
Post-Traumatic Arthritis: Definitions and Burden of Disease

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Introduction

Osteoarthritis is the most common form of arthritis. It accounts for more mobility disability than any other disease and is one of the leading causes of disability in the USA and worldwide [1]. Data from the National Arthritis Data Workgroup in the USA suggests that roughly 6 % of adults aged 30 and over have symptomatic OA of the knee and of those aged 60 and over, the prevalence rises to 12 % [2]. The prevalence of symptomatic hip OA is approximately half that of knee OA. The prevalence of knee OA in the UK is roughly similar to estimates in the USA [3]. Ankle OA, while often uniquely post-traumatic, is much less prevalent [4] than arthritis in the knee or hip. Roughly 7 % of older persons have symptomatic hand OA [5] and based on population surveys, hand OA more often has effects

on pain and function than commonly acknowledged. These prevalence estimates are based on counting persons with a positive X-ray for OA and joint pain in the affected joint as having disease. Since it has become clear that radiographic changes of OA occur late in disease and many persons without X-ray OA may have joint pain with MRIs showing OA [6], the prevalence of OA is likely to be even higher than current prevalence estimates suggest.

The prevalence of knee OA in China appears to be at least as high as in the USA [7] but, like the USA, most of it is not associated with major prior joint injury. However, the high rates of knee OA in rural communities including in China suggest that joint injury, either acute or chronic, plays a major etiologic role in knee OA.

Knee OA prevalence is rising in the USA and there is a commensurate rise in the rates of knee replacement. While most of this increase in prevalence may be due to aging and increased ponderosity of the US population, other factors are also at play. For one, given the same severity of radiographic knee OA, persons currently seem to be more inclined to complain of knee pain and OA symptoms than their predecessors [8].

Major joint injury causes a large percentage of OA of the knee in the community and causes the majority of cases of OA in joints that are otherwise rarely affected by disease including ankle, wrist, and elbow. Also, post-traumatic knee OA secondary to sports-related injuries may be increasing.

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Post-Traumatic Osteoarthritis

Post-traumatic osteoarthritis (PTOA), the osteoarthritis that develops following joint injury, causes life-long pain and disability for millions of people [9–11]. Acute joint injury and post-traumatic residual joint abnormalities, primarily instability and articular surface incongruity, lead to progressive loss of articular cartilage, to bone remodeling, and to changes in the joint soft tissues, resulting in PTOA. Unfortunately, current treatments of joint injuries all too often fail to prevent PTOA [9, 10, 12].

PTOA is due to synovial joint degeneration initiated by mechanical joint injury followed by localized and whole-joint biologic responses, including release of inflammatory mediators, that contribute to progressive tissue destruction as well as repair responses [9, 13–17]. Such injuries include joint dislocations, joint ligament and capsular tears, meniscal injuries, intra-articular fractures, and articular surface blunt impact injuries and contusions [9, 13, 18–22]. A substantial fraction (approximately 12 %) of the overall burden of disease of OA in hips, knees, and ankles arises secondary to joint trauma [10, 23]. In addition, PTOA due to intra-articular fractures (IAF) is the most common cause of combat-related disability in US military service personnel [24].

Clinical and epidemiologic studies show that joint injuries dramatically increase the risk of OA [25, 26]. A study of 1,321 former medical students found that 13.9 % of those who had had a knee injury (including meniscal, ligamentous, or bone injuries) during adolescence or young adulthood developed knee OA, as compared with just 6 % of those who did not have a knee injury [26]. Other studies have shown that even with the best current treatment, as many as one in four patients develop OA after fractures of the acetabulum [27, 28], between 23 and 44 % of patients develop knee OA after intra-articular fractures of the knee [29–31], and more than 50 % of patients with fractures of the distal tibial articular surface develop OA [32–34]. A long-term follow-up study indicates that patients who suffer from ligamentous and meniscal injuries of the knee have a

tenfold increased risk of OA, compared to patients who do not have a knee injury [35]. In the Framingham Study, a reported history of major knee injury (sufficient to require a cane or crutch) increased the risk of subsequent knee OA 3.5-fold in men and less so in women [36] and led to an estimate that roughly 10 % of knee OA was due to antecedent major knee trauma.

