Common Outcome Measurements in Early Pre-radiographic Osteoarthritis

A Post-OARSI Discussion Meeting

Sunday May 3, 2015
12:30-6:00

Co-sponsored by

Alberta Innovates Health Solutions

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OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Common Outcome Measurements in Early Pre-radiographic Osteoarthritis

Sunday May 3, 2015
Sheraton Seattle Hotel – Cedar Room

Co-Chairs – Dr. Carolyn Emery (Canada) and Dr. Nigel Arden (UK)

Schedule:

15 minutes allotted per topic area inclusive of 10 minute presentation and 5 minutes discussion
Written feedback, comments and suggested additions will be encouraged also throughout meeting.

12:30-1:30 Lunch provided

12:40-12:45 Introduction: Carolyn Emery (Canada) Common Data Elements Early OA Outcomes
12:45-1:00 Early OA Overview: Stefan Lohmander (Sweden)
1:00-1:15 Patient-reported outcome measures: Ewa Roos (Denmark) (early presentation due to flight schedule)

Early pre-radiographic cohort studies
1:15-1:30 Early PTOA ACL Cohort Study: May Arna Riseberg (Norway)
1:30-1:45 Early PTOA ACL + Meniscal Cohort Studies: Kim Bennell (Australia)
1:45-2:00 Early PTOA Cohort Study: Jackie Whittaker (Canada)

2:00-2:15 Discussion

Group 1
2:15-2:30 Early OA vs normal aging: An epidemiological perspective Martin Englund (Sweden)
2:30-2:45 Prognostic Modeling/Risk Assessment: Nigel Arden (UK) and Elina Losina (USA)

Group 2
2:45-3:00 Imaging: David Hunter (Australia) and Ali Guermazi (USA)

Group 3
3:00-3:15 Functional Outcomes: Jackie Whittaker (Canada), Kim Bennell (Australia), Frank Luyten (Belgium), Sabine Verschueren, Lynne Snyder-Mackler (USA), May Arna Riseberg (Norway), Carolyn Emery (Canada)

Group 4
3:15-3:30 Early clinical signs and symptoms/Pain: Jos Runar (The Netherlands), *Sita Bierma-Zeinstra (The Netherlands), George Peat (UK)*

Discussion 3:30-3:45

Break 3:45-4:00

Group 5
4:00-4:15 Physical Activity, Nutrition and Adiposity: Clodagh Toomey (Canada), *Raylene Reimer (Canada), Linda Woodhouse (Canada), Dylan Thompson (UK)*

Group 6
4:15-4:30 Biomechanics: Janet Ronsky (Canada), David Lloyd (Australia), Tom Andriacchi (USA), Gregor Kuntze (Canada)

Group 7
4:30-4:45 Biomarkers: Virginia Kraus (USA), Ali Mobasheri (UK)

4:45-5:00 Interface between biomechanics, imaging and biomarkers Tom Andriacchi (USA)

Group 8
5:00-5:15 Translation from animal models: *Walter Herzog* (Canada), *Rami Korhonen* (Finland), Kelsey Collins (Canada)

5:15-5:45 Discussion

5:45-6:00 Next Steps: Carolyn Emery (Canada) and Nigel Arden (UK)

TOPIC: Prognostic Modelling and Risk Assessment in Early Osteoarthritis

Nigel Arden

The ability to predict disease progression, and to identify the mechanisms driving the risk, is the holy grail of chronic disease management. This is often a difficult task, particularly in heterogeneous diseases, increasing sophisticated statistical methodology and the availability of large population-based cohort studies is now making this a viable option. The FRAX tool to predict the risk of hip and osteoporotic fractures has demonstrated the ability, not only to produce such a tool, but also to translate it into clinical practice and modify disease management. Osteoporotic fracture, however, has a less heterogeneous phenotype and aetiology than osteoarthritis and the added complexity of reproducing this process in osteoarthritis should not be underestimated.

Although the definition of early osteoarthritis (OA) and appropriate outcomes are in their infancy, we already know from established OA that it is a very heterogeneous disease, not only in terms of its presentation, but also in terms of its progression. We know that many patients with knee OA do not progress even over a period of ten years. (1, 2). This emphasises the importance of being able to predict progression in such patients.

Early work has shown the ability to predict the incidence of OA with papers from Rotterdam and Chingford showing the ability to predict incident radiographic knee OA with areas under the curve (AUC) of approximately 0.8 (3). Data from Chingford cohort Study has also demonstrated the ability to predict the onset of radiographic hip OA and total hip replacements over 20 years with an AUC of 0.81.

When accessing risk assessment and producing a predictive model for early osteoarthritis there are numerous important aspects that need to be decided upon before the process is undertaken;

1. The exact definition of the outcome needs to be defined.
2. The exposures and their definitions need to be defined.
3. Important compounding variables and interactions terms need to be defined.
4. The duration of the prediction period is also important. This needs to be a clinically relevant period of time, such as 5-10 years. It is possible that risk factors and their importance will differ between short term outcomes, eg one year and long term outcomes of 10-20 years
5. The setting in which the risk prediction tool will be used is important. It is likely that this tool will be used in primary care and therefore expensive and intensive methodology, such as MRI scans and biomarkers are unlikely to feature in this model. Models for research or secondary care however can include more complex and expensive procedures.

It is also important to note, particularly in a heterogeneous disease such as OA, that identifying risk factors and predicting incidents and progression may be very different from the risk factors involved in predicting response to either secondary prevention or treatment strategies. It is therefore likely that more than one set of risk factors and models may need to be produced.

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TOPIC: Imaging

David J. Hunter and Ali Guermazi

Radiography only depicts OA when the disease has already progressed with morphologic changes and therefore this is not a suitable modality for "early OA" imaging. We can go one step earlier with MRI – morphologic (conventional) MRI, and we can go even one more step earlier with compositional MRI. MRI also affords the opportunity to visualize multiple different articular structures that are not visible on plain radiography. Recently a definition of OA was proposed on MRI (Hunter et al 2011) to facilitate earlier detection and this has recently been utilized in a couple of studies investigating early and or post-traumatic OA (PTOA).

Semiquantitative MRI:
Conventional MRI enables evaluation of morphologic changes related to early OA, including but not limited to cartilage damage, meniscal tear, synovitis, bone marrow lesions, and ligamentous damage. These changes are important because they cannot be directly visualized on radiography. Semiquantitative MRI evaluation can be done using several available scoring systems but the most up-to-date system is MOAKS. Specifically for synovitis assessment, contrast-enhanced MRI should be used and there are semiquantitative scoring system based on contrast-enhanced MRI. Recent population-based study showed a very high proportion of radiographically normal knees has osteophytes and cartilage damage (Guermazi et al. BMJ 2012; Hayashi et al. 2014). Another population based study showed severe cartilage damage (assessed using WORMS) can be present within a subregion of the knee joint that has no or very small osteophytes (Roemer et al. 2012). Also, a high proportion of knees with no, equivocal or very small osteophytes do have MRI-detected cartilage damage, and some of them are high WORMS grade (5 and 6) (Roemer et al. 2012). Data from OAI/POMA suggests cartilage damage, bone marrow lesions, medial meniscal damage, Hoffa synovitis and effusion synovitis are related to incident radiographic OA after one year (Roemer et al. 2014).

