between the ages of 7 to 12 years, including 6038 player-seasons, found that most commonly injured joint was the ankle (87%) followed by knee (68%), then foot/toe (52%) [8].

The knee ligaments, particularly the ACL and meniscus, are prone to injury when supporting structures are not able to handle the forces delivered through the joint. This is most commonly seen with lateral and rotational stresses through the knee joint. Five out of the ten male sports with highest participation involve repetitive stresses on the knee joints due to quick changes in direction: football (1 million), basketball (550,000), soccer (450,000), Wrestling 245,000, tennis (158,000). In addition, six out of the ten sports with highest participation for females are associated with repetitive stresses on the knee joint: volleyball (444,000), basketball (430,000), soccer (388,000), cheerleading (144,000), lacrosse (93,000). Based on this epidemiological data, there is a large population prone to traumatic injuries and subsequently prone to developing osteoarthritis [4]. The studies above demonstrate the burden of lower extremity joint injury as being a major expenditure of medical care.

Onset of PTOA after injury

A recent systematic review and meta-analysis has demonstrated that knee injury is a major risk

factor for the development of knee osteoarthritis [9,10] In one review, 13 papers were reviewed with 27,326 total number of participants. Twelve of these studies showed increased risk of knee OA with a prior injury. In 2017, Moatshe et al looked at 65 surgically treated knee dislocations at a Level I trauma center to evaluate long term outcomes and the prevalence of knee OA. At 10 years follow-up they found the incidence of radiological osteoarthritis was 42% following knee dislocation treated with surgery. Patients below the age of 30 had a lower risk of developing OA compared to those older than 30 at the time of surgery [11].

Osteoarthritis also occurs following anterior cruciate ligament (ACL) rupture in various populations. In a study following soccer players with anterior cruciate ligament tears at 14 year follow-up, 41% of this study population developed advanced degenerative PTOA [12]. In female soccer players with a 51% incidence of radiographic osteoarthritis noted 12 years of ACL injury regardless of whether an ACL reconstruction was performed or not. Furthermore, a history of previous knee surgery, particularly ACL reconstruction or partial meniscectomy, has been associated with knee OA in elite football players. It is thought that treatment of knee injuries in football athletes should consider chondroprotection, including meniscal preservation and cartilage repair, when possible [13].

PTOA injuries induce molecular pathologic cascades within the affected joint, leading to acute and chronic inflammation. Without early intervention, some of the long term sequelae may be irreversible. It is speculated that the initial injury represents a major risk factor for secondary OA at a certain interval following the trauma [14]. Knowing the former, it appears clear that better interventions are needed immediately following these injuries in youth. Additional interventions to support the articular cartilage from future deterioration should be examined along with restoring ligament and joint integrity.

Concerns after meniscal resection

The association between meniscal tears and the development of PTOA has been previously noted [15]. There are also concerns with partial meniscectomy in the treatment of traumatic meniscal tears. Paradowski et al performed a retrospective cohort to determine the prevalence, incidence and progression of radiographic knee OA 15-20 years post meniscectomy. Subjects who underwent unilateral meniscectomy were identified and evaluated after two follow up appointments for knee x-rays. The average time after meniscectomy for the first follow up appointment was 17.7 years. Of patients who had surgery, 48% developed radiographic ipsilateral tibiofemoral OA and 14% developed patellofemoral OA. Furthermore, a subset of these groups also developed radiographic contralateral knee tibiofemoral and patellofemoral OA, 19% and 5% respectively. The second follow up (24.7 years post surgery) demonstrated additional increases of 20% and 9% from the first follow up for ipsilateral tibiofemoral and patellofemoral OA. The grades of OA also had increased between the two follow ups: 1-2 grades for tibiofemoral OA and 1 grade in patellofemoral OA [16-18].

