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Post-traumatic OA (PTOA): what have we learned to advance osteoarthritis?

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Post-traumatic OA (PTOA): what have we learned to advance osteoarthritis?

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The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Abstract

Purpose of review: Current thinking in the study of post-traumatic osteoarthritis (PTOA) is overviewed: the osteoarthritis which follows acute joint injury. The review particularly highlights important publications in the last 18 months, also reflecting on key older literature, in terms of what have we have we learned and have yet to learn from PTOA which can advance the OA field as a whole.

Recent findings: PTOA is a mechanically-driven disease, giving insight into mechanical drivers for OA. A mechanosensitive molecular tissue injury response (which includes activation of pain, degradative and also repair pathways) is triggered by acute joint injury and seen in OA. Imaging features of PTOA are highly similar to OA, arguing against it being a different phenotype. The inflammatory pathways activated by injury contribute to early joint symptoms. However later structural changes appear to be dissociated from traditional measures of synovial inflammation.

Summary: PTOA remains an important niche in which to understand processes underlying OA and seek interventional targets. Whether PTOA has true molecular or clinical differences to OA as a whole remains to be understood. This knowledge is important for a field where animal modelling of the disease relies heavily on the link between injury and OA.

Keywords:

Osteoarthritis; Injury; Post-traumatic; Inflammation; Mechanical

Introduction

Musculoskeletal disorders are the second largest cause of years lived with disability worldwide: this is mostly due to the high prevalence of osteoarthritis (OA), the most common form of arthritis, affecting ~21 million people in the U.S alone(1). Representing a major societal challenge, OA has arguably received less focus than it deserves. Perhaps in part this is due to a misconception that OA is an inevitable part of ageing. Although ageing is an important risk factor, only ~50% of people develop disease in their lifetime. Much of our modern understanding of disease pathogenesis has arisen from work interrogating the link between tissue damage or joint injury and OA, in the laboratory, in preclinical models and in humans. The osteoarthritis which follows significant joint injury is so-called 'post-traumatic OA' (PTOA)(2).

Significant knee joint injury such as anterior cruciate ligament (ACL) rupture and acute meniscal tear is one of the single biggest risk factors for knee OA and increasing in incidence(3, 4). For any given knee injury for example, ~50% of individuals will develop subsequent symptomatic disease, irrespective of whether surgical intervention occurs(5, 6). PTOA in its purest form is thought to account for ~12% of all cases of OA(7). Some believe that PTOA represents a disease 'subgroup' or phenotype, i.e. a different manifestation of the disease.

Often silent at onset, insidious and intensively variable in its progression, with molecular and structural change often predating symptoms by many years, interrogating the earliest processes of OA has often felt intractable. Studying and intervening in advanced human disease requires consideration of many different factors, for example the individual experience of pain and its influences (on which many patient-reported outcomes depend) and the influence of comorbidities on the onset and course of disease(8, 9). The advantage of following those with joint trauma is that they are typically younger, with less comorbidity (at least at the outset) and the exact timing of the risk exposure is typically known, so initiating processes can be more easily studied. Animal models of PTOA also exist which are well-established, tractable platforms for studying OA, in which translation of findings to human cohorts and the clinic is possible(10, 11).

1 This review overviews current thinking, particularly seeking to highlight important publications in the
2 last 18 months, but also reflecting on key older literature, in terms of what have we have we learned,
3 and have yet to learn from PTOA which can advance the OA field as a whole.
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10 **Mechanical load, injurious or otherwise, is central to OA pathogenesis**

11 There has been an increasing understanding that OA is a mechanically-driven, active cellular process
12 with potential for intervention and cartilage regeneration which is associated with substantial genetic
13 but also other individual identifiable risk. Much, but not all of this knowledge has relied on
14 investigating the relationship between injurious load and OA in different settings.
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22 *Epidemiology*