Quantitative Cartilage Measurement:
Nearly half of knee injuries that result in an ACL rupture also cause direct articular cartilage damage, particularly on the medial (41-43%) and lateral (20%) femoral condyles (Tandogan R, et al.2004, Brophy R, et al. 2010). Direct cartilage damage is associated with short-term matrix disruption, chondrocyte necrosis and proteoglycan loss (Johnson D et al 1998). Though it is not yet known whether these changes are ultimately reversible, or become irreversible if a certain amount of damage is sustained, it is possible that the initial trauma plays a role in instigating the well-described progressive cartilage loss that is characteristic of osteoarthritis.

A recent study by Frobell *et al* using data from the longitudinal KANON trial reported that two years post-injury significant cartilage thickening was observed in the central medial aspect of the femur, whilst marked thinning had occurred in the femoral trochlea and the posterior aspects of both the medial and lateral aspects of the femur (Frobell R. 2011). These findings were particularly interesting in the context of osteoarthritis, given that osteoarthritis occurs predominantly in the medial compartment, and that animal models have demonstrated that cartilage hypertrophy precedes the characteristic cartilage breakdown (van der Kraan P, et al. 2012).

Bone shape:
One joint tissue that is pivotally involved in OA pathogenesis and responds promptly to altered load is the subchondral bone. There is also emerging evidence that structural changes in the shape of subchondral bone at both the hip and knee may be involved in the pathogenesis of OA (Ganz R, et

al. 2003. Haverkamp DJ, et al. 2011. Neogi T, et al. 2013.) Whilst there is still considerable debate, many studies suggest that alterations in bone may precede other structural changes in OA (Anderson-MacKenzie JM, et al. 2005, Hayami T, et al. 2006, Hutton CW, et al. 1986, Ding C, et al. 2007). Neogi et al. found that a wider and flatter femoral condyle predicted later onset of radiographic OA (Neogi T, et al. 2013.). Hunter *et al* recently reported that flattening of the femur and increased depression of the tibial surface was detectable within three months of ACL injury (Hunter et al 2014).

Compositional MRI:

Advanced MRI techniques enable evaluation of the biochemical or ultrastructural composition of articular cartilage, meniscus and other tissues relevant to OA research (Burstein et al. 2009; Baum et al. 2013). To date, its application is mainly focusing on cartilage imaging. These compositional MRI techniques have the potential to supplement clinical MRI sequences in identifying cartilage degeneration at an earlier stage than is possible today using morphologic sequences only. Compositional MRI techniques include T2 mapping, T2* Mapping, T1 rho, dGEMRIC, gagCEST, sodium imaging and diffusion weighted imaging (Burstein et al. 2009; Crema et al 2011). The different techniques are complementary. Some focus on isotropy or the collagen network (e.g. T2 mapping) and others are more specific in regard to tissue composition, e.g. gagCEST or dGEMRIC that convey information on the GAG concentration. To date, however, the relevance of these techniques to clinical or structural outcomes is unclear and there is a lack of studies focusing on responsiveness. In addition to the different tissue components that are targeted by the different techniques, applicability and feasibility will play an important role in the implementation of the different methodologies in a larger research audience or to clinical practice. While some, like T2 mapping and dGEMRIC, are easily applied at standard clinical platforms at 1.5 or 3.0T, others require either dedicated hardware or software (like T1rho, gagCEST or sodium). Although the particular strengths and weaknesses of the different compositional MRI techniques still need to be determined, they seem to offer much in terms of predicting structural and clinical outcomes, taking into account feasibility of application, reliability and responsiveness of the different techniques available today.

Fractal Signature Analysis:

The subchondral bone is thought to play a key role in the pathogenesis of OA. Efforts to quantify trabecular bone structural changes in patients have included computed tomography, MRI, and radiography. One approach for assessing trabecular integrity from radiographs uses fractal signature analysis that provides an indication of the number, spacing, and cross-connectivity of bone trabeculae. Studies have shown that the baseline bone trabecular integrity (BTI) of the medial tibial plateau predicted medial knee joint space narrowing over the ensuing three years with 75% accuracy (Kraus et al. 2009) and that BTI predicts structural OA progression as determined by radiographic and MRI outcomes (Kraus et al. 2013). BTI may therefore be worthy of study as an outcome measure for early OA studies and clinical trials.

Recommendations

1. The utility of plain radiography in early OA is limited due to inability to detect early structural changes.
2. MRI has superior sensitivity to change and validity in the context of early OA.
3. Further MRI research on the predictive validity (related to longer term development of OA) and utility in clinical trials (both as a prognostic but also as efficacy of intervention markers) is required before making defined recommendations about one MRI measure over another.

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TOPIC: Physical Function Outcomes

Jackie Whittaker, Kim Bennell, May Arna Risberg, Sabine Verschueren, Frank Luyten, Lynn Snyder-Mackler, Carolyn Emery

Background: Osteoarthritis (OA) is multifaceted and thought to result from the interplay of multiple etiological factors, several of which are modifiable.[1-4] It is important to ensure that clinical research evaluating 'at risk' (intra-articular knee injury, morphological characteristics and/or obese) and 'early-OA' (symptomatic KL grade 0-1) populations incorporate robust population-specific physical function outcome measures. These outcomes may provide clues vital to informing the early detection of OA, disease trajectory and development of interventions aimed at halting or slowing disease progression.[5] There is a lack of consensus regarding which physical function outcomes are most relevant for use in these populations. This overview provides a summary of physical function outcomes in these populations based on review of published evidence, emerging evidence (ongoing studies) and clinical expertise informing best practice. A core (including those supported by moderate-strong measurement properties evidence) and a recommended set of outcomes (supported by emerging-minimal evidence and clinical expertise) are proposed.

Physical function is defined as 'physiological functions' and 'the ability to move around and to perform daily activities' that can be classified as 'body functions' or 'activities' using the World Health Organization International Classification of Functioning, Disability and Health (ICF) model.[6] Physical function is multi-dimensional as such both performance-based and physical impairment measures (requiring specialized pieces of equipment and raters) are included. ICF categories, equipment, recommended age range and clinimetric properties summarized in table 1.

Core Physical Function Outcome Set Candidates – * Strong † Moderate evidence

1. Performance-based
   a. Single Leg Hop for distance[7-12] *
   b. Cross Hop for distance[7-11] †
   c. 6 meter Timed Hop Test[7-11] †
   d. Star Excursion balance test (SEBT)[12-17] †
   e. 30-second Chair Stand Test[18-20]
   f. 6-minute walk test (6MWT) [21 22]

Items a through c test similar constructs. As such, it would be ideal to choose one.