A systematic review by Salta et al evaluated clinical outcomes in patients undergoing meniscectomy. They noted that involvement of the meniscal rim was significantly associated with the presence of OA. Among the patients evaluated for symptomatic and radiographic OA, positive findings correlated more with degenerative tears rather than acute tears of the meniscus. This may suggest inflammatory mediators and cytokines cause more damage and dysfunction than the structural abnormality itself. In this review, meniscal repairs associated with ACL deficiency had worse outcomes than those with an ACL; associated with subchondral lesions which can induce inflammatory cytokines [19]. Another study demonstrated development of new cartilage lesions after 2-year follow-up in patients with arthroscopic ACLR as detected by MR imaging. There was a multi-compartmental pattern of cartilage involvement with the lateral compartment most severely affected. Partial meniscectomy at the time of arthroscopic ACLR was suggested as an additional risk factor for the progression of chondral lesions [20]. They noted that quality of tear was a poor correlator of post-operative outcomes versus the quantity of meniscus removed.

Implications of joint traumahemarthrosis

Traumatic injuries are one of the leading causes of joint hemarthrosis, and can result in damage of the periarticular structures. Olsson et al reviewed the epidemiology of intra and periarticular structural injuries in a traumatic knee joint hemarthrosis (n=1145). All of the patients were seen in the emergency department post trauma with intra-articular joint swelling who were referred for subacute MRI. The highest incidence that was associated with a knee hemarthrosis was ACL rupture (52%) followed by meniscal tear (41%) across all age groups over 16 years of age. However, most of these injuries demonstrated combined injury (70%) rather than isolated incidences of ACL (12%). In the pediatric population less than 16 years of age, lateral patella dislocation was the leading cause greater than that of ACL rupture and meniscal injury [21,22].

Many factors contribute to the progression of joint destruction after acute joint hemarthrosis. This has been well researched in the hemophilic population. Pathophysiologically, blood in the joint cavity results in hemosiderin deposition in the synovium. The build-up of iron-laden synoviocytes stimulates proliferation and hypertrophy leading to tissue fibrosis [23]. This results in a recruitment of lymphocytes and monocytes resulting in a cytokine "storm". The combination of iron from red blood cells and hydrogen peroxide release from chondrocytes in the presence of

IL-1 from macrophages results in abnormal osteocyte differentiation at the expense of chondroblast apoptosis [24].

There is a dose dependent harm done to the joint correlating to the amount of blood displaced into the joint itself. At a certain threshold, the synovium is unable to reabsorb blood efficiently. Thus, the synovium will hypertrophy leading to inflammatory synovitis. Cartilage apoptosis has been seen within 4 days after an acute joint bleed in canine models which have a faster blood resorption rates than humans [25]. This has also been thoroughly studied in vitro human studies which concluded only 10% of joint volume filled with blood over 2 days is required for irreversible cartilage apoptosis [26]. Thus, rapid aspiration following an acute joint hemarthrosis period is critical for chondroprotection.

It has been noted that prolonged presence of blood in joints change the chemical and viscoelastic properties of the articular cartilage. Articular cartilage loses its compliance durability attributed to the iron deposition in synocytes and decreases the ability to produce effective matrix cross-linking proteoglycans [27]. This has been studied in animal models in vivo and in vitro with increased expression of p53-binding protein [28]. These mechanical changes can lead to pain and limitations of function in the immediate stages post injury [21,29]. Safran et al studied the effect of joint hemarthrosis on joint range of motion in a rabbit model. Their study demonstrated that blood in the joint resulted in decreased range of motion from pain and reactive muscle spasms.

There is evidence that traumatic hemarthrosis can also have long term sequelae. A major concern of Olsson et al demonstrated that knees suffering traumatic hemarthrosis with an intact ACL had a 64% chance of developing nonspecific bone marrow lesions (BML). In the setting of an ACL tear, the percentage of associated nonspecific BML had increased up to 90% in their sample. In other studies, post-traumatic BML have been suggested to be predictive of joint degeneration likely from inflammatory mediators released at the time of injury [30].

