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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 progression[1]. 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 radiographs[2]. 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 trials[3]. 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 suggested[4–6]. 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 reviews[2,4,7]. 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.

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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* [8].

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 on plain X-rays using standardized radiographic protocols of the flexed knee[9]. A reduction in cartilage thickness is inferred from a reduction in this space[9,10].

Recent analyses suggest that the better the positioning in terms of medial tibial rim alignment (or interim distance) with the X-ray beam, the greater is 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 condyles[14]. There remains however considerable controversy over the preferred method of knee radiographic acquisition[9,15,16] and joint space width (JSW) measurement[10,17–20]. 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 methods[20,21] 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 OA 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 acquisitions[22–25]. 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[6]. 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 JSN)[26].

The 3D coverage of an entire cartilaginous region by MRI allows for the direct quantification of cartilage volume, surface areas and thickness[4]. 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[4]. 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[5,27–29] (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 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.

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 age[34,35], female gender[34–36], low systemic bone density[37,38], higher insulin-like growth factor-1 (IGF-1)[39], higher c-reactive protein (CRP)[40], non-smoking status[41], and never using estrogen compared to current estrogen use[42] have all been associated

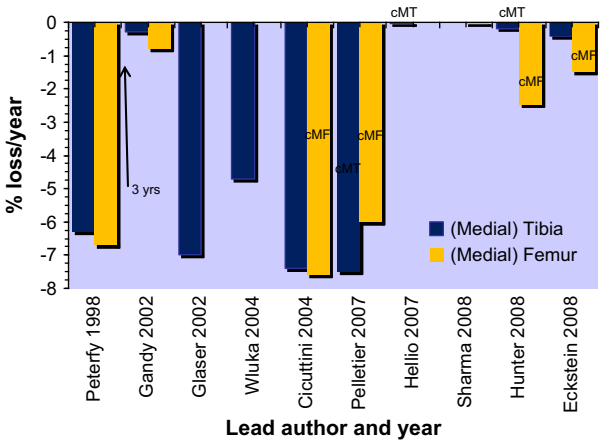

Fig. 1. Longitudinal change of knee cartilage volume with MRI from different studies[4,5,27–33].

with a mildly increased risk for knee OA progression[8]. The presence of generalized or nodal OA[35,36,43,44], low Vitamin D[45] and obesity[34,35,43,46,47] have also been associated with a more pronounced increased risk of knee OA progression[8]. It is important to note that the results of the influence of Vitamin D deficiency on the risk of progression are conflicting[45,48]. 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 alignment[49].

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 collagen[50] or the ratio of two collagenase-generated cleavage epitopes in the helical region (C1, 2C to C2C)[51] can each make this distinction. Preliminary plain radiographic studies suggest that COMP may be a useful prognostic marker of disease progression in knee[52–54] and hip OA[55]. In addition serum measurement of hyaluronic acid and keratan sulfate may be helpful prognostic predictors of persons at risk for knee OA progression[56,57]. The data is conflicting and not all studies show that biomarkers can predict progression[58,59].

When stratifying risk it is 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) joint[27,60] and the presence on MRI of subchondral bone marrow lesions (BML)[61] or meniscal abnormalities[62]. The presence of knee pain has also been associated inconsistently with an increased risk for knee OA progression[34,43,63]. 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, respectively[60]. 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 progression[60,64]. In an MRI-based study, varus malalignment predicted medial tibial cartilage volume and thickness loss, and tibial and femoral denuded 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 obesity[49], quadriceps strength[65], laxity[65] and stage of disease[60,64]. 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 plane[66]. The adduction moment at the knee has been related to the progression of medial compartment OA[67,68].