2. Physical Impairment
   a. Quadriceps strength[7 8 12 23] †

Recommended Physical Function Outcomes

1. Performance-based
   a. Vertical Drop Jump[12 24]
   b. Single Leg Squat[12 25 26]
   c. Unipedal Dynamic Balance (UPDB)[12 27]
   d. 20 meter Shuttle Run[12 28]
2. Physical Impairment
   a. Hamstring strength (enables calculation of knee extensor and flexor ratio).[12]
   b. Hip abductors/adductors strength[12] (enables calculation of hip abductor/adductor ratio).[12]

Recommendations:

1. The minimal core set of physical functions outcomes in 'at risk' and 'early-OA' cohorts should include some or all of the following; a single leg and cross hop for distance test, 6 meter timed hop test, the SEBT, 6 minute walk test and a measure of quadriceps strength.
2. Additional outcomes that may be relevant depending on sample characteristics (i.e. age) and setting include; vertical drop jump, single leg squat, UPDB and 20m shuttle run. Further, measures of hamstring, hip abductor and adductor strength may be considered.
3. Further research validating functional outcomes in 'at risk' (intra-articular knee injury and/or obese) and 'early-OA' populations is required.

Table 1: ICF codes, equipment needed, clinimetric properties (related to knee OA) and recommended age range of core and recommended physical function outcomes

Measure	ICF Code(s)	Measure	Equipment Required	Reliability			Measurement Error	Validity		Responsive	Interpretability	Appropriate Age / Risk group
				Intra	Inter	Retest		Structural	Hypothesis testing			
SLHD	b710, 715, 730, 760, d455, 920	Length (cm)	MT	+++	0	0	?	0	+/-	?	0	≤45 yrs / PT
XHD	b710, 715, 730, 760, d455, 920	Length (cm)	MT, line	++	0	0	?	0	+/-	?	0	≤45 yrs / PT
6MTH	b710, 715, 730, 760, d455, 920	Time (sec)	MT	++	0	0	?	0	+	?	0	≤45 yrs / PT
SEBT	b760, b715, d415, 920	Length (% leg length)	Measuring mat, MT, skilled rater (leg length)	++	++	+	+	0	+/-	?	0	All / PT, O
30s-CST*	d410	Count	Chair, timer	+	+	0	0	0	0	0	0	All / PT, O
6MWT	d410, 450, 455	Length (m)	Flat 20m walking area, colored tape, timer, chair	0	0	?	?	0	0	?	0	All / O
Quadricep strength	b730	Force (Nm/Kg)	HH or isokinetic dynamometer, skilled rater	+	+	+	+	+	+	+	+	All / PT, O
VDJ	b710, 730, 760, d410, 455, 920	Risk rating	31cm high box	+	+	0	?	0	+/-	?	0	≤45 yrs / PT
SLS	b710, 730, 760, d 410, 455, 920	Risk rating	none	+	+	0	?	+/-	+/-	?	0	All / PT, O
UPDB	b715, b740, d415, 920	Time (sec)	Balance pad, timer	0	+	+	?	+	+	?	0	All / PT, O
Shuttle Run (20m)	b710, 740, 760, d450, 920	Stage	Colored tape, recorded instructions.	0	0	+	+	-/+	+	?	0	≤45 yrs / PT
Hamstring strength	b730	Force (Nm/Kg)	HH or isokinetic dynamometer, skilled rater	+	+	+	+	+/-	+/-	+/-	+	All / PT, O
Hip add / abductor strength	b730	Force (Nm/Kg)	HH or isokinetic dynamometer, skilled rater	+	+	+	+	?	+/-	?	0	All / PT, O

SLHD = single leg hop for distance, XHD = cross hop for distance, 6MTH = 6 meter timed hop test, SEBT = star excursion balance test, 30s-CST = 30-second chair stand test, * clinimetrics limited to persons with OA, 6MWT = 6 minute walk test, VDJ = vertical drop jump, SLS = single leg squat, UPDB = unipedal dynamic balance, + = positive rating, - = negative rating; +++ or --- = strong evidence, ++ or -- = moderate evidence, + of - = limited evidence, +/- = conflicting evidence, ? Unknown, 0 = no evidence, HH = hand-held, MT = measuring tape, O = Obese, PT = post-trauma. Adapted from Kroman et al.[11]

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TOPIC: Early Signs and Symptoms (Inclusive Of Koos/Qol and Pain)

Ewa Roos, Sita Bierma-Zeinstra, George Peat

Osteoarthritis (OA) develops slowly. For example, it may take 10-15 years from having a major knee injury until structural changes are seen on radiographs. Most available patient-reported outcome measures (PRO) were developed to assess either young patients with a knee injury (e.g. Lysholm) or older patients with established (radiographic) OA (e.g. WOMAC). These and other available instruments are presented in detail, including their psychometric properties, from previous reviews of measures of adult pain[1] and knee function[2] published in 2011.

Sources of Evidence on Early Signs and Symptoms of OA
Our knowledge of the early signs and symptoms of OA, and the performance of new and existing measures of these, comes from three main sources.

First-hand narrative accounts of early symptom experiences of people with OA. Among qualitative studies eliciting first-hand accounts of early symptom experiences, the studies by Gooberman-Hill et al.[3], Hawker et al. [4], and Maly & Cott[5] are particularly noteworthy. Specific themes that emerge from these studies are:

- The insidious onset of symptoms and variable interval before presentation to health care services. The precise timing and nature of initial symptoms may be difficult to recall or otherwise determine. Initial symptoms may not even be comfortably labelled as 'pain'. Instead they may be experienced as 'an awareness' of the knee, loss of confidence (see later section on KOOS item), or needing to 'be careful'.
- The often intermittent nature of symptoms in the early stages of OA and the predictability of these. Classification and measurement of OA pain has traditionally been informed explicitly or implicitly by the idea of OA pain as 'constant' or 'present on most days'. As a result, existing measures may have floor effects in early OA.
- The early emergence of adaptive behaviours. Symptom frequency and intensity may be preserved through selection (e.g. performing some activities less often), optimisation (e.g. greater advance planning of activities, including anticipatory analgesic use), and compensatory (e.g. modifying the way activities are performed) adaptations.[6] Pain systems are not hard-wired and individuals are not passive.[7] The use of adaptive behaviours is a legitimate topic for outcome measurement in early OA. Future studies on the psychometric properties of the recently-published Questionnaire to Identify Knee Symptoms (QuIKS[8]) offer one promising avenue.

These studies have given rise to proposed qualitative descriptions of early, mid, and advanced OA symptoms which have been recently used in a novel quantitative study to evaluate state transition in knee OA,[9] and the development of the OA-specific Intermittent and Constant Osteoarthritis Pain (ICOAP) measure which includes a subscale on intermittent symptoms.[10] The ICOAP has a growing body of evidence on its psychometric properties (>8 original papers since the latest review[1]).

Recorded observations made by healthcare professionals to whom OA presents in its early phase. Primary care would be an obvious starting point but there appears to be remarkably few formally recorded observations of early OA published in the medical literature.

Quantitative observational analytic studies (cross-sectional and longitudinal) using patient-reported outcome measures (PRO) and observer-assessed measures. To identify symptoms and signs of early osteoarthritis (OA) different methods can be used. One can search for symptoms and signs or functional tests in prospective longitudinal studies that predict evident OA at a later time point; the study population in such prospective longitudinal studies could be subjects with recent onset complaints, subjects at high risk for OA, or subjects from the general population. Cross-sectional

studies can be used when signs and symptoms or functional tests can be identified that associate with early structural changes of OA. Hereby measures like predictive values, sensitivity, specificity, likelihood ratios (LR), areas under the curve (AUC) are important to interpret the discriminate value of the signs, symptoms, tests or their combinations.

