Review
Risk stratification for knee osteoarthritis progression: a narrative review
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Summary

Objective: A narrative review describing the assessment of osteoarthritis (OA) progression, and more specifically the risk factors which assist in delineating strata of individuals at greatest risk for more rapid progression.

Design: A narrative review based on selected recent medical literature.

Results: With little currently available in the treatment of this disease, better understanding of responsive and valid endpoints is essential to identifying potential new interventions for treatment of OA. Efforts to stratify those at greatest risk for progression can use a number of systemic or local risk factors that may assist in delineating populations at greater risk for progression.

Conclusions: Current data suggests that stratification of risk is feasible to ascertain those at risk for rapid progression using a number of different metrics including knee alignment, meniscal damage, bone marrow lesions and late stage disease. Identifying persons at greatest risk for progression has important implications for clinical trial planning and can enhance study efficiency.

Key words: Progression, Risk stratification.

Introduction

The paper is a narrative review of selected recent literature of some methods of stratification of knee osteoarthritis (OA) progression.

One proposed OA treatment goal is modification of the underlying joint structure. This treatment goal has become a major focus of drug development in OA. Some studies with varying levels of evidence suggest that glucosamine sulfate, chondroitin sulfate, sodium hyaluronan, doxycycline, matrix metalloproteinase (MMP) inhibitors, bisphosphonates, calcitonin, diacerein and avocado-soybean unsaponifiables may modify disease progression1. However, further definitive structure modifying therapeutic development is constrained by the need for long-term follow-up to observe changes in structure (and potential drug effects on it). Therefore, accurate, highly reproducible and responsive measures of the rate of disease progression are a prerequisite for assessing structural change in clinical trials.

Traditionally measurement of OA structural change has been performed using radiographs2. Due to inherent limitations in plain radiograph technology, further research and development has investigated other techniques that may improve the assessment of disease, its early development and its progression. Foremost among these is Magnetic Resonance Imaging (MRI), a non-invasive three dimensional (3D) method for assessing joint morphology that may supplant the widespread use of plain radiographs in clinical trials3. However, whilst MRI has enormous potential, recent studies provide a note of caution for its immediate ability to supersede the weight-bearing radiograph. The responsiveness of different measures of cartilage morphometry may not be as great as early data suggested4,5. Conservative study designs based on large MRI progression series currently in the public domain require large sample sizes, if quantitative cartilage morphometry measures are used as the endpoint. If one could confidently design studies based on smaller sample sizes and/or shorter study durations, this would greatly reduce the resource implications for MRI-based interventional studies.

Several studies have suggested that baseline clinical, biomarker and imaging features are predictive of progression of cartilage loss in the medial compartment of the knee and could be used to provide greater study power by selecting a population at greater risk for more rapid progression.

This narrative review will be broadly divided into three major areas. Firstly the methods of assessment of OA progression will be briefly discussed. For further detail on this please see other recent reviews6,7. Following this, examples of the risk factors which assist in delineating strata of individuals at greatest risk for more rapid progression will be appraised. Ultimately, the use of these strata can impact clinical trial efficiency and the implications of the use of these risk factors on trial design will also be considered.

Methods

The paper is a narrative review of methods of stratification of knee OA progression. The included studies were identified through manual and electronic searches. The manual searches included scanning of bibliographies, journals, and conference proceedings and correspondence with experts.
The electronic searches were performed in the Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Reviews of Effects and MEDLINE. No limitations were used for year of publication or language. The keywords used in the electronic searches included “knee OA,” “progression,” and “stratification.” The searches were completed on February 12, 2009. Like all narrative reviews, this is not a systematic approach to obtain primary data, or to integrate findings, or to test hypotheses. Interpretation is dependent on the opinion of the reviewer. In addition there is no use of explicit standards to evaluate the quality of the studies under review and no attempt is made to synthesize the data quantitatively. For readers interested in a systematic review of prognostic factors for knee OA progression please see the recent review by Belo et al.36

MEASURES OF OA PROGRESSION

Plain radiography

Traditionally the progression of knee OA has been assessed by measuring changes in the width of the space between the medial femoral condyle and medial tibial plateau in the X-ray beam, the greater the sensitivity to detect OA progression and the more accurate identification of the location of joint space narrowing (JSN)11–13. A number of different radiographic protocols of the knee in flexion have been developed and shown to improve the detection of JSN by providing a better exposure of the location of the greater cartilage changes in the posterior area of the femoral condyles14. There remains however considerable controversy over the preferred method of knee radiographic acquisition15,16 and joint space width (JSW) measurements17–20. The smallest standard deviation (SD) of the difference between test–retest measurements of minimum JSW in pairs of radiographs reaches about 0.1 mm in the most reproducible methods20–22 indicating a smallest detectable difference (SDD) of at least 0.2 mm, which remains relatively large considering the 0.10–0.15 mm expected average annual JSN of knee joints.