23 Identifying major aetiological factors for OA which are likely to predict risk at an individual level has
24 been exemplified by injury. Joint injury increases the risk of OA 4-7 fold, being more common in
25 professional sports people(12-14). This is a major public health problem, affecting people during their
26 young, working lives(3). Just considering ACL rupture, one of a host of clinically significant soft tissue
27 injuries at the knee alone, in the U.S. there are an estimated 252,000 ACL injuries per year for example,
28 and this incidence appears to be increasing(4, 7, 15, 16). It is thought that approximately 50% of people
29 with significant knee joint injuries such as ACL rupture and/or acute meniscal tear subsequently
30 develop symptomatic radiographic OA within 10 years(5); at least 33% of those with acute ACL rupture
31 will have MRI-defined whole joint OA after 5 years(17, 18), with higher prevalence in the longer
32 term(19). The presence of meniscal tear or chondral lesions have been reproducibly shown to be
33 independent predictors of adverse outcome after ACL rupture(20-23). This reaffirms the importance
34 of the integrity of the meniscus in knee OA as a whole. Extrusion or defunctioning of the medial
35 meniscus, acutely or chronically, appears to be a central step for many developing medial knee OA(24,
36 25). It may be that these groups of individuals with either acute traumatic meniscal tear or acute
37 symptomatic degenerative meniscal tear and associated OA are interesting 'bridging' groups with
38 translational potential for our understanding of OA as a whole(26, 27).
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Laboratory and animal studies

Modelling tissue injury in the laboratory is a translational approach which seeks to exploit the association of joint injury with OA. It has arguably taught us about processes in normal joint tissue physiology as well as responses in tissues which might lead to degradation(28). It has been known for some time that connective tissues such as articular cartilage respond directly to experimental injury by activation of pathways leading to degradation and tissue repair(29-31). Activation of these same pathways is also seen in OA, suggesting that studies of injured tissues may shed light on processes relevant to OA as a whole.

This connective tissue injury response is a discrete cellular response characterised by a rapid wave (within seconds) of inflammatory signalling and subsequent inflammatory gene transcription (31, 32). This is similar to, but distinct from that induced by interleukin-(IL)-1. IL-1 has been frequently used to activate similar pathways to study degradation in articular cartilage *in vitro*. However, there is a lack of definitive evidence that classical inflammatory cytokines such as IL-1 or TNF α are induced or secreted at biologically significant levels during either injury or OA, or that they are pathological drivers of this process in the way they are in for example RA(33). FGF-2 release from the matrix on tissue injury mediates some of the inflammatory pathway activation and appears to be an important physiological regulator in cartilage(31, 34). It was first isolated because of its large scale release from articular cartilage on experimental sharp injury(35). However, a pro-inflammatory factor secreted following tissue injury which is responsible for the remaining inflammatory signalling activation has never been identified, suggesting that this may in fact be a 'hard wired' tissue response, directly responding to mechanical injury *per se*. The JNK-2 pathway would appear important for much IL-1-induced aggrecan degradation *in vitro* (36) and also after experimental acute meniscal destabilisation(37); it is not clear if this is true of injury-induced pathways in humans.

Several injury-induced models of OA, primarily in rodents, are now in wide use with differing levels of validation. These rely on various forms of experimental joint injury reliably leading to osteoarthritic features, particularly in genetically homogeneous models. Some models acutely destabilize the joint

1 by surgical transection, by destabilization or removal of the medial meniscus, or anterior cruciate
2 ligament transection (ACLT). Others use some form of controlled external loading to cause injuries
3 such as acute ACL rupture (ACLR) or osteochondral fracture(38-41). There are considerations for use
4 of each particular model(38). ACLT/r models will reliably lead to blood in the joint (haemarthrosis),
5 likely to be an important clinical factor in some injuries which benefits from its inclusion(42). On the
6 other hand, removing the effects of blood and other less well-controlled tissue trauma may lead to a
7 more reliable signal and easier interrogation of the connective tissue response to the mechanical
8 destabilisation itself. One particularly utilised model is destabilisation of the medial meniscus (DMM).
9 Here, the medial meniscus of the mouse knee is surgically destabilised by transecting the meniscotibial
10 ligament leading to acute extrusion of the meniscus, similar to an acute peripheral detachment of
11 medial meniscus seen in humans(10, 27, 30).
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26 Several experimental observations come from this model which are arguably highly relevant to our
27 approach to investigation of human disease: i) the joint injury response and subsequent OA
28 development is variable rather than inevitable, dependent on a number of individual factors (for
29 example, gender and genetic strain modify rates of disease substantially)(43); ii) some reparative
30 elements of the mechanosensitive molecular response to initial injury and destabilisation are
31 protective of later OA(44, 45); iii) subsequent relevant signalling and disease in an acutely unstable
32 joint is largely dependent on mechanical joint loading(30, 46); and iv) this is a process in which we can
33 successfully intervene (e.g. joint offloading or modifying certain signalling pathways reduces
34 subsequent OA)(30, 47, 48) (Figure 1).
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48 *Clinical studies and trials*