Focus on KOOS

The Knee injury and Osteoarthritis Outcome Score (KOOS) was developed for self-report of patient-relevant outcomes across the lifespan, from time of knee injury until knee osteoarthritis eventually develops.[11] More recently KOOS-Child was developed for evaluation of children with knee problems.[12,13] KOOS' psychometric properties have been reported in more than 35 publications and are well known in young, middle-aged and elderly groups with knee injury or OA, and across the spectrum of treatments from acute knee injury via degenerative meniscal tear and early OA to total joint replacement.[14] The KOOS is feasible to administer electronically with similar psychometric properties to the paper version.[15] For comparative reasons, population-based KOOS reference data are available.[16] The KOOS is in the public domain and freely available in 45 language versions (www.koos.nu). Longitudinal KOOS data have been collected from more than 100.000 unique patients in surgical registries of anterior cruciate ligament reconstruction and knee replacement in the Scandinavian countries, the UK, the US and Australia. KOOS data are also freely available from the at-risk cohort and the cohort with established disease in the NIH-sponsored OA Initiative.

The KOOS assesses perceived pain and other symptoms, perceived difficulty with function during daily life and sport and recreational activities, and knee-related quality of life, in five separate subscales. Each subscale is scored from 0 to 100 on a worst to best scale. A users guide, a scoring manual and a scoring file, are available from www.koos.nu.

To ensure content validity and relevance for patients of diverse age and functional activity levels, the KOOS holds two subscales relating to physical function. The KOOS ADL subscale is equivalent to the Function subscale of WOMAC 3.0, and holds items related to activities of daily living. The ADL subscale measures large effects from total knee replacement in the elderly but is the subscale that is the least relevant at younger ages, and change related to treatment of knee injury in young adults is small. The KOOS Sport/Rec subscale assesses the perceived difficulty with items such as running, jumping, squatting, kneeling and pivoting, of relevance for activities beyond daily living. These items are of great relevance to younger populations and consequently the subscale is responsive to treatment. Interestingly, every other elderly person having knee replacement confirms these items being of high relevance and improvements are seen following surgery.[17,18]

KOOS Pain assesses pain frequency and pain perceived during different activities and during night. KOOS symptoms encompasses a range of clinical symptoms and signs such as swelling, stiffness, mechanical symptoms and range of motion. These symptoms are not necessarily closely correlated in one patient and the trajectory of each symptom may vary widely among patients. Thus the psychometric properties of this subscale are inferior compared to the other KOOS subscales. Finally, KOOS QOL assesses impact of the knee problem on trust in knee, life style and life in general. The item Q3 asking "How much are you troubled with lack of confidence in your knee" is increasingly used as an individual item to report on this aspect.[19,20]

In summary, KOOS was developed with the intention to capture symptoms, function and quality of life across the life span, from time of knee injury to development of osteoarthritis. Its psychometric properties are well-established and good to excellent across different age and treatment groups.

Conclusions

It cannot be assumed that condition-specific measures developed for more advanced OA will have adequate psychometric properties when applied in early OA: content validity and responsiveness are

particular concerns. Yet the requirement for adequate performance in early OA must be balanced against the benefits for a coherent evidence base that comes from using common measures across the spectrum from early to advanced OA. Of existing measures, the KOOS and ICOAP appear to best strike this balance and are therefore strong candidates for evaluating early, pre-radiographic OA. While KOOS evaluates pain, other symptoms, function and quality of life, the ICOAP focuses on aspects of pain. Both have the advantage of being freely available. We would encourage the earlier reviews of the psychometric properties of these two measures to be systematically updated with specific attention to their performance in early OA.

Recommendations:

1. Ultra-brief 1 or 2-item unidimensional generic measures – 11-point numerical rating scale (NRS), SF-36 Bodily Pain Scale (BPS) – already recommended in previous reviews[1,21] are likely to be applicable also in early OA. However, as noted in these reviews, these measures give a restrictive view of pain intensity only.
2. The Knee Injury and Osteoarthritis Outcome Score (KOOS) can be used to capture pain during activity, other symptoms, function in daily life and during sport and recreational activities, and quality of life across age and treatment groups.
3. ICOAP for evaluation of constant and intermittent pain
4. Clinical signs, functional tests

Abbreviations

BPS Bodily Pain Scale; ICOAP Intermittent and Constant Osteoarthritis Pain; QuIKS Questionnaire to Identify Knee Symptoms; KOOS Knee injury and Osteoarthritis Outcome Score; NRS Numerical Rating Scale; OA Osteoarthritis; PRO Patient Reported Outcome Measure; SF-36 Short-Form-36; WOMAC Western Ontario & McMaster Osteoarthritis Index;

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TOPIC: Adiposity, Physical Activity and Nutrition

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Osteoarthritis (OA) typically develops over decades, offering a window of time to potentially alter its course.[1] Aside from joint trauma, the presence of modifiable OA risk factors, such as obesity, physical activity and dietary risk factors, may lead to a more severe outcome. While these factors have been examined in detail in end-stage OA, unmet needs exist to monitor and address the modifiable risk factors for early pre-radiographic inflammation and to prevent or delay the development of early OA in high risk individuals (e.g. following joint injury in youth sport).

Adiposity Outcome Measures

1. Body Mass Index (BMI): Measured as body mass/height^2 (kg/m^2), recent systematic reviews have shown some evidence of an association between BMI ≥25kg/m^2 (overweight) or ≥30kg/m^2 (obese) and radiographic hip or knee OA,[2] limited evidence for a significant association between increased BMI and reduced cartilage volume[3] and moderate evidence for a relationship between obesity and bone marrow lesions at the knee.[4] In 255 40-79 year olds with self-reported knee pain, radiographic OA (K/L grade ≥2) was associated with BMI but pre-radiographic OA (magnetic resonance cartilage score ≥2) was not.[5] *Extrapolation/Summary:* In a population with pre-radiographic OA, possibly attributable to a traumatic joint injury through sport, high BMI can be a result of high lean mass as opposed to high fat mass (athletic phenotype) and therefore may not be the most appropriate outcome measure of adiposity.
2. Total Fat (Fat Mass (FM;kg), FM%, FM Index (FM/height^2): Measured using dual-energy x-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), and anthropometry allows a direct measure of adiposity. FM is positively associated with increased risk of cartilage defects and bone marrow lesions in the knee in a relatively healthy population (age 25-60y), [6] and in women (not men) with structural (MRI) diagnosed OA.[7] Similar trends are apparent in longitudinal analyses, where FM and FM% are negatively associated with the annual change in medial cartilage volume in older adults (age 51-81y) over 2 years[8] and in healthy, community-based adults (age 50-79y) over 10 years.[9] In a youth sport cohort, Myer *et al*[10] has shown that female athletes (age 11-20y) with knee injuries will increase their FM by up to 1.5% compared to their non-injured peers within the first year of injury, indicating that injury during the growing years may be associated with unfavorable changes in adiposity, thus compounding the risk of early OA. *Extrapolation/Summary:* In addition to an increased mechanical load, adiposity is thought to play a metabolic role in OA. Therefore a more direct measure of adiposity (FM, FM%, FMI) is required to account for its influence, independent of lean mass, in a pre-radiographic OA population.
3. Waist-Height Ratio (WHR), Waist Circumference (WC): Measured using anthropometric tape (cm), an elevated WC is one of five criteria that define the metabolic syndrome, representing a surrogate measure of abdominal or visceral adiposity and inferring 6.7 times the risk (WHR 2.2 times the risk) of severe knee OA.[11] In a non-loadbearing model, WHR was associated with clinically diagnosed hand OA in men and to a lesser extent in women.[12] In multivariate analysis of pre-radiographic OA, WC and WHR had no association with the loss of tibial cartilage volume in community-based adults[9] or the loss of patella cartilage or defects in healthy adults.[13] *Extrapolation/Summary:* In order to detect a change in visceral fat in this early stage, more accurate assessments of adiposity are needed.
4. Visceral Adipose Tissue (VAT): VAT is measured using computed tomography (CT), magnetic resonance imaging (MRI) or DXA in cm^3. In the Netherlands Epidemiology of Obesity (NEO) study, MRI-measured VAT was positively associated with hand OA in men but not women.[12] *Extrapolation/Summary:* Limited research to date. However, VAT may be involved in the pathogenesis of systemic OA due to the high quantity of pro-inflammatory cytokines (e.g. TNF-α)