MRI

Broadly speaking, MRIs of OA structure can be measured semi-quantitatively or quantitatively, and either morphological or compositional measurements of articular cartilage can be obtained. Semi-quantitative scoring of MRIs is a valuable method for performing multi-feature assessment of the knee using conventional MRI acquisitions22–25. Such approaches score, in an observer-dependent semi-quantitative manner, a variety of features that are currently believed to be relevant to the functional integrity of the knee. The observed sensitivity to change has been relatively small. At the present time, the limited longitudinal data on these scoring systems compared to quantitative morphological cartilage measurement somewhat precludes their use as primary outcome. However, recent data suggests that full thickness defects may occur as part of early disease and that quantitative morphometry appears most useful (sensitive to change) in persons with late stage disease (in those with established disease and that quantitative morphometry appears most useful (sensitive to change) in persons with late stage disease (in those with established disease). The 3D coverage of an entire cartilaginous region by MRI allows for the direct quantification of cartilage volume, surface area, and thickness.26 Early longitudinal studies demonstrated changes of cartilage volume on the order of –4% to –6% (SD of ~5%) occur per annum in OA in most knee compartments followed for periods up to 3 years.27 More recent studies, however, observed smaller rates of change than those quoted above with rates of about –1% to –3% and standardized response means (SRM) of –0.3 to –0.5 per year.24–26 (see Fig. 1 delineating greater change in examples of earlier studies than examples of more recent analyses).

RISK FACTORS FOR OA PROGRESSION

Due to limitations in the responsiveness of both radiographic and MRI measures of progression, efforts are being made to stratify those who are at highest risk of progression. Several studies have suggested that baseline clinical, biomarker and imaging features are predictive of progression of cartilage loss in the native compartment of the knee and could be used to provide greater study power by selecting a population at greater risk for more rapid progression.

Broadly these risk/prognostic factors can be characterized into systemic (age, gender, bone density, etc.) vs local factors (malalignment, meniscal damage, etc.). Of the systemic factors, increasing age34,35, female gender34,36, low systemic bone density27,28, higher c-reactive protein (CRP)12, non-smoking status12, and never using estrogen compared to current estrogen use37 have all been associated with higher risk of knee OA progression.38

In a recent review by Belo et al.36 it is suggested that biomarkers can predict progression39,40. The presence of generalized or nodal OA36–38,44,45, low Vitamin D39 and obesity40,41,42 have also been associated with a more pronounced increased risk of knee OA progression.36,43 It is important to note that the results of the influence of Vitamin D deficiency on the risk of progression are conflicting45,46. Similarly the influence of obesity on progression (unlike its unquestionably important effects on OA incidence) is also conflicting and much of this effect appears to be mediated by alignment47.

Biochemical markers are typically systemic measures of local pathology. The ability to use biochemical markers to predict disease progression and identify patients most likely to progress may accelerate the pace of therapeutic development. Research on type II collagen has suggested that assays for type II collagen degradation when used in combination or with markers of collagen synthesis can distinguish populations with knee OA that exhibit progression of joint damage from non-progressors. The ratio of the type II collagen crosslinking C-telopeptide (CTX-II) to the amino-propeptide of type IIA collagen48 or the ratio of two collagenase-generated cleavage epitopes in the helical region (C1, 2C to C2C)49 can each make this distinction. Preliminary plain radiographic studies suggest that COMP may be a useful prognostic marker of disease progression in knee50–52 and hip OA53. In addition serum measurement of hyaluronic acid and keratan sulfate may be helpful prognostic predictors of persons at risk for knee OA progression54. The data is conflicting and not all studies show that biomarkers can predict progression54,55.

Thus stratifying risk is it important that the effects of risk factors are broadly consistent across studies, they are preferably potent risk factors and that the effect does not produce substantial potential for misclassification. In this light, the local factors discussed below show great promise. Local factors include the presence of varus malalignment at the tibiofemoral (TF) joint57,58 and the presence on MRI of subchondral bone marrow lesions (BML)59 or meniscal abnormalities60. The presence of knee pain has also been associated inconsistently with an increased risk for knee OA progression54,56,61. What follows is a more extensive description of these local factors.

Alignment

Mechanical factors are the dominant risk factor for structural progression. Varus and valgus malalignment have been shown to increase the risk of subsequent medial and lateral knee OA radiographic progression, respectively57,62,63. Varus malalignment has been shown to lead to a 4-fold amplification of focal medial knee OA progression while valgus malalignment has been shown to predispose to a 2- to 5-fold increase in lateral OA progression56,64. In an MRI-based study, varus malalignment predicted medial tibial cartilage volume and thickness loss, and tibial and femoral deranged bone increase, after adjusting for other local factors (meniscal damage and extrusion, laxity)27. Understanding the role alignment plays in OA progression is important because it modulates the effect of standard risk factors for knee OA progression including obesity57,58, quadriceps strength59,60, and stage of disease60,61. Acquisition of the radiographs for alignment measurement, and their processing, are relatively inexpensive and readily available.