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50 The immediate tissue injury response is also detectable after joint injury at a protein level in synovial
51 fluid in humans *in vivo*, with levels of most proteins falling over time(49-52). This initial molecular
52 response has been associated with measures of joint degradation and later structural outcomes(53,
53 54). Although this response is detectable systemically, there are often far lower levels in
54 serum/plasma with poor correlation with SF (51, 52). SF is an ultrafiltrate of plasma but bathes the
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connective tissues in the joint, so more closely reflects molecular changes in the secretome of these joint-facing tissues. Serum and plasma proteins are in addition also influenced by non-joint sources. This appears to be an important consideration when searching for biomarkers of the joint injury response or indeed for OA in general, where reliability and clinical utility are sought.

One hypothesis is that many of the pathways responsible for PTOA progression might also be common to non-traumatic OA, through common pathways relating to mechanical overload or micro-injury. Such theories are best tested in cohort or experimental medicine studies. Cohort studies of individuals with degenerative meniscal tear find that SF biomarker findings often recapitulate the findings in joint injury, and may also be associated with outcomes such as knee pain(51, 52, 55).

Does re-stabilisation of the knee joint protect from OA after injury? Surgical reconstructive surgery after ACL remains controversial in terms of whether it protects from OA in the shorter, or longer term(6, 18, 19). But studies usually are in comparison to physiotherapy, which also seeks to restabilise the joint, with both likely having an effect. If mechanical overload is detrimental or even causative in OA, is there other evidence that offloading may be positive for the joint? In a relatively experimental surgical intervention for OA, joint distraction, an external fixator causes joint surfaces to be pulled apart ('distracted') by ~5 mm. Groups in the Netherlands and in Japan have reported apparent clinical benefits for several years following this 6 week intervention(56, 57). This 'offloading' of the joint would intriguingly appear to lead to cartilage regeneration in the most affected compartment by MRI (58). As the biological effects appear to be mechanically induced, can markers of the injury response give us any insight into the molecular processes underlying this apparent successful cartilage repair? A panel of 10 markers from the DMM mouse model, validated in a cohort of those with acute human knee joint injury was measured in the SF of just 20 individuals at 3 time points during the distraction period and change related to patient reported outcome(59). Interestingly 6/10 markers modulated by injury were also influenced by this offloading. An increase in two molecules over the course of distraction, FGF-2 and TGF β was associated with clinical response over a 6 month period. This study

suggests that mechanoresponsive genes and markers identified in a joint injury setting may be informative translational markers for OA as a whole.

Inflammatory pathways are mechanically activated targets in joint injury and in OA

It is clear then that when we refer to inflammatory pathways in OA, that this is largely tissue-based inflammation, perhaps associated with innate immune pathway activation (60, 61) (rather than a humoral response as is seen in RA). It is impossible to discuss this in isolation from mechanosensitive pathways as these appear one and the same. However, it is worthwhile examining some of the inflammatory targets that have come out of injury/PTOA studies.

It is worth reminding ourselves of the striking molecular similarities particularly relating to the outcome of inflammatory pathway activation, matrix-olysis in the injured knee and the osteoarthritic knee, albeit with difference in the magnitude of elevations of fragments of COMP, collagen II and aggrecan, suggesting a similar process, acute versus chronic (62-66)

Laboratory and animal studies

Recent studies in DMM have identified molecules which if blocked modify disease-relevant readouts and would thus appear to be potential therapeutic targets; for example, molecules driving pain such as NGF (which is already in advanced human trials of the monoclonal antibody) or CCL-2 (MCP-1), a molecule which has been variously targeted in oncological and inflammatory disease(67-69). Other pathways if enhanced may lead to regeneration, such as TGF β , CTGF and FGF-2, albeit with safety considerations in humans(45).

IL-6 or its signalling pathway have also been implicated in the pathogenesis of murine PTOA(48). However, experiments in animal models can give conflicting findings(70). IL-6 has been associated with OA progression in the disease as a whole, having been targeted in recent clinical trials of established OA(71, 72). Translational studies in humans are needed to deconvolute the role of IL-6 and its signalling pathway and whether or not it truly represents a treatment target in either PTOA, established disease or both(2).