secreted from visceral *vs.* subcutaneous tissue. A similar gender difference regarding VAT has been described previously in a study on cardiometabolic risk; VAT was observed to be of greater relevance in men, whereas total FM was of most importance in women.[14]

Physical Activity Outcome Measures

Participation in physical activity (PA) delays the onset of functional limitation, prevents obesity, and is essential for normal joint health.[15] In addition, PA has been shown to reduce pain and disability among persons with OA and increase their physical performance and self-efficacy. [16-18]

1. Self-Reported Methods: Subjective methods rely on the individual either to record activities as they occur or to recall previous activities. Many variations exist that include physical activity (PA) questionnaires (global, short recall or quantitative history) or PA diaries/logs. While some epidemiological studies suggest that self-reported PA is associated with cartilage degeneration, [19,20] others have discounted these conclusions. [21,22] In an analysis of 128 asymptomatic adults (mean age 50.7 years) with reported risk factors for OA, self-reported light exercise [measured via Physical Activity Scale for the Elderly (PASE)] was associated with more intact tibiofemoral collagen architecture (lower T2 relaxation times) compared to sedentary lifestyle or vigorous PA.[23] This trend was also shown in this cohort in a 4-year longitudinal analysis.[24] *Extrapolation/Summary:* Overall, validation studies of self-reported methods show strong correlations and agreement with other construct criteria measures for vigorous intensity PA, but they are generally less accurate for light-moderate intensity activities. The difficulty in delineating the relationship between activity and OA may be partly due to the subjective nature of the methods employed to assess PA levels.
2. Wearable Monitors: Wearable devices that measure body motion can be used to assess PA and estimate energy expenditure. The most commonly used sensor is an accelerometer, which measures acceleration (usually in 3 planes), capturing frequency, intensity and duration of PA in a time-stamped manner. Farr *et al*[25] attempted to quantify PA levels in early knee OA patients (K/L grade 1-2) using Actigraph (MTI) waist-worn accelerometers, finding that only 30% of subjects achieved ACSM recommended PA levels. Using Actigraph (GT1M) waist-worn accelerometry, Dunlop *et al*[26] have demonstrated in 1,680 community-dwelling adults ≥49y with (or at risk of) knee OA, that greater time spent in light intensity PA is associated with reduced onset or progression of disability. *Extrapolation/Summary:* Objective PA measures compared to self-report have stronger relationships with function in OA[27] and offer a more accurate assessment of PA and sedentary lifestyle. PA measurement is a rapidly evolving field and new approaches and techniques are being developed.[28] Recent literature has provided evidence-based appraisals and application information[29] and recommendations for multidimensional PA profiling. [30]

Nutrition Outcome Measures

Identification of weight loss[31, 32] as an intervention to improve OA symptoms, and deficiencies in vitamin C[33] & D[34], low omega-3 polyunsaturated fatty acids[35] and high fat diets[36] as risk factors for OA, warrant a need for monitoring dietary intakes in a pre-radiographic OA population.

1. Food Frequency Questionnaire (FFQ): The FFQ consists of a list of foods and a selection of options relating to the frequency of consumption of each of the foods listed (e.g. times per day, daily, weekly, monthly). FFQs are designed to collect dietary information from large numbers of individuals and are normally self-administered, aiming to capture habitual intake. Although easy to administer, FFQ show low but acceptable correlation with a 9-day food diary reference method. [37]
2. 24-hr Diet Recall: As a retrospective method, the 24-hr recall relies on an accurate memory of food and fluid intake, reliability of the respondent not to under / misreport, and an ability to estimate portion size. The primary limitation of this method is that recording consumption for a single day is seldom representative of a person's usual intake due to day-to-day variation. Three consecutive daily recalls appear more optimal for estimating energy intake. [38]

3. Food Diaries: Weighed food records involve the participant weighing each and every item of food and drink prior to consumption. Weighed records can be kept for 3,4,5 or 7 days. The 7 day weighed record has often been taken as the 'gold standard' of food diaries. [39] Food records can also be estimated, where household measures or food photographs are used to estimate intake. This is a widely used research method with lower respondent burden. The 3-day food diary has shown high correlation and agreement with the 9-day food diary.[37] *Extrapolation/Summary:* Food diaries provide an accurate measure of energy intake, which may be important in an early OA population to estimate macronutrient (e.g. fat intake) and micronutrient (e.g. vitamin D) intakes. However, all self-reported measures are subject to under-reporting.

Recommendations:

1. Due to the inherent inaccuracies of BMI, total adiposity should be measured by fat mass relative to body mass (fat mass percentage) or height^2 (fat mass index), while regional adiposity (visceral adipose tissue) measurement may be useful to determine the systemic effect on osteoarthritis
2. Assessment of physical activity is recommended using a validated hip mounted accelerometer, to accurately capture activity through each domain and intensity. If feasible, additional physiological measures can be integrated alongside measures of movement to form a multidimensional PA profile
3. Administration of a 3-day food diary to measure dietary intake is recommended as the most appropriate nutrition outcome measure due to its low burden and accurate estimation of macro- and micronutrients, important determinants in a pre-radiographic osteoarthritis cohort