Inciting trauma provokes high bone/cartilage turnover and increased vascularisation via capillary leakage. Reducing cell turnover may eventually decrease proinflammatory cytokine levels and prevent long term complications like osteoarthritis [31]. Like hemophiliacs with recurrent joint hemarthrosis, young adults with knee injuries are at considerably increased risk for osteoarthritis later in life and should be targeted in its primary prevention [32].

Implication of cytokines in the acceleration of the degenerative process and after acute injury

Cytokines are small secreted proteins released by cells that have a targeted effect on the interactions between cells. Cytokines are predominantly produced by helper T cells and macrophages. In addition, cytokines are capable of cell signalling via autocrine, paracrine, and endocrine mechanisms. In the setting of degenerative arthritis, pro-inflammatory cytokines originate predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions [33].

As stated previously, traumatic meniscal and ACL tears accelerate the progression of degenerative OA. In addition, degenerative OA has been associated with elevated synovial cytokines [34]. In a cross-sectional study, Siqueira et al compared synovial fluid cytokine levels between knees undergoing arthroscopy due to a documented inciting injury compared knees undergoing primary TKA due to end stage OA. Results indicated that IL-6, IL-8 and TNF- α were elevated in end stage OA compared to the knee injury group. This suggests that IL-6 and IL-8 may progressively rise after an inciting injury and contribute to cartilage degradation. IL-6 has been reported to remain increased within the joint and thought to play a role in long-term cartilage degradation. Trauma induced OA may have a different cytokine profile compared with non-trauma induced OA; this could be due to a two different possibilities: other cytokines may play a more dominant role in progression to end stage OA (TNF- α and IL-1 β), or trauma induced OA may result from a variety of intra-articular tissues. Based on this study, it is possible that IL-6 and IL-8 blockade may serve as important treatment targets for OA in the future [35].

Various monocyte chemokine systems are increased in expression

in OA, however, the hierarchy of chemokines and chemokine receptors in mediating monocyte/macrophage recruitment to the OA joint is not well defined. In human OA synovium, CCR2 cells are abundant and the CCR2 macrophages line invade and are associated with the erosion of OA cartilage [36]. Raghu et al demonstrated in a mouse model, that monocytes recruited via CCL2/CCR2, rather than by CCL5/CCR5, propagate inflammation and tissue damage in OA. Selective targeting of the CCL2/CCR2 system represents a promising therapeutic approach for OA [37].

High concentrations of active TGF- β 1 have also been found in synovial fluid from arthritic joints, OA and RA where it may have profound effects on chondrocyte, synoviocyte, osteoblast and osteoclast metabolism [38-40]. Using a mouse model, Van Beunigen et al, injected TGF- β 1 into normal knee joints of mice, and measured the patellar cartilage proteoglycan content with histochemical and biological methods. Injections into normal joints induced inflammation, synovial hyperplasia, osteophyte formation and prolonged elevation of proteoglycan synthesis and content in articular cartilage [41]. Progressive cartilage damage due to PTOA is thought to be partially due to the promotion of fibroblastic phenotype signalling in joint cells. Down-regulation of TGF β pathways has also been shown to play a protective role to limit disease associated fibrosis and in maintaining healthy tendon homeostasis [42]. Biologic agents which interfere with inhibition of TGF β 1 activities may enhance endogenous cartilage repair in vivo and also improve the properties of tissue-engineered cartilage for implantation [43].

In a collaborative study performed in Germany, Austria and Egypt, RT-PCR of frozen synovial tissue samples of patients with either RA, joint trauma (JT) or OA were analyzed using double immunofluorescence confocal microscopy of pro/anti-inflammatory mediators and immune cell markers. It was found that up-regulation of pro-inflammatory mediators (IL-1 β , TNF- α , and 5-LOX) contributed predominantly to the catabolic inflammatory process in JT and RA synovium, whereas up-regulation of anabolic anti-inflammatory mediators (15-LOX, FPR2, and IL-10) counteracted inflammation and caused inferior inflammatory process in OA synovium [44].

