Epidemiology of peripheral joint osteoarthritis

"...our knowledge of the disease is incomplete, perhaps because it is one of those dull commonplace disorders that are hard to study with enthusiasm, but new knowledge of osteoarthritis must be gained if the later years of our lengthening lives are not to be plagued by increasing pain and disability." JH Kellgren, 1961

Despite considerable increases in knowledge in the last 35 years osteoarthritis remains ill understood. As rheumatologists we may have a “clinical feel” for the condition, readily recognise it, know that it is common, and have a stepwise approach to its management. Yet we still have difficulty in defining and classifying osteoarthritis, identifying risk factors for development and progression, measuring severity and change, delivering effective treatment, and predicting outcome. This is true of most rheumatological conditions, but the sheer magnitude of the community burden of osteoarthritis justifies its high position on any list of locomotor priorities. There is a pressing need for good descriptive and analytical epidemiological studies to unravel the causes and natural history of osteoarthritis, determine health care needs, improve treatments for those affected, and to devise and test primary prevention strategies. In February this year a EULAR workshop on the epidemiology of osteoarthritis of peripheral joints was convened in Öreönä Slott, Sweden, to review current data and discuss methodological issues. The proceedings of this informative meeting are published in this issue of the Annals. Its reading is highly recommended. Some of the issues that particularly captured delegates’ interest during discussions are perhaps worthy of emphasis (table).

**Case definition**

This is clearly crucial to any epidemiology study. Unfortunately for “osteoarthritis” there is no accepted unifying definition. Historically most emphasis in population surveys has centred on structural change assessed by radiographs. Problems arise, however, because of the variable correlation between structural change, symptoms, and the functional and psychosocial impact on the individual (fig 1). Clinicians, of course, are used to all three being present in the index joint of an osteoarthritis patient, and definitions including anything less may seem too limited a surrogate for “osteoarthritis”. Such discordance, however, should not pose a problem. We have instruments to measure aspects of all three dimensions and the choice of which forms the principal measure will clearly vary according to the questions posed. Studies should continue to record separate data on these three and not chase elusive definitions that bow to clinical prejudice. When undertaken, separate assessment may reveal different associations for pain and disability than for structural change, thus broadening our perspectives of “osteoarthritis”.

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**Some issues relating to the epidemiological study of osteoarthritis (OA).**

**Disease definition and assessment**

- Pain radiographs, using appropriate views and meticulous standardisation, remain the best method of assessing structural change for epidemiological purposes.
- Assessment of individual radiographic features has many advantages
- For knee studies assessment of all three compartments is warranted
- Classification criteria for “generalised OA” require validation

**Risk factors**

- Individual joints need individual consideration and may vary with respect to risk factors for development and progression
- Inclusion of OA assessment in studies of oestrogen supplementation or inhibition (tamoxifen) seems justified
- Study of recreational or occupational risk for OA development requires consideration of multiple factors including defined locomotor injury, aerobic fitness, muscle training and associated lifestyle
- Consideration of a hip/knee ratio might be of interest when determining risk factors
- Study of polygenic predisposition to OA is warranted, though fraught with difficulty
- Strategies for primary and secondary prevention of OA deserve testing

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**Interrelations between structural change, pain, and disability in osteoarthritis.**
Radiographic assessment
Although relatively insensitive, the radiograph remains the most practical method of assessing osteoarthritic structural change for epidemiological purposes. Meticulous technique and standardisation of positioning are clearly required. For published scoring systems intraobserver agreements are usually reasonable to good, but interobserver variation is often large. Therefore for meaningful comparison between populations not only is the same method of assessment required but also, ideally, a shared observer (as undertaken, for example, by Lawrence for 11 population samples totalling 2018 subjects17). The gold standard of radiographic assessment for many studies is the Kellgren and Lawrence summated grading system designed for comparison with a standard radiograph atlas.8 Although such excellent work has been accomplished with this system, or variants of it, it has inherent problems, not least of which is where the cut-off for biological and clinical significance lies. For example, how much joint space narrowing, osteophyte, or sclerosis do you need before it is called “osteoarthritis”? Do you need narrowing plus osteophyte or will one suffice? Is osteophyte or narrowing the most relevant for definition? Furthermore such composite grading assumes that individual radiographic features relate to the same pathophysiology of “osteoarthritis” and progress together in a standard fashion. Alternative methods that score individual radiographic features or directly measure minimal joint space9 give more information and have become increasingly preferred. Separate assessment of pain and disability may then allow some justification of measurement cut-offs that correlate with clinical problems.10 Using this approach it appears that minimal joint space at the hip is the most reproducible feature that correlates best with hip pain in men,10 whereas at the knee osteophyte shows the closest correlation with pain,11 though narrowing may be the best predictor of progression.12 Further work is still required, however, to define normal ranges of interosseous distance, and the influence of gender and age, for many of the joints targeted by osteoarthritis.