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TOPIC: Biomechanics

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The knee OA disease pathway is influenced by age, obesity, and joint trauma[1,2] and results in progressive cartilage thinning and loss. Anterior cruciate ligament (ACL) rupture and/or meniscal injury/repair results in elevated risks of developing post-traumatic OA (PTOA)[2],[3]. Current radiographic grading methods are insensitive to early disease changes [4] and new approaches are sought to detect pre-radiographic change. Such approaches require knowledge of the in-vivo biomechanics of OA. Clinically symptomatic PTOA likely develops through interactions of initial acute joint trauma, alteration of joint loading patterns[5], changes to muscle morphology and function, and chronic joint inflammation[6]. Interactions amongst these factors may reduce the load-bearing capacity of the cartilages early on after injury and predispose cartilage to mechanical damage. Altered joint motions (kinematics) and joint loads (kinetics) are typically reported following injury, in radiographic OA, and in ageing. Common causes for joint mechanics changes are related to altered joint alignment[7,8], increased joint laxity and loss of dynamic joint stability (gait and balance), neuromuscular deficits of muscle atrophy and inhibition resulting in muscle weakness, and compensatory muscle activation strategies (co-contraction). The mechanical properties of cartilage appear to change due to injury and OA predisposing it to potential damage due to altered cartilage surface motions and loads. This is reflected in altered regional cartilage thicknesses (physical outcome) and longitudinal cartilage thinning (clinical outcome). However, in order to verify this mechanism it is necessary to combine and co-register a subject's own joint mechanics and regional cartilage thickness (using e.g. magnetic resonance imaging). Furthermore, estimates of joint mechanics can integrate the changes the neuromuscular deficits using new forms of patient-specific joint kinematic and neuromusculoskeletal models by combining medical imaging and motion analysis[36-39].

Recommended Biomechanics (Knee joint) Outcome Measures - based on Table 2 summary

a. Knee internal/external rotation (stance)
b. Knee flexion angle (heel strike, stance)
c. AP translation (heel strike, stance)
d. Knee adduction moment (early stance)
e. Knee flexion moment (early & late stance)
f. Center-Of-Pressure (Med-Lat excursion)
g. Multi-muscle coordination (stance)
h. Muscle inhibition/weakness (isometric/isokinetic contraction)
i. Knee joint kinematics and contact forces

Comments

1. Walking speed – controlled and self-selected needed
2. More dynamic and challenging tasks (stair climb and squats appear to bring out the motor control aspects more directly), with side cuts and running showing the most difference [9]
3. Co-contraction tied to altered gait patterns in OA subjects [10]
4. Increased use of medical imaging (RSA, MRI and CT, Motion Capture) with dual fluoroscopy and kinematic[11–13] and neuromusculoskeletal[36-39] modelling
5. Obesity is major risk factor [14]
6. General understanding of variation in whole body and segmental kinematics (e.g. trunk lean) to get at alignment effects on joint kinetics [10,40]

Recommendations

1. Tasks should involve both cyclic activities of daily living such as walking (controlled speed as well as self-selected), as well as more challenging activities such as stair ascent or descent, or single leg squat to provoke larger alterations loading and neuromotor responses necessary to distinguish differences in a pre-OA population.

2. Further understanding of role of muscle weakness (atrophy and inhibition) in balance, pain, obesity and aging in relation to joint kinematics and kinetics and cartilage thinning is required
3. Well-controlled intervention studies focusing on approaches to alter knee kinematics and kinetics, and muscle co-contraction patterns in pre-OA individuals with primary risk factors (obesity, ACL injury or ACLR, aging) are needed.
4. Develop and apply kinematic and neuromusculoskeletal models that enable refined and validated estimates of joint kinematics and cartilage loading (net force and stress/strains) to co-register with regional cartilage changes

Table 2: Summary of Common Biomechanics Outcome Measures for Knee Joint in Populations with OA or Primary Risk of OA.

Biomechanics Measure (Knee)	Phase of Movement	Measurement Type	Population	Injury Status	OA Status	Physical Outcome	Clinical Outcome
Rotation offset [15]	Stance (walk)	Imaging		Meniscus injury	Pre-OA	Thickness location	X
Rotation offset [16]	Stance (walk)	3D MAS, force plate		ACL injury	Pre-OA	Thickness location	Cartilage thinning
Rotation (↑ ext tibial) [11–13]	Stance (stair ascent [11,12], knee bend [13])	Bilateral RSA [11] Img. & DF [12,13]	Inj vs C-lat [11] Inj vs Cntl [13]	ACLD	Pre-OA		
Rotation (ext) [17]	Stance phase (running)	Stereoradiography		ACLR	Pre-OA	Thickness location	Cartilage thinning
Knee Flexion [18]	Heel strike (walk)	3D MAS	Aging	none	Pre-OA	Thickness location	Cartilage thinning
Knee Flexion [19]	Heel strike (walk)	3D MAS, force plate		?	OA	Pain	Symptoms, pain
Knee Flexion [14]	Heel strike (walk)	3D MAS, force plate	Obese	none	OA Med comp		
Knee Flexion [20]	Stance (walk)	3D MAS, force plate	Obese	none	Pre-OA	Thickness location	X
AP translation [18]	Heel strike (walk)	3D MAS	Aging	none	Pre-OA	Thickness location	Cartilage thinning
AP translation (↑) [11–13]	Stance (stair ascent [11,12], knee bend [13])	Bilateral RSA [11] Img. & DF [12,13]	Inj vs C-latl [11] Inj vs Cntl [13]	ACLD	Pre-OA		
Adduction Moment [21]	1st pk, early stance (walk)	3D MAS, force plate	Obese & Aging	None	Pre-OA	Med/lat thickness	Cartilage thinning
Adduction Moment [22,23]	1st pk, early stance (walk)	3D MAS, force plate [22], Force implant [23]		Tib- osteot., Varied	OA Med comp	Med/lat thickness	Disease progression
Adduction Moment [33]	pk stance (fast walk)	3D MAS, force plate, imaging		Partial meniscectomy	Pre-OA		Med cartilage defects
Flexion Moment [19,23]	1st pk, early stance (walk) [23], Pk late stance (walk) [19]	Force implant [23], 3D MAS [19]		?	OA [19], Med comp. [23]	Pain	Symptoms, pain
Flexion Moment [33]	pk stance (walk)	3D MAS, force plate, imaging		Partial meniscectomy	Pre-OA		↓ PT cartilage volume
BalanceSL Stance [24]	COP Med/lat exc.	Force Plate	Youth /sport	Varied	Pre-OA		X
Muscle Co-contraction [19,20,25–27]	Stance (walk)	EMG		Varied	Pre-OA [20,25–27] OA [19]	Function Pain	Symptoms, pain
Muscle Co-contraction[28]	Stance (walk)	EMG		TKA	Pre-OA		
Muscle Weakness / Inhibition [29–32]	Isometric contraction	Twitch Interpolation / Summation		Varied	Pre-OA		
Muscle Atrophy[34-35]		MRI		ACLR	Pre-OA		↓ muscle volume & PCSA

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TOPIC: Biomarkers

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Osteoarthritis (OA) is one of the most common types of arthritis and a major cause of pain and disability in older individuals. Cartilage damage in OA is detected radiographically by decreases in joint space width (JSW). However, radiographic evidence is seen only after significant cartilage degradation has already taken place. The early stages of the disease may remain latent and asymptomatic for many years. Therefore, there is an acute need for reliable biomarkers and diagnostic tests that can facilitate earlier diagnosis of OA, and inform the prognosis, monitoring and therapeutic strategies for chronic and disabling forms of this disease. However, there is currently a lack of reliable, quantifiable and easily measured biomarkers that provide an earlier diagnosis of OA, inform on the prognostic of the disease and monitor and predict responses to therapeutic modalities. Biomarkers of tissue turnover in joints can reflect disease relevant biological activity and provide valuable information that may be useful diagnostically and therapeutically, potentially enabling a more rational and personalized approach to healthcare management.