Various studies have noted that proteases and inflammatory cytokines are released in the joint following trauma which leads to progressive degradation cartilage. Increased expression of inflammatory cytokines that include IL-6, IL-1 β , TNF- α , IL-10, IL-13 and IL-4 and known to be pro-inflammatory proteins which can accelerate the degenerative process [45]. In animal models, these inflammatory mediators targeted, including IL-1 and TNF α , have shown to reduce inflammation and down-regulate cartilage matrix metalloproteinases, respectively [46].

Role of dexamethasone for joint protection

A review article by Wernecke et al. analyzed multiple corticosteroids and their effect on articular cartilage. Hydrocortisone, methylprednisolone, betamethasone, dexamethasone, prednisolone, and triamcinolone have individually shown to have a small therapeutic window in the milligram range with a dose dependent deleterious effect profile. The duration, dose, and total number of injections varied between each corticosteroid and give little influence in developing a therapy with therapeutic concentrations [47].

The hypothalamic-pituitary-adrenal axis plays a major role in signaling by the glucocorticoid receptor (GR). The GR, which is present in virtually all cells, act by transcription and expression of molecules associated with inflammatory processes. GR binds with high affinity to cortisol and inhibits inflammation via direct and indirect genomic effects and nongenomic mechanisms [48]. Glucocorticoids (GC) operate by binding to intracellular GR, and repress expression of cytokines, including IL-1 β , IL-4, IL-6, IL-10, TNF- α , and cyclooxygenase-2 [49-53]. Due to this mechanism of action, intra-articular injection of GC have been studied and has been established as a treatment option for both chronic OA and rheumatoid arthritis (RA) [54,55].

As previously discussed, the microenvironment of joints change after injury; hemarthrosis and cytokine cascades can ultimately lead to early onset of OA. There is evidence that nanogram doses of dexamethasone can be chondro-protective following a joint injury [54,56-61] One study

demonstrated dexamethasone loaded microspheres embedded in chondrocyte-seeded agarose hydrogels promoted the development of mechanically functional cartilage in culture. In addition, these chondrocytes had also been preserved over 4 weeks with exposure to IL1- α [62]. This study, including other evidence of dexamethasone inhibiting other cytokines, suggests dexamethasone can potentially be a chondroprotective and restorative intervention in vivo.

4Dexamethasone (DEX) is a potent synthetic GC that binds with high affinity to GR. DEX has been used widely for variable applications and including its applications in the joint microenvironment. In extremely low doses, it has the ability to potentiate progenitor cells to undergo chondrogenic differentiation and to synthesize cartilage proteoglycans [63-65]. It has also been demonstrated that short-term DEX treatment arrests catabolic effects exerted by the combination of pro-inflammatory cytokines and mechanical injury and regulates the catabolic response of chondrocytes [59,60,66]. Due to rapid clearance of drugs from the intra-articular joint space, however, multiple injections or sustained release doses are often used to obtain long term effects. Bajpayee et al have proposed a novel method of using a charge based intra-cartilage delivery of single dose DEX with Avidin nano-carriers to suppress cytokine-induced cartilage PTOA [56].