Since articular fractures and other joint injuries that lead people to seek medical attention occur at a rate estimated at 8.7 per 100 persons per year [37], the number of people at risk of PTOA is substantial. For these reasons, PTOA is almost certainly much more common than has been recognized [26]. A report from the University of Iowa supports this contention [10]. This study of patients presenting to the University of Iowa Department of Orthopedics and Rehabilitation with disabling hip, knee, and ankle OA showed that 1.6 % of patients with hip OA, 9.8 % of patients with knee OA, and 79.5 % of patients with ankle OA had a verified history of one or more joint injuries [4, 10]. Extrapolation from this patient population suggests that the total number of patients in the USA with disabling PTOA of hip, knee, or ankle approaches six million, and that PTOA accounts for approximately 12 % of societal expenditures for OA as a whole. In addition, unlike most other forms of OA, PTOA often affects younger adults for whom joint replacement is not a desirable treatment; in a study of patients with disabling hip, knee, and ankle OA, the patients with a history of joint trauma on average were more than 10 years younger at the time of presentation to the clinic than were patients without a history of joint trauma [4].

The time from injury to the onset of PTOA varies. Following severe joint injuries, including intra-articular fractures, PTOA may develop in less than a year; less severe injuries, including some articular surface fractures, joint dislocations, and ligamentous, meniscal, and joint capsular injuries, may not lead to PTOA for decades. With the best current care of significant joint injuries, the known lifetime risk of PTOA in those who have sustained major joint injuries ranges from about 20 % to more than 50 % [9]. And, despite the evolution of surgical interventions for the

treatment of joint injuries (in particular, articular fractures and anterior cruciate ligament tears), the risk of PTOA has not decreased appreciably in the last 25 years [9, 38].

Mechanisms Responsible for PTOA

Clinical experience and experimental data show that the mechanical causes of PTOA fall into two general categories: acute structural damage induced by the intense loads occurring at the instant of joint injury, and gradual-onset structural damage and cartilage compositional degradation due to chronic loading abnormalities of injured joints. In addition to structural damage, most acute joint injuries cause clinically apparent joint inflammation. In the specific case of articular surface impaction injuries, acute contusion of the cartilage may or may not be associated with clinically detectable articular surface fracture even though there may be significant cell death [39]. As regards articulation abnormalities responsible for gradual onset of progressive tissue damage and degradation after joint trauma, two common causes are joint instability and residual articular incongruity, both of which involve well-documented levels of chronic local contact stress elevation [9, 40–42].

Acute high-intensity joint injuries that initiate joint degeneration involve damage of the articular surface. In many instances, that damage includes macroscopic structural disruption of articular cartilage and subchondral bone: intra-articular fracture. Recent studies of human distal tibial articular surface joint fractures showed that the risk of PTOA following an acute articular surface injury is closely related to the mechanical energy absorbed at the instant of the joint injury: intra-articular fractures of the tibial plafond that involve absorbed energy levels exceeding a specific threshold predictably lead to OA within 2 years [43].

However, many acute joint injuries cause tissue damage even in the absence of visible disruption of the articular surface [9, 39, 44]. In these instances, the acute impact damage may be limited to alterations in matrix composition or

microstructure, accompanied by localized cell death [38, 45–47]. As discussed above, evidence from *in vitro* studies shows that acute cartilage injuries initiate biologic responses that cause progressive cell death, extending from the site of the impact [9, 48]. In addition, cells that survive in damaged cartilage typically exhibit metabolic disturbances that tend to amplify the initial mechanically induced structural disruption, thus serving to further weaken the cartilage matrix and lower its tolerance for mechanical stress [9, 14, 48].