Predictive biomarkers provide an early warning of joint degeneration, and have the capacity for advancing personalized medicine by prompting earlier and more targeted treatment. In the context of this proposal biomarkers are also crucial for efficient pharmaceutical product development and can be used as tools to facilitate OA drug discovery. For example, biomarkers can be used to select or deselect patients for inclusion in clinical trials, evaluate dose-responses and optimal regimens for desired pharmacologic effect, determine dose-response for toxicity and determine the role of factors such as diet, obesity, metabolic and endocrine disorders on disease progression.

There is increased recognition within the field that inflammatory pathways and biomechanical stimuli conspire to promote a pathogenic environment. Thus, it is also crucially important to study biomarkers that may be associated with a better capacity for promoting joint repair. In doing this it should be possible to delineate both pathogenic and chondroprotective mechanisms in stratified cohorts.

What biomarkers do we currently have in our toolbox?

At the present time, the majority of biomarker available are markers of incident radiographic OA. We do not have biomarkers of early OA or reliable markers of OA progression. We also need to develop biomarkers of acute joint injury (i.e. traumatic knee injury).

Biomarkers of Incident Radiographic OA

Incident OA studies have identified some of the earliest molecular abnormalities. The study by Ling and co-workers showed that 10 years prior to radiographic hand or knee OA four serum proteins were altered in OA cases compared with controls who did not develop rOA (Ling et al., 2009). The proteins studied included matrix metalloproteinase-7 (increased), interleukin-15 (increased), plasminogen activator inhibitor-1 (increased) and soluble vascular adhesion protein-1 (decreased). Serum COMP and hyaluronan predicted the occurrence, 7 years later, of incident knee joint space narrowing (COMP and HA) and osteophyte (using COMP as a biomarker of osteophyte burden) (Golightly et al., 2010). Serum COMP was a useful biomarker that predicted the development of radiographic hip OA between 6-8 years later (Kelman et al., 2006; Chaganti et al., 2008). Mean baseline serum osteocalcin levels were associated with 3-year incident (KL >2) radiographic hand OA (>60% lower; $P = 0.02$) or knee OA (20% lower; P not significant) OA (Sowers et al., 1999). The average 3-year change in serum osteocalcin levels declined in women with incident hand OA or knee OA but increased in women without incident OA ($P < 0.02$ and $P < 0.05$, respectively) (Sowers et al., 1999).

Biomarkers of 'Early' OA – New Information from Lipidomic and Metabolomic Studies

There is increasing interest in bioactive lipids as markers of pain and inflammation. However, until

recently, there have been no sensitive analytical methods to detect these lipid species at low concentrations in biological fluids. Furthermore, it is challenging to specifically associate changes in levels of bioactive lipids to disease progression in OA patients. In addition, their location and function in synovial fluid remains to be discovered. Lipids are multifunctional molecules that regulate many biological processes, including stress responses, proliferation and differentiation, apoptosis, and senescence. New evidence suggests that certain species of sphingomyelin and ceramides may be involved in the pathogenesis of OA and RA (Kosinska et al., 2014). Lipidomic studies have shown that a broad spectrum of sphingolipid species, their precursors, and intermediate metabolites are present in human SF and mass spectrometric analysis of lipids in SF from patients with early OA, late OA, and RA knee joints indicate disease and stage-dependent differences. In synovial fluid samples sphingomyelin was the most abundant followed by ceramide and many other lipids were differentially present on early OA and late OA versus controls (Kosinska et al., 2014).

Metabolomics is an emerging "omics" field dealing with the comprehensive characterization of small metabolites in biological systems. "Metabolomic fingerprints" can be used to characterize physiological (steady state) and pathophysiological states or responses to drugs and other interventions. Metabolic profiling of biological fluids and joint tissues can provide a global view of the physiologic state of the intra-articular environment. One of the earliest metabolomic studies used NMR and principal component analysis to identify a unique urinary metabolite profile associated with OA in humans and guinea pigs (Lamers et al., 2005). Although no specific molecules were identified in this study, a disease 'signature' was reported. Adams et al., (2012) used metabolomics to identify metabolic profiles that can differentiate between OA and control synovium samples. Global metabolic profiling identified over a hundred distinct compounds with 11 compounds showing significantly different relative concentrations between end-stage and no/early disease groups. Metabolites specific to collagen metabolism, branched-chain amino acid metabolism, energy metabolism and tryptophan metabolism were amongst the most significant compounds, suggesting an altered metabolic state with disease progression (Adams et al., 2012). Future metabolomic studies of OA should ideally focus on synovial fluid to avoid the involvement of interfering metabolites from other organ systems and other inflammatory co-morbidities.

In summary, proteomic, lipidomic and metabolomic tools are increasingly used to study the profiles of cartilage and synovial tissue from patients with OA. The profiling of biological fluids and joint tissues can provide a global view of the physiologic state of the intra-articular environment of an OA joint. Refinements in omics approaches and advances in analytical techniques will enable improved metabolic profiling of different stages of disease. To be clinically useful these biomarkers would need to be properly qualified. Qualification is a process linking a biomarker with biological and clinical end points, i.e. early preradiographic OA.

Recommendations:

1. Proteomics: The latest proteomics technologies will need to be employed for the discovery of novel molecules (proteins and peptides) with biomarker utility for early OA. Identification and verification of early OA protein/peptide biomarkers is a high priority.

2. Metabolomics: "Metabolomic fingerprints" can be used to characterise physiological (steady state) and pathophysiological states or responses to drugs and other interventions. Metabolic profiling of biological fluids and joint tissues can provide a global view of the physiologic state of the intra-articular environment in early OA. Recent metabolomic studies suggest the presence of an altered "metabolic state" with disease progression. We need to learn more about metabolic changes that occur in early OA and explore analytical platforms that may deliver new biomarker assays.

3. Lipidomics: Accumulating evidence suggests that lipid mediators play important regulatory roles in joint inflammation and OA. Eicosanoids participate in the initiation of inflammation and our

knowledge of NSAIDs is largely based on prostaglandin pharmacology. However, much less is known about the regulation of pro-resolving mechanisms in chronic inflammatory diseases, which are essential for suppressing inflammation and helping restoration of tissue homeostasis. Poly-unsaturated fatty acid metabolites such as lipoxins, resolvins, protectins and maresins are recognized as potent regulators of inflammatory resolution. These mediators are generated by oxidation of poly-unsaturated fatty acids by enzymes such as cyclooxygenases and lipoxygenases. One relevant function of these mediators is believed to be modulation of immune cell function, pro-inflammatory cytokine release and reduction of pain. However, their role in the context of regulating chronic joint diseases, such as OA, requires more in-depth study using advanced methodologies in cohort of knee OA patients.