Combination therapies with dexamethasone and other cytokine targeted therapies are also promising. In a model using arthritic mice, targeted IL-4 therapy with dexamethasone induced a state of tolerance by promoting T regulatory cells and macrophages [67]. In young bovine and human arthritic models, a combination of insulin-like growth factor-1 and DEX have been shown to prevent cytokine-mediated cartilage degradation, a particularly useful tool with relevance to prevention of PTOA [68]. In addition to the benefits of DEX on OA, oral nonsteroidal anti-inflammatory (NSAIDs) such as diclofenac have also been shown to be beneficial for acute and chronic OA treatment, however, prolonged use can have severe side effects such as gastrointestinal bleeding and cardiovascular effects [69]. In a rat model, liposomal dexamethasone-diclofenac combinations were used for local osteoarthritis treatment while preventing the potential side effects. The study found that the most effective treatment was used of a combination of both drugs in bioadhesive liposome carrying hyaluronan (HA) vehicle as opposed to a collagen vehicle. It was found that a single dose reduced inflammation volume down to 12.9% over a 17 day period. Even though further studies are warranted to evaluate longer term effects, this combination is a promising treatment as well [70].

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Injection of other agents for joint protection

Even though the specific pathogenesis of OA remains undefined, much progress has been made in identifying inflammatory markers and proteases. There have been many promising animal and human studies with evidence for agents including alpha-2-macroglobulin (α 2M), TAK-1, mesenchymal stem cells, interleukin-1 receptor antagonist protein (IRAP), herbal formulations, and other potential agents that may be used to arrest cartilage degradation in the early stages.

α 2M is a protein in the joint was found to be a bio-inhibitor helpful in reducing inflammatory mediators, specifically the activities of ADAMTS-4, ADAMTS-5, ADAMTS-7, and ADAMTS-12 following trauma [71-74]. In an interesting study by Wang et al, it was found that even though plasma protease inhibitor α 2M is present in the joint space, there are insufficient concentrations to inactivate the high concentrations of catabolic factors found in OA, therefore supplemental intra-articular α 2M was injected to provide chondral protection in posttraumatic OA [71]. In a recent

study by Zhang et al, they further designed a targeted variant ($\alpha 2M-108$) with enhanced function over the wild type $\alpha 2M$ in attenuating cartilage degradation in a bovine model [75].

As previously stated, TGF β has been shown to have an inflammatory effects on joints negatively impacting chondrocyte, synoviocyte, osteoblast and osteoclast metabolism. Transforming growth factor β -activated kinase 1 (TAK1), a member of the MAPK kinase (MAP3K) family, inhibits the action of TGF- β , thus arresting the inflammatory cartilage degradation and exerting a positive effect cartilage homeostasis [76-78]. In a recent study, *in vivo* evidence confirmed that TAK1 contributes to OA by disrupting cartilage homeostasis, therefore could be a potential target for OA mitigation. A small molecule inhibitor, 5Z-7, was utilized in a rat model, representing a potential therapeutic candidate that needs to be further studied on human cartilage [79].

In addition to cytokines and hemarthrosis, lipid peroxidation has been shown to be a potential factor in cartilage damage leading to OA [80]. Using an *in vivo* mouse model, carbazate-modified polyvinyl alcohol, which decreases the production of highly reactive aldehydes by products of peroxidation of phospholipids, was cross-linked to hyaluronan gel and demonstrated suppressed of apoptotic effects in cartilage destruction related to OA. In addition to pain mitigation, the hyaluronic acid molecule presents an opportunity to use covalent coupling of additional molecules to the gel as a vehicle to prevent the onset of OA [81]. It has been suggested that preventing cell membrane disruption would help contain the inflammatory cascade. Agents promoting cell membrane integrity such as surfactants have been suggested to reduce apoptosis and promote chondroprotection in the acute phase of injury as well in animal models. This was achieved by inhibiting the IL-6 pathway and other apoptotic proteins, preventing cell death [82,83].

As previously mentioned, the primary cytokines produced in an inflammatory joint environment after trauma are IL-1 β and TNF- α , the up-regulation of which triggers a catabolic pathway and ultimately disrupting cartilage homeostasis. IL-1 Receptor Antagonist Protein (IRAP) is a naturally occurring protein in the body that effectively binds to the IL-1 receptor on chondrocyte membranes and blocks IL-1 α/β from triggering its catabolic pathway [84,85]. Basic science and clinical studies have demonstrated the efficacy of IRAP in reducing catabolic activities in animal models as an early intervention treatment to significantly reduce cartilage degeneration and synovial inflammation [86-91]. Different methods to specifically inhibit IL-1 include: application of soluble IL-1 receptors, monoclonal antibodies against IL-1 or IL-1 receptor 1, blocking the formation of active IL-1 β , gene therapy, and the application of IRAP [92].