One of the most important recent advances in understanding of PTOA has been the recognition that while mechanical injury causes direct tissue damage, PTOA is not a direct or inevitable consequence of the initial mechanical damage. For example, an *in vitro* study of intra-articular fractures in human ankle joints showed that even high-energy joint impact kills relatively few chondrocytes, but the proportion of dead cells increases steadily over the 48 h following injury suggesting that mediators released from the damaged cartilage cause progressive cell death [49]. Other *in vitro* studies have shown that inhibiting or blocking reactive oxygen species and other mediators, including alarmins, that are released from damaged cartilage decreased injury-induced chondrocyte death [9, 14, 16, 17, 48, 50–52].

As suggested by the above studies of progressive cell death following cartilage injury, an increasing body of evidence shows that joint biologic responses to mechanical injury, including release of inflammatory mediators, play a key role in the onset and progression of cartilage loss following joint injury [9, 14, 48–51, 53–57]. This understanding, combined with *in vitro* identification of post-traumatic biologic mediators of progressive matrix degradation and chondrocyte dysfunction and death [9, 14, 48, 51, 58], in concert with improved understanding of how increased articular surface contact stress causes cartilage loss, creates the opportunity for development of new biologic and mechanical interventions to decrease the risk of PTOA [9].

The second major cause of PTOA is gradual structural deterioration caused by chronic loading abnormalities stemming mostly from effects of the acute injury. Based on clinical experience

surgeons have assumed that residual joint surface incongruity following an intra-articular fracture and joint instability following a ligamentous, meniscal, or joint capsular injury increases the risk of PTOA. A recent study confirmed the role of incongruity in causing PTOA and that articular cartilage is lost first in the areas of the highest cumulative contact stress [43]. Although clinical experience shows that joint instability due to ligamentous injury—for example, ACL tears—increases the risk of PTOA, quantifying joint mechanical instability in living humans and studying its relationship to OA are challenging. However, a study of human ankle joints *in vitro*, using a methodology (Tekscan) that measured instantaneous joint surface contact stress, showed that joint ligamentous instability increased peak contact stress by 20–25 %, and that it increased the magnitude of peak positive and peak negative contact stress time rates of change by 115 % and 170 %, respectively, in joints with a 2 mm step-off incongruity [40, 41, 59]. Investigation of varying degrees of knee joint instability in rabbits found that increased degrees of instability following partial versus complete ACL transections correlated directly with the development of histologically apparent articular cartilage damage [42]. These experimental studies support the clinical impression that joint instability increases joint contact stresses and stress rates of change, and that over time, increased contact stress leads to PTOA.

These experimental studies have suggested a role of injury-related joint instability as a cause of joint damage. However, they have not measured the degree of instability, or shown whether increased joint instability is associated with evidence of increased joint damage over time. To explore this important issue Tochigi and coinvestigators developed an *in vivo* model of variable instability in which joint stiffness could be measured, both for complete ACL transections and for graded partial ACL transections. That study demonstrated that increased joint instability is associated with increased cartilage degeneration, continuously over the range of instability increase [42].

Some PTOA patients have combinations of initial tissue damage due to intense acute injury

and chronic post-injury joint abnormality, while others have primarily one or the other of these problems. For example, patients with comminuted intra-articular fractures have sustained not only a high-intensity joint injury, but also in many instances have residual joint incongruity. In contrast, mild (noncontact) ligament or capsule tears may not cause clinically apparent articular surface injury or joint inflammation, but nevertheless can lead to PTOA over a period of years, possibly due to increased joint instability.

Since the pathways through which the two general mechanical causes of PTOA (acute injury and chronic loading abnormality) that lead to joint degeneration are not well understood, and since it is usually not possible to separate their respective effects in studies of human joint injuries, it has been difficult to develop methods of evaluating an acute joint injury that will accurately predict which patients will progress to PTOA. This uncertainty obviously also hinders efforts to devise better treatments to forestall, mitigate, or prevent that progression.