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TOPIC: Translation from Animal Models

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Preclinical animal models of OA are invaluable for quantifying early OA changes in a well-controlled manner as well as assessing outcomes *in vivo* that cannot currently be evaluated in humans. The probability of animals developing OA within weeks of trauma is greater than 50%, similar to reports in humans[1–3]. Insight from preclinical models should be explored and evaluated in clinical studies when appropriate, as both our understanding of OA and technology advance. Below, key outcomes are summarized that occur early after post-traumatic and spontaneous early OA across several animal models. Based on these findings, promising translational opportunities are recommended for evaluation in human early OA populations.

Cell Volume, Number, and Spatial organization. Impact loading and consequential cell death reduces the number of chondrocytes[4]. However, both rats and humans demonstrate specific angular changes in chondrocyte orientation in early OA which are associated with location and severity of OA lesions[5]. Moreover, collagen orientation angle primarily controls cell volume and shape in osteoarthritis human hip joint cartilage[6]. Furthermore, in rabbits, chondrocyte behavior is altered four weeks post anterior cruciate ligament transection (ACL-T) with loading, such that cell volume increases in ACL-T, while decreases in cell volume are observed in healthy cartilage[7]. Cell volumetric changes may be modulated by collagen fibril properties and changes in the peri-cellular matrix[8]. These findings may help explain previous observations of chondrocyte and cartilage tissue swelling in early OA in humans[9,10].

Collagen orientation, Fibrillation, and Matrix Changes. Changes in the microscale viscoelastic behavior of the cartilage surface are a functional hallmark of early OA – likely due to microstructural re-organization of the collagenous extracellular matrix[11]. Specifically, superficial zone chondrocytes become less parallel, and proteoglycan content is reduced[4,7]. Three days after ACL-T, rabbits demonstrate changes in cell volumetric behavior and proteoglycan content, but not changes in collagen orientation[12,13]. Four weeks post ACL-T in rabbits, femoral condyle cartilage experiences the greatest structural and mechanical alterations[14]. Moreover, collagen content increases in the middle and deep zones of ACL-T – especially in the lateral femoral condyle, which may be an upregulating response to increases in mechanical changes due to loss of superficial zone integrity[14]. Changes in these parameters can lead to altered surface interactions, or changes in contact area, and this change in surface interactions correlates well with OA damage induced by ACL-T in sheep[15]. In meniscus, collagen fibril orientations and mechanical changes are observed 6-weeks post ACL-T[16].

Subchondral Bone Microarchitecture. Healthy cartilage likely relies on subchondral bone integrity[17]. Subchondral bone is implicated in early OA changes likely due to molecular cross-talk, subchondral bone sclerosis and subsequent increases in the subchondral bone stiffness gradient. Subchondral bone changes have been suggested to precede cartilage changes[18] in some species. Specifically, significant decreases in medial subchondral bone plate thickness and trabecular thickness is evident 4 weeks after ACL-T in rabbits[19]. Moreover, in the guinea pig model of spontaneous OA, subchondral bone structural changes precede microscopic cartilage degeneration[20]. However, more work is needed to clarify the role of subchondral bone microarchitecture in early OA.

Muscle weakness. Muscle weakness is associated with OA, but it is unclear if muscle weakness leads to OA, or is a consequence of OA. In the guinea pig model of spontaneous OA, altered gene expression of myosin heavy chain in muscle is observed before OA initiation[21]. Using a Botulinum Toxin-A (BTX) model of denervation, BTX-induced muscle weakness leads to OA, and further, BTX-A + ACL-T leads to similar damage as BTX-A alone[22]. These OA-related changes are evident as early as four weeks post BTX-A[22]. *In vivo* patellar tendon and gastrocnemius forces are decreased in as few as 5 days post ACL-T, and force is increased in the non-surgical contralateral limb[23]. Furthermore, loss of

contractile material may precede OA progression in non-surgical OA models (Collins & Herzog, *unpublished observation)* but early time-course characterization of these changes is needed to clarify the role of muscle in spontaneous OA.

Synovial Fluid Concentration. Synovial inflammation may be a critical mediator in the initiation of early OA[24]. Synovial fluid is responsible for providing nutrients to tissues within the joint, providing joint lubrication to maintain the integrity of cartilage surfaces, and contributes to repair of tissues within the joint as a source of stem cells and inflammatory mediators[25]. Harvesting, profiling, and quantifying synovial fluid contents may provide insight into intra-articular changes. Boundary lubrication changes have been observed, with PRG4, or lubricin, increased, and HA decreased 2-4 weeks after ACL-T in sheep[26]. Furthermore, 2 weeks post ACL-T, metabolic profiling of synovial fluid can separate ACL-T from control surgical groups, and may be used to begin understanding the changes associated with early OA[27]. Moreover, intra-articular inflammatory interventions have been found beneficial post-trauma, while similar interventions were unsuccessful when administered systemically[28]. Notably, clinical sub-populations presenting with different systemic and intra-articular inflammatory environments that drive OA differentially have been identified[29], emphasizing the importance of the joint environment. Multiplexing arrays of inflammatory markers in synovial fluid and serum provide an in-depth profile of these factors [30,31]. In humans, this technology has been applied to differentiate patients by OA severity using protein levels in serum and synovial fluid[32]. This method could be useful in the development of our understanding of early OA, in addition to identifying at-risk individuals, and those likely to progress faster to end-stage OA.

Recommendations: Here, evaluated tissues from animal models were evaluated in isolation to draw conclusions about early OA pathology. In patients, identifying opportunities to study these phenomena may lead to increased understanding of early OA. Therefore, selected methods are proposed, as they are particularly promising for translating animal model findings to human populations:

1. High resolution μCT and 7 and 9.4 Tesla MRI may provide opportunities to evaluate structural and volumetric cartilage and subchondral bone changes at early time points post-trauma[33], before gross pathology may be observed. Even though *in vivo* imaging applications for humans have shown their potential, they have limitations[34,35]. As the resolution and real-time capabilities of these imaging technologies are advancing for human use, findings from animal models using high resolution quantitative μCT and 7 and 9.4 Tesla MRI may be considered in the human context[34,36–38].
2. With developments of real-time *in vivo* imaging, quantifying and tracking changes in cell shape and signaling, and tissue structure is possible in live animals. Specifically, chondrocyte mechanics and signaling, and cartilage collagen and proteoglycan structure can now be studied in intact joints of live animals, using physiologically relevant joint loading through controlled muscular contractions[39]. As imaging technologies advance, this approach may become of use in humans as a non-invasive indicator of cells and tissue structure *in vivo*. Currently, computational modeling is the only method enabling analysis of chondrocyte deformation behavior in the knee[40].
3. Extracting synovial fluid may be a useful tool to understand the intra-articular environment. Specifically, synovial fluid could be characterized using multiplex, sequencing, or metabolic profiling. As understanding clinical subpopulations within the OA cohort becomes critical to developing novel, rational, and targeted treatments for disease onset and trajectory, these datasets could inform or triage individuals, and mitigate risk, based on local inflammatory/protein profiles.

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