Clinical studies and Trials

There is currently no accepted model for delivering prevention of OA studies after joint injury (conventional outcomes such as radiography would require these trials to be many years long). However, short terms studies, primarily focussing on knee-based symptomatic outcomes or molecular outcomes have been carried out for two agents in this space. An initial proof of concept randomised controlled trial (RCT) delivering i.a. anakinra or placebo to just 11 subjects ((73) sought to shift this paradigm, reporting possible effects over a fairly short time frame. The second RCT was in young people with ACL injury, with patient reported outcomes and biomarkers collected after randomisation to intra-articular dexamethasone or saline (74). This showed a substantial effect of dexamethasone on measures such as the collagen degradation marker in SF, CTX-II. Injury and its resolution or otherwise this would appear to be a critical time for the joint. What relative effects corticosteroids have simultaneous repair pathways and how they influence longer term clinical outcomes is yet to be understood. This is of interest, given the reports of negative effects on cartilage of repeated steroid treatments in knee OA progression(75).

There have been a number of disappointments for inflammatory targets in OA clinical trials; it seemed an obvious hypothesis that traditional anti-rheumatic drugs and biologics used in the treatment of RA might suppress the inflammatory processes and associated symptoms in OA. But their outcome is less than resounding, and has left many questioning whether this rules out rather than rules in 'classical' inflammation' as a disease target in human OA(76-78). Part of this assumption was that synovial inflammation present in OA was a treatment target as it is in RA. But insight from the PTOA setting is that synovial inflammation may be dislinked from other processes in the disease or simply a bystander or secondary phenomenon. Its presence by MRI or biomarker measurement at 2 years after knee injury did not correlate with later outcomes, either structural (17) or patient reported (79). More work is needed to understand whether measurement of processes nearer to the time of injury may have more bearing on these outcomes.

1 Not all inflammation is the same. Modulating a single potentially adverse but often short-lived process
2 near to an injury may be very different to attempting to modulate such pathways in a chronic way in
3 perhaps irreversibly damaged joint tissue or an irreversibly mechanically-challenged joint
4 environment, as may be true in established radiographic disease. Joint injury may be quite different
5 to OA in this respect, but we have done little so far to test this.
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10 11 12 13 14 **Insights from imaging post-traumatic OA** 15

16 Imaging outcomes in OA research have been challenging in OA, with many agreeing that issues of
17 sensitivity and specificity of X-ray and MRI outcomes respectively have held back progress in the field
18 generally, reducing our ability to take potentially viable targets through clinical trials(80). Assessment
19 of joint injury by these two modalities has thrown a spotlight on some particular issues and
20 unanswered questions for the field as a whole. How can cartilage swell (get thicker) on MRI after injury
21 but yet be associated with joint space narrowing on X-ray?(81) Why should we focus on articular
22 cartilage change when the bone changes in response to joint destabilisation arguably occurs far
23 earlier(82, 83). It is also intriguing that the pattern of flattening and condylar osteophytosis, whether
24 in an ACL-deficient knee or primary OA knee appears the same (83) and mirrors that seen in DMM in
25 the mouse (84). This suggests that, whatever the aetiology, the effects of mechanical forces in the
26 disease may be fairly universal, and the shared aspects of PTOA and non-PTOA perhaps greater than
27 the perceived differences.
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47 **PTOA as a platform for designing experimental medicine studies and trials** 48

49 Interventional studies at or near the time of joint injury which seek to prevent an adverse process in
50 the joint in the longer term are a form of secondary prevention (where preventing the injury in the
51 first place would be primary prevention(85). Such an approach is really quite different to what we seek
52 to do in drug trials in OA (Figure 2).
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1 In recent years, considerations about the definition of early OA have followed guidelines around the
2 conduct of trials in established OA. These are important if we are to successfully intervene earlier in
3 the disease(86, 87). However, there is no international consensus on the design and conduct of trials
4 testing interventions seeking to prevent OA after joint injury and a number of challenges and
5 opportunities have been identified by triallists in this area(88, 89). As such, there is no FDA 'label' for
6 OA prevention, creating a barrier to clinical translation.