Malalignment however, provides only a static impression of the mechanical forces being imparted on a joint in one plane62. The adduction moment at the knee has been related to the progression of medial compartment OA57,66.

**Fig. 1. Longitudinal change of knee cartilage volume with MRI from different studies**4,5,27–33
The number of gait laboratories that are suitable for acquiring data on the ad- 
duction moment, and the time and expense to acquire and process this data, 
make this risk factor less suitable for stratifying risk of progression in large 
multi-center studies.

Meniscal damage

The menisci have many functions in the knee, including the equal distribu-
tion of stress between the relatively incongruous TF joint surfaces, stability 
enhancement and lubrication. The absence of a functioning meniscus in- 
creases peak and average contact stresses in the medial compartment in 
a range of 40–70%.

Early radiographic studies appear to demonstrate that persons with a prior 
history of joint injury and meniscectomy are at in- 
creased risk of knee OA progression. Biswal et al. studied 43 subjects and 
demonstrated that in the 26 subjects who had sustained meniscal tears 
they had a higher average rate of progression of cartilage loss (22%) than 
that seen in those who had intact menisci (14.9%) (P < 0.018). Berthiaume et al. 
investigated the relation between knee meniscus structural damage and 
cartilage degradation in 32 subjects and found similar effects. We dem- 
onstrated a strong association of meniscal position and meniscal damage 
and cartilage loss with the highest quartile of medial meniscal damage hav- 
ing an odds of medial progression of 6.3 (3.1–12.6). Each aspect of menis- 
cal abnormality (whether change in position or damage) had a major effect 
on risk of cartilage loss. To ascertain if a trial participant has meniscal dam- 
age requires acquisition of an MRI during screening and having that read 
with inherent concerns for both cost and participant burden prior to determin- 
ing study eligibility.

BML

BML have also been found to be associated with compartment-specific 
OA progression measured semi-quantitatively. Medial TF com- 
partment BML occurred mostly in those with varus malalignment, and lateral 
TF lesions in those with valgus limbs. Of 75 knees with medial lesions, 25 
(36.0%) showed medial progression vs only 12/148 knees (8.1%) without les- 
sions [odds ratio (OR) for progression = 6.5, 95% confidence interval (CI) 
3.0,14.0]. 69% of knees destined to progress medially had medial lesions. 
Lateral lesions conferred a similar marked risk of lateral progression. These 
increased risks were attenuated by 30–50% after adjusting for limb align- 
ment. This demonstrates that BMLs are a potent risk factor for predicting pro-
gression in knee OA, and their relation to progression is explained, in part, by 
their association with limb alignment. Like meniscal damage, to ascertain if 
a trial participant has a BML requires acquisition of an MRI during screening 
and having that read with inherent concerns for both cost and participant bur- 
den prior to determining study eligibility.

Stage of disease

By selecting participants with the presence of a pre-existing JSN on X-ray 
or full thickness cartilage defects on MRI the ability to demonstrate 
progression in that region is markedly improved. A recent longitudinal anal- 
ysis demonstrated that by selecting persons with Kellgren and Lawrence (K&L) 
Grade – 3 at baseline this group demonstrated the greatest change in 
JSW over 12 months. A recent MRI study demonstrates that by selecting 
participants and regions with the presence of a full thickness cartilage defect 
(denuded area), the ability to demonstrate change in cartilage loss in that 
plate was markedly improved. Prior to stratification, the highest SRM for 
any region was 0.35, and after stratification and selection of those with a de- 
nuded area this improved to 0.62.

Whilst it is inherently appealing to identify participants at greatest risk for 
progression, this methodology would include acquisition and processing of 
a radiograph for JSN or MRI for denuded area during the screening process 
with implications for participant burden and cost. If the central medial femur 
were chosen as the region of interest only 30% of the OA1 progression cohort 
participants will have a focal defect in this region with implicit impact on the 
screen failure rate.

Muscle strength

Quadriiceps weakness is common among patients with knee OA, in whom 
it had been believed to be a manifestation of disuse atrophy, which develops 
because of unloading of the painful extremity. Some studies, however, 
have indicated that quadriiceps weakness may be present in persons with ra- 
diographic changes of OA who have no history of knee pain, and in whom 
lower extremity muscle mass is increased, rather than decreased. Quadri- 
iceps weakness was hence considered a risk factor for the development of 
knee OA, presumably by decreasing stability of the knee joint and reducing 
the shock-attenuating capacity of the muscle.