Although overlap exists between the two general mechanical causes of PTOA, there is a substantial difference between the PTOA that develops primarily as a result of acute intense joint injury, versus the PTOA that develops chronically due primarily to instability or incongruity. Acute joint injuries are a single discrete event, causing immediate structural damage and cell death and triggering acute inflammatory and repair responses. By contrast, the PTOA arising primarily from residual instability and incongruity is the result of repeated smaller mechanical insults not involving significant fractional cell death or pronounced inflammatory responses, but instead involving gradual degradation of cell metabolic function, and reduced maintenance of matrix composition and structural integrity.

Evaluation of Joint Injuries and Risk of Post-Traumatic Osteoarthritis

Currently, physicians treating patients with joint injuries have limited ability to assess the severity of the injury. The patient's history of the injury and the physical examination of injured joint(s)

provide a general impression of the tissue damage, but do not reliably predict the risk of PTOA.

Commonly used methods of assessing a damaged articular surface include plain radiographs, CT scans, and MRI. Plain radiographic and CT scan studies of intra-articular fractures can demonstrate the disruption of the articular surface and the degree of displacement of the fracture fragments, and they therefore have been used to classify injury patterns. However, the reliability of current articular fracture classification systems is questionable [60, 61], and even articular fracture classifications based on three-dimensional CT reconstructions have disappointing reliability [62]. It is not surprising, therefore, that articular fracture classification systems have been characterized as useful in describing injuries, but not as being helpful in selecting a treatment [63].

MRI can demonstrate some types of articular cartilage disruption, but only recently have investigators started to define the relationships between MRI signal characteristics and changes in articular cartilage composition and mechanical properties [64–68]. And, as of yet, relationships between specific MRI changes following acute joint injury and development of PTOA have not been defined. Currently, therefore, there is limited understanding of the relationships between the severity of the structural injury to a joint, the biologic response to injury, and the onset and progression of PTOA.

Physicians currently base treatments intended to prevent PTOA on clinical impressions and accumulated experience. They have little basic scientific and bioengineering research to guide their clinical practice. Because the biologic response of the joint tissues to injury is not well understood, molecular- and cell-based treatments to minimize progressive joint damage are not a part of current injury management. Orthopedic surgeons routinely perform extensive surgical procedures in an effort to restore the alignment and congruity of articular surfaces following intra-articular fractures [69]. The purpose of these anatomic reconstruction procedures is to decrease residual joint incongruity, and thereby decrease focal elevations of contact stress presumed to be responsible for PTOA. Unfortunately, surgical exposure, reduction, and fixation of a

fractured articular surface can lead to serious complications such as necrosis of bone fragments or soft tissues, infection, and nerve and blood vessel injuries. In some instances the complications of surgical treatment of fractured articular surfaces lead to disability and/or even to amputation. Surgeons also reconstruct torn ligaments, menisci, and joint capsules, partially to decrease instability and thereby lower the risk of PTOA.

The ability of surgeons to restore joint stability and articular surface congruity has improved dramatically in the last 25 years. However, a number of clinical follow-up studies show that between a fifth and over half of patients still develop OA following current surgical treatments of common articular surface and ligamentous injuries [28, 38, 70], an observation that suggests that the best current surgical restorations of joint stability and congruity alone neither prevent nor perhaps even significantly decrease the lifetime risk of PTOA for many patients. Surgical treatments of joint injuries will continue to improve, but better understanding of how mechanical injury leads to PTOA has the potential to lead to new methods of treating joint injuries that, combined with surgical treatment, decrease or prevent progressive loss of the articular surface.

Age and Post-Traumatic OA

After age 40, the incidence of OA rises dramatically with every passing decade [37, 71]. Articular cartilage normally undergoes significant structural, matrix compositional, and mechanical changes with age [72–77]. But, these changes differ in many respects from those seen in osteoarthritic joints, and therefore by themselves do not explain the association between increasing age and increasing incidence of OA [78].