Site specificity
There is clear agreement that each joint site justifies separate consideration. The correlation between pain and structural change varies between joints; individual radiographic features may have different associations and relevance at different sites; certain risk factors for development and progression appear site specific; and outcomes for different joints certainly vary. Clearer division within individual large joints, or within joint groups such as the hand, is also warranted. For example the patellofemoral compartment, often omitted from earlier knee studies, appears a common target site for osteoarthritis and an important source of pain;13 the skyline is emerging as the best radiographic view to assess this compartment.14 Similarly at the hip different patterns of cartilage loss and femoral head migration may have different associations and different outcomes.15 The possibility that osteophyte at different sites within a joint (for example, acetabular, femoral head, or femoral neck osteophyte at the hip) may have different associations has not yet been tested.

Characterisation of polyarticular osteoarthritis
The tendency for certain individuals to develop osteoarthritis at multiple sites and the association of this phenomenon in some families with Heberden’s nodes is strongly suggested16 and the clinical entity “primary generalised nodal osteoarthritis”17 is widely recognised. Confirmation of such a discrete subset, however, requires demonstration of a bimodal distribution (age and gender adjusted) for the number of joints involved, as recently shown for polyarticular hand osteoarthritis.18 Lawrence suggested involvement of three or more joint groups as a working definition,19 but clearer classification criteria, substantiated by association with putative subset characteristics,20 are still needed. We recognise that constitutional predisposition to osteoarthritis, even as simply reflected by multiple Heberden’s nodes, may influence development of mechanically induced osteoarthriti,11 but better means of assessing the “dose” of generalised predisposition are required to determine the attributable risk of individual factors.

Determination and explanation of risk factors
Several constitutional and extrinsic risk factors for development of osteoarthritis at specific sites have now been identified. However, explanations for these are often difficult to unravel. For example, obesity is clearly an important constitutional risk factor for knee osteoarthritis but whether this relates to mechanical or metabolic factors, or both, remains unclear.21 The association between increased obesity, increased bone mass, and large joint osteoarthritis suggests that oestrogen may be an important disease moderator,22 but a precise mode of action and the explanation for associations with only certain joint sites have not been forthcoming. The role of oestrogen may best be clarified by inclusion of osteoarthritis assessments in large prospective studies, which are already in progress, of tamoxifen (low oestrogen status) and hormone replacement therapy (maintained/high oestrogen status). There seems sufficient justification for such an approach, though late inclusion of multiple secondary outcome measures in large studies designed for different end points inevitably causes problems.

The increased risk of knee osteoarthritis following anterior cruciate rupture, or of hip osteoarthritis following slipped upper femoral epiphysis, seem readily explicable in terms of altered biomechanics. But for many putative extrinsic mechanical risk factors the situation is potentially complex. For example, to study the reported association between knee osteoarthritis and sports such as football, account must be taken of associated defined injury (for example, cruciate ligament tears), the possible benefits of aerobic fitness and muscle training, and associated aspects of lifestyle (for example, non-smoking, which negatively correlates with knee osteoarthritis). It is therefore more difficult than at first sight to estimate the attributable risks associated with the activity of football itself, such as running, rapid turning, jumping, or kicking.23 Multiple confounding variables thus need careful consideration in studies adding recreational and occupational risk factors (positive or negative).

The hip/knee ratio
An interesting observation is that in different genetic, occupational and recreational groups many of the identified risk factors appear to target either the hip or the knee. Although both are large, weight bearing, lower limb synovial joints there are clear differences in design and function, and inclusion of a “hip/knee ratio” in future studies might be of interest in confirming this possible dichotomy of risk factors.

Difficulties of genetic study
Although a strong heritable component is apparent for certain subsets, osteoarthritis presents special problems with respect to family linkage studies. The problem of case
definition, for example of nodal osteoarthritis, has already been mentioned, but the late phenotypic expression of osteoarthritis makes it difficult to collect families of adequate size, and to attribute with confidence the status of “unaffected” to any but the very elderly. It is therefore not surprising that recent studies have largely focused on atypical families with young onset multiple joint osteoarthritis, often with dysplasia, some of which show abnormalities of the type II collagen gene (COL 2A1).

Inherited factors relating to “osteoarthritides” are likely to be polygenic, but even for more simple monogenic diseases subjects with the abnormal gene may not express the disease (reduced penetrance), may show varying degrees of severity, or varying multiple aspects of the condition (pleiotropy). Abnormalities of disparate genes may also cause similar phenotypic expression. We should therefore not be surprised when studies of more typical nodal osteoarthritis do not find associations with COL 2A1 or suggest associations with genes previously not perceived as obvious candidates. Notwithstanding the difficulties mentioned, genetic studies of well characterised families expressing common forms of osteoarthritis may well give important, possibly novel, insights into pathogenesis.

No three day meeting can hope to be comprehensive. The spine was intentionally excluded by the title, but it was interesting that no mention was made of the first metatarsophalangeal joint (a common and early site of osteoarthritis) or the glenohumeral joint (an important site of osteoarthritis in the elderly), perhaps reflecting our paucity of data and historical lack of interest in these sites. Also the potential for primary prevention of osteoarthritis by lifestyle modification (reducing obesity, increasing exercise) and protecting against joint injury (recreational, occupational) was raised only at the eleventh hour, though there is increasing interest in this issue. Nevertheless the meeting was an outstanding success and more than achieved its stated objectives. The organisers are to be congratulated, especially on attracting so many of the major contributors to the field. Spurred by such quality meetings, we hope that during the next 35 years of epidemiological study our knowledge of osteoarthritis will advance considerably.

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