The effects of strength and strength training in the setting of established 
OA have been investigated, however, more work is needed to clearly estab- 
lish an appropriate risk profile. There is some evidence from an observational 
study suggesting that persons with weakened knees and greater quadriiceps 
strength are at greater risk for progression than those with weaker quadri- 
iceps. More research is required to tease out this relationship as the long-term 
effects of strength training on knee OA progression and the mecha- 
nisms underlying the progression (mechanical loading, altered alignment, 
altered body and fat composition) are unclear. Using muscle strength as a 
risk factor for stratifying risk of progression may be more complex and 
less direct than other methods, especially alignment; particularly given the 
risk of muscle strength on progression may be mediated by altered alignment.

Other risk factors or profiling indices

Synovitis is frequently present in OA and may correlate with pain and 
other clinical outcomes. Whilst synovitis may play a role in mediating 
symptoms, its role in predisposing to further structural progression appears 
controversial.

Among those with established knee OA, an estimated 20–35% have an 
incidental anterior cruciate ligament (ACL) tear identified by MRI. The ef- 
effect of an incidental complete ACL tear on the risk for cartilage loss appears 
to be mediated by concurrent meniscal pathology, so using this as 
a method for identifying those at high risk of progression is less direct.

Compositional assessment may provide opportunities for future risk stratifi-
cation. Applications of parametric mapping techniques sensitive to early 
cartilage damage including T2 mapping, delayed gadolinium enhanced 
MR of cartilage (dGEMRIC) and T1rho have been extensively reviewed 
elsewhere. There is limited data on the longitudinal assessment of compo-
stitutional measures in comparison with the aforementioned constructs. Intu- 
tively compositional measures may have a great role to play in examining 
changes that occur in early disease before gross defects are apparent, whereas 
morphologic measures — both semi-quantitative and quantitative — may have 
greater role in later stages of disease. Particularly for supposedly “early” 
changes of OA, however, the natural course of these changes and the relation-
ship with clinical outcome remain to be established. dGEMRIC appears to be 
helpful in determining those persons with hip dysplasia who have a poorer pro-
gnosis and may be helpful in ascertaining those at greatest risk of progression.

The data available on stratifying risk of progression for knee OA using compo-
stitutional measures is limited.

IMPLICATIONS FOR TRIAL DESIGN

In an effort to shorten discovery and development timelines, clinical trial 
brevity is paramount. This is particularly the case during phase II and III stud- 
ies, where the content of this review is directly applicable. As OA is typically 
a very slow progressive condition, one can optimize trial efficiency by finding 
more responsive endpoint/s and/or stratifying the study sample to further en- 
hance efficiency. Without stratification the options would be to include 
a larger number of subjects and/or follow them for a longer period of time, 
cognizant of the fact that trials of a shorter duration typically have a lower 
dropout rate (Fig. 2).

There are a number of critical decisions that need to be made in clinical 
trial planning early in the design phase including the selection of the appro- 
priate primary outcome. Ideally this measure should be simple (relatively 
easy to perform, preferably non-invasive and widely available at a number of 
centers), reliable (reproducible and standardizable across multiple 

Fig. 2. Timing of risk stratification and characteristics of an ideal 
method for risk stratification for an idealized trial design.
centers), responsive (changes can be detected in a relatively small population and in a relatively short period of time), and clinically relevant (changes in marker should translate into improved, meaningful clinical outcomes).

Once the decision of an appropriate outcome is made, further measures of stratification, including many of the risk factors discussed before such as alignment, meniscal lesions, etc., may enhance the responsiveness of this outcome. Before applying one of these screening tests for detecting rapid progression in the design of a clinical trial, one should consider the following ideals:

1. expense of acquisition and processing of screening test,
2. minimally burdensome both to the trial participant and timeliness of readout for trial timeline,
3. readily available at multiple centers,
4. high positive predictive value for detecting rapid progression, and
5. low screen failure rate.

The impact of a screening test to enhance responsiveness of a structural outcome in a OA trial is seen most immediately when assessing the sample size requirements. Projected sample size requirements depend on (1) the expected rate of progression in participants treated with placebo, (2) the minimum magnitude of the drug effect, or rate of progression expected in the active treatment arm(s), (3) the variation in progression rate that occurs between participants, and (4) the precision of the measurement technique. Take the following theoretical example where we vary the rate of progression in the placebo group by selecting different SRMs. For this example I have set the following parameters: 80% power, 1-sided α = 0.05, and assume the drug causes a 50% drop in cartilage loss. If placebo treated knees have an annual loss of cartilage with an SRM of 0.4 a 50% drop in cartilage loss due to the active drug this would yield an SRM of 0.2 for the active drug arm. The sample size estimate in a two arm, 1 year parallel design trial would be 310 per arm. At present the highest SRM in the recently published cartilage morphometry studies is ~ 0.45

References