Early human clinical trials with intra-articular injections were proved to be efficacious and safe [93], however, IRAP is cleared rapidly from the joint space. Several studies have also explored methods to both improve delivery and to prolong the time in the joint space [94-98]. Currently, there are four commercially available IRAP products: recombinant Anakinra™, autologous Orthokine™, Arthrex™ and Arthrokinex™ [99]. There continue to be mouse model studies that show promise for newer agents to target the inhibition of IL-1 β [100-102]. Similar to MSCs, however, there are no standardized reporting methods for valid comparisons and further clinical studies are required to establish the true efficacy of these systems.

Mesenchymal stem cells (MSCs) are another potential agent which can be utilized to arrest cartilage damage leading to OA. Stem cells are undifferentiated cells that have the ability, at the single cell level, to self-renew and differentiate to produce mature progeny cells. These mature cell lines include both non-renewing progenitors and terminally differentiated effectors [103]. MSCs are adult stem cells isolated from various tissue sources that are able to differentiate into multiple types of mature tissue, to include cartilage. For this reason, the isolation and manipulation of adult stem cells is not only a promising tool for understanding tissue development and regeneration, but also for studying the engineered repair of tissues and organs [104-108]. It has been found in both animal and human models that MSCs derived from bone marrow can be differentiated into chondrogenic phenotype when induced, with potential use as seed cells for cartilage tissue engineering [109-115]. Bone marrow concentrate (BMC) has been used to deliver MSCs to damaged cartilage [116]. Fortier et al found that

the average concentration of IL-1ra in bone marrow aspirate (BMA) was 4510 pg/mL, which was then increased 3-5 fold, using two commercially available systems [117-119]. For effective therapy, IL-1ra/IL F 1 ratios of 10:1 to 100:1 have been reported as sufficient to block IL-1 [85,120].

Since the early 2000s, research and clinical use of percutaneous injected MSC has expanded. Due to the time, cost intensiveness and FDA restrictions of culture expansion of MSC, many commercial products have become available for bedside concentration of bone marrow aspirate as an alternative. A review of currently available commercial systems was recently published, noting that currently there are no standardized reporting methods for valid comparisons and further clinical studies are required to establish the true efficacy of these systems [121].

Free radical scavengers have been suggested as an intervention in this degenerative pathway such as N-acetyl-cysteine (NAC), superoxide dismutase, rotenone, and nitric oxide blockers [122-125]. In addition, pro-apoptotic proteins have been seen as a target for intervention. Pan caspase inhibitor (Z-VAD-FMK) reduced cartilage degradation via caspase 3 and p85 in ACL model [126]. These interventions rely on the regulation of the mitochondria to promote chondrocyte viability [123]. This may be beneficial as an immediate therapy before the signalling cascade is activated in the setting of traumatic hemarthrosis.

Potential guidance for prevention of long-term arthritis in youth after sports injury

There are currently no standard guidelines for the treatment of young athletes following joint injuries to prevent future osteoarthritis. Current standard treatments include: icing, compression, bracing and protected weight-bearing. Many clinicians will also aspirate the joint but this is quite variable and aspiration is not stressed as an important treatment intervention. Based on the literature reviewed, it is important to recognize the presence of a hemarthrosis injury and intervene early to prevent the future development of osteoarthritis. Some important injuries likely to result in hemarthrosis and chondrocyte injury include ligament tears, cartilage damage, patellar dislocations, bone contusions, and microfractures. [124-128]. Studies have demonstrated that elevated levels of catabolic enzymes and specific cytokines in the joint microenvironment induce chondrocyte death and cartilage matrix degeneration that can start as early as one week after joint injury [129-131]. Therefore early intervention strategies should focus on early intervention to reduce cartilage degrading processes.