In contrast with the extensive studies of aging changes in articular cartilage matrix composition, age-related differences in healing of articular cartilage injuries following joint trauma have not been well investigated. However, basic scientific studies show that articular cartilage chondrocytes undergo aging changes that could affect their ability to repair articular surface damage, or maintain undamaged articular cartilage following

a joint injury. These changes include declining response to IGF-I, decreased mitotic activity and cell senescence, and oxidative damage [58, 73, 74, 76, 79–81].

The available clinical studies indicate that the risk of developing post-traumatic OA following joint injury increases with age. The risk of OA following an intra-articular fracture of the knee increases as much as three- to fourfold after 50 years of age [29, 30, 82]. Other clinical studies demonstrate that age increases the risk, or decreases the time until development of OA following ligamentous and meniscal injuries [83, 84].

Increasing age and joint injury are the two most significant risk factors for PTOA. Taken together, the scientific and clinical observations reviewed above suggest that increased age significantly increases the risk of OA following joint injury, possibly as a result of an age-related decrease in the ability of chondrocytes, and possibly other cells, to restore and maintain the articular surface

Is Most OA Post-injury OA?

The current clinical definition of post-traumatic osteoarthritis is osteoarthritis that develops following a specific clinically apparent joint injury including ligamentous, capsular, and meniscal injuries and injuries to the articular surface. And based on evidence from epidemiologic studies in which subjects are queried about a history of joint injury and surgery, roughly 10 % of combined knee, hip, and ankle OA is due, in large part, to a memorable acute joint injury.

As noted earlier, joint changes with age including senescent changes in cartilage may make joint cartilage and other soft tissues within the joint more fragile and easily damaged. Recent evidence suggests that trivial joint injuries, often unappreciated when they occur, may account for a large percentage of OA, especially in the knees of older persons. Englund et al. [85] found that up to 50 % of persons in their 50s and 60s had meniscal tears, degenerative tears that were present without any recollection of knee injury and often without accompanying evidence of osteoarthritis.

When followed in a longitudinal study in which subjects got repeated MRIs, these subjects had a threefold increased risk of developing radiographic OA of the knee when compared to others of the same age and sex who did not have tears [86]. Among those whose knees showed no cartilage defects, meniscal tears increased the risk of disease tenfold. While degenerative meniscal changes may indicate a more diffuse process of senescent change that also affects hyaline cartilage, Chang et al. [87] have shown that solitary degenerative tears create later cartilage defects at the site of the tear and not diffusely, suggesting that the tears caused disease. Given the high prevalence of meniscal tears in the knees of middle-aged and older men and women and the high attendant risk of OA conferred by these tears, up to 50 % of knee OA may be caused by them [88], far more than the proportion of disease caused by acute severe knee injuries. Ultimately, however, since these injuries are only occasionally recognized when they occur, it is unclear whether these injuries could be detected and, given the poor tissue substrate on which they occur, whether the progression to OA could be mitigated or prevented.

Implications

Recent clinical and experimental in vivo and in vitro studies of the relationship between injurious mechanical forces applied to synovial joints and articular surfaces and loss of articular cartilage have added considerably to the understanding of PTOA. Epidemiologic studies have confirmed a strong relationship between joint injury and PTOA. The magnitude of the acute and repetitive mechanical forces that cause PTOA in patients with tibial plafond fractures has been defined. Biologic mediators of cartilage destruction, including inflammatory mediators, triggered by mechanical forces have been identified, and a variety of agents that inhibit the actions of these mediators have shown promise as potential methods of decreasing articular cartilage degradation. These observations suggest that new surgical treatments of joint injuries to minimize

post-traumatic joint incongruity and new biologic treatments of joint injuries to inhibit the actions of biologic mediators of cartilage destruction have the potential to decrease the risk of PTOA following a wide range of joint injuries.

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