14 In 2017, an international consensus workshop of international experts and stakeholders produced the
15 first considerations in this therapeutic area(90). One of the identified key unmet research needs was
16 for valid biomarkers which can stratify patients for trials (selecting those at highest risk to weight trials
17 towards 'success' in identifying a signal) or act as surrogate endpoints (to shorten trials and make
18 them financially viable). It is interesting to consider that these have been recognised as arguably two
19 of the biggest priorities for OA research overall(91, 92).

29 If we are to develop and translate our findings to the clinic, continued validation work in cohorts to
30 support guidelines development including all aspects of design and delivery is necessary (Figure 3).
31 Involving Pharma and regulators would seem essential in accelerating drug development and
32 potentially opening up a fresh approach for OA therapeutics.

39 *Changing the paradigm: stratification and intervening to prevent*

41 Not all OA progresses: there is evidence that it may reverse or stabilise in a substantial number(93).
42 Whilst risk factors for OA progression are fairly well-established, there is no clinically accepted way of
43 predicting outcome, at an individual level or even in populations with OA. Recently a large FNIH-OARSI
44 consortium was created to identify biomarkers of progression. To date, most work has been
45 performed in serum or plasma, primarily measuring cartilage matrix proteins or their fragments which
46 are lost upon degeneration. Although effects in prognostic models were seen, for CTX-II and urinary
47 NTX-1 for example(94) and certain imaging biomarkers(95), their effects once other factors are
48 accounted for appear relatively weak. It is difficult to see how this will map to an algorithm fit for

1 clinical trials or the clinic. Clinical factors such as age, gender and obesity and the radiographic stage
2 of the disease are still the most reliable predictors of progression in OA.
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5 So can we do better in PTOA? If we can identify molecular pathways or their markers which predict at
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7 the time of their joint injury those individuals at high risk of later PTOA, we can make progress in
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9 intervening in this process to prevent OA. There are a number of positives here. There is a strong
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11 clinical argument for stratification in this setting. Patients want to know their risk; those at highest risk
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13 would likely benefit from an effective therapeutic, but safety and cost would likely argue against
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15 treating all (given the proportion who do well). There is less comorbidity and other pharmacology to
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17 confound outcomes than are seen in established OA cohorts seeking valid biomarkers. And the ability
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19 to make measurements at the time of injury and sequentially from this point theoretically makes any
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21 biomarker easier to follow in a population.
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28 **How similar is PTOA to non-traumatic OA?**

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30 One of the biggest questions for this field is how similar (or different) PTOA and other OA truly are.
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32 Whether there are any subgroups that are actually definable in OA remains uncertain(96). There have
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34 been reports that PTOA is different because it occurs in in younger people (because of when these
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36 injuries occur) or is faster progressing (still uncertain given the risk of ascertainment bias here).
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38 However, there remains little compelling radiological, clinical or molecular evidence that truly
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40 delineates PTOA as a different disease or even a true subgroup or different phenotype of OA. The
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42 clinical endpoint looks remarkably similar, albeit in an often younger person (“young people with old
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44 knees”-L.S.Lohmander). The structural appearances look the same (83) and the molecular changes
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46 within the joint look similar at the point of developing disease, as far as has been described at a
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48 candidate protein level(62, 97). Is a person with PTOA someone who has brought forward the OA that
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50 they would have developed anyway, because of other risk factors? Or are there different processes at
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52 play which are governed by different genetic risk and predisposing factors? We know that obesity,
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54 ageing, malalignment and a defunctioning meniscus are important in predicting accelerated knee OA,
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whether you have been exposed to joint trauma or not (98, 99) (Figure 4). Those developing accelerated knee OA which is non-traumatic were twice as likely to have degeneration of ACL, again suggesting a common pathway may be likely (100).

Are PTOA and more 'usual' OA genetically the same, or different? Knowing what genes confer risk of PTOA would be invaluable in answering this. About 60% of all knee OA risk is estimated to be heritable. Despite large-scale genome wide association studies (GWAS) in OA which often exclude cases of PTOA, there are no validated genetic predictive markers for knee OA, although this approach has reproducibly identified a number of loci and relevant biological pathways. Now a total of ~90 loci have been associated with OA, with a growing number as case-control studies get ever larger(101, 102). It is interesting to note that several 'hits' are in genes known to be mechanosensitive, or in repair pathways. However, an individual's genetic risk of OA after an acute joint injury is unknown, as is the extent of any such risk being shared with those at risk of non-traumatic OA. Interestingly, some OA risk variants conferred higher risk in those giving a retrospective history of knee injury than that seen in non-traumatic cases(103). However, retrospective injury ascertainment likely lacks specificity, including those with early OA presentation. No genomics studies have been performed in prospective acute knee injury cohorts or examined more recently identified loci. Testing whether some of these genes might mediate their effects via mechanically-induced pathways might be amenable to a PTOA setting.