Diagnostics at an early stage may include ultrasound, contrast enhanced ultrasound or MRI for early detection of injury [13,132-135]. After early imaging to detect injury, aspiration of joint effusions may be best attained with ultrasound guidance to ensure complete evacuation of the blood from the joint. Ultrasound guided arthrocentesis has been shown to be more precise and the preferred method to obtaining joint fluid compared to landmark based aspiration [136-140].

Interventions at early stages of injury, in addition to the current standard of care should likely include abortive treatments of the cytokine inflammatory cascade. This may include a combination or tailored cocktail treatment with low doses of DEX or introduction of other biologic agents such as alpha-2-macroglobulin ($\alpha 2M$), TAK-1, mesenchymal stem cells, interleukin-1 receptor antagonist protein (IRAP) and possible herbal formulations. Further *in vivo* studies need to be performed in order to determine the optimal combination of these interventions to reduce future OA (Table 1).

Conclusions

Joint injuries in youth are common and associated with increased risk of degenerative joint disease. Currently, there is no standard model to treat these injuries in a more proactive model to decrease the risk of future cartilage degeneration leading to significant degenerative arthritis and functional decline. There are well-known chemical changes which occur following these injuries as well as the known negative effects which occur following a hemarthrosis. In this article the known chemokine alterations which can result in cartilage degradation have been elucidated.

Future treatments that need further study would include rapid aspiration

Table 1. Combination or tailored cocktail treatment with low doses of DEX or introduction of other biologic agents such as alpha-2-macroglobulin (α 2M), TAK-1, mesenchymal stem cells, interleukin-1 receptor antagonist protein (IRAP) and possible herbal formulations.

Treatment Agents	Level of evidence	Proposed Mechanism of action	Commercially available formulations
Alpha-2-macroglobulin (α 2M)	V-In vivo	Reducing inflammatory mediators ADAMTS-4, ADAMTS-5, ADAMTS-7 and ADAMTS-12	A2Ml can also be made in the office using platelet-poor plasma
Transforming growth factor β -activated kinase 1 (TAK1)	V-In vivo	Inhibits the action of TGF-1 β	N/A
Lipid Peroxidation	V-In vivo	Decreases the production of highly reactive aldehydes	N/A
Surfactants	V-In vivo	Reduce apoptosis and promote chondroprotection	N/A
Mesenchymal stem cells	V-In vitro	Differentiation into multiple types of mature tissue including cartilage	Numerous available systems
Interleukin-1 receptor antagonist protein (IRAP)	I-RCT	Blocks IL-1 α/β	Anakinra™, autologous Orthokine™, Arthrex™ and Arthrokinex™
N-acetyl-cysteine (NAC), superoxide dismutase, rotenone, and nitric oxide blockers: Free radical scavengers	V-In vitro	Free radical scavengers	
Pro-apoptotic proteins	V-In vitro	Regulation of the mitochondria to promote chondrocyte viability	N/A
Dextromethorphan	V-In vitro	Suppression of MMP-13, NF- κ B and AP-1 signaling pathways	N/A

of the hemarthrosis with subsequent injection of low dose corticosteroids or various potential orthobiologic agents. The goal being to slow down and hopefully arrest the inflammatory cytokine mediated cascade.

Under this model, follow-up visits may also include repeat joint aspiration with targeted proteomics to monitor cytokine levels. Follow-up after injury will remain a crucial aspect in monitoring recovery and altering the course of treatment as needed. Periodic monitoring may also require serial imaging with MRI, ultrasound, contrast enhanced ultrasound or X-rays. Our ultimate hope is that early detection, treatment interventions and monitoring can prevent long term sequelae of arthritis following acute injury in youth.

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