Conclusion

Clinically significant injury to a joint can be thought of as a 'joint attack', akin to a heart attack: a dangerous situation for some with an opportunity for prevention and outcome modification which is time urgent. Whether considered as a subgroup of OA or the same disease, studies in PTOA to date have been an achievable way of making traction in our understanding of OA. We need to discover more about individual responses to tissue injury, whether these are governed by genetic variants and

indeed whether there are true OA ‘subgroups’ (Figure 4). This will allow us to stratify and move to treat those at risk. Careful analysis, testing unproven hypotheses around disease phenotyping is much needed. PTOA may be a minority sport, but researching a well-defined niche will likely allow us a much-needed foothold on the insurmountable problem of OA.

Key Points

- PTOA is a mechanically-driven disease which has provided insight into mechanically driven processes underlying OA as a whole.
- A cellular, mechanosensitive, inflammatory injury response in joint tissues is triggered by acute joint injury and this response is also seen in OA.
- Imaging features of PTOA are highly similar to OA, arguing against it being a different phenotype, but true similarities and differences need to be better understood.
- PTOA may allow us to approach the development of targeted novel therapeutics which seek to prevent OA.
- PTOA remains an important and tractable niche in which to better understand processes underlying OA.

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The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflicts of interest

FW has received previous clinical study grants from Pfizer and Astellas Pharma in relation to studies in osteoarthritis not related to this work.

Figure legends

Figure 1. The pathway from injury to OA: what have we learned from animal models?

Destabilising injuries bring about abnormal mechanical load by surgical or non-surgical surrogate injury. The subsequent abnormal loading across the joint appears necessary to initiate signalling pathways which bring about joint damage and later OA. Although this appears a linear process, it would appear both a modifiable and potentially reversible one, influenced by many individual and exogenous factors in both humans and mice (see Figure 4).

Figure 2. Intervening to prevent PTOA

A preventive intervention in the context of injury can be delivered in a 'window of opportunity', near to the time of the injury. This is a different approach to delivering disease-modifying interventions in early or established disease and is a therapeutic opportunity which is unique to PTOA, but could inform our approach to treatment of OA.

Figure 3. Considerations for the design and delivery of interventional studies at the time of injury

In designing studies at the time of joint injury, aspects such as governance and approvals, who to include (and exclude) in such trials using approaches including stratification, when interventions need to occur (the 'window of opportunity') and how they should be delivered (mode, challenges of intra-articular delivery). An additional consideration is what molecular, clinical and imaging outcomes are informative, how they relate to each other and whether true 'surrogate endpoints' can be established which shorten studies.

Figure 4. Factors influencing development of PTOA are similar to OA

A number of factors influence or predict the development of PTOA, although more work is needed to fully understand their relative influence. These can be divided into related groups of injury factors,

person factors and biological factors. It can be seen that there is likely to be much overlap with OA as
a whole.

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UK based analysis of usual clinical care data seeking to quantify the true increase in relative risk of OA after joint injury.

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Further analysis from the KANON data set examining both synovial fluid biomarkers and imaging based measures of synovial inflammation and their relationship to imaging based outcomes.

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Very long term follow-up of cases after ACL rupture, demonstrating its prevalence at this late time.

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Important systematic review in this area, bringing together data which suggests that meniscal and chondral injury are both important independent risk factors, regardless of the nature of other injury.

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Synovial fluid biomarkers of joint injury are tested in another mechanodependent situation, knee joint distraction with evidence of clinically relevant translation to this OA setting of selected markers.

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3D exploration showing rapid bone shape changes after joint injury in a particular pattern, highlighting the similarities with bone remodelling patterns in OA overall.

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First clinical trial considerations paper in this area around the design and conduction of studies seeking to prevent OA after injury, based on a consensus exercise and highlighting key areas and research needs.

Figure 1

Figure 2

Pre-trial

Population

Intervention

Comparator

Intervention/Comparator

PROMs
Novel
imaging
Other
biomarker

Surrogate endpoint

X-ray/MR
Imaging

Outcome

Figure 3

Figure 4

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