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The epidemiology and impact of pain in osteoarthritis

T. Neogi*

Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, USA

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SUMMARY

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability worldwide, largely due to pain, the primary symptom of the disease. The pain experience in knee OA in particular is well-recognized as typically transitioning from intermittent weight-bearing pain to a more persistent, chronic pain. Methods to validly assess pain in OA studies have been developed to address the complex nature of the pain experience. The etiology of pain in OA is recognized to be multifactorial, with both intra-articular and extra-articular risk factors. Nonetheless, greater insights are needed into pain mechanisms in OA to enable rational mechanism-based management of pain. Consequences of pain related to OA contribute to a substantial socioeconomic burden.

Introduction

The hallmark symptom of osteoarthritis (OA), the most common form of arthritis, is pain. This is the symptom that drives individuals to seek medical attention, and contributes to functional limitations and reduced quality of life[1–4]. Largely because of pain, lower extremity OA is well-recognized as the leading cause of mobility impairment in older adults in the US[5,6].

The scope of the problem

Approximately 27 million US adults and 8.5 million UK adults are estimated to have clinical OA defined on the basis of symptoms and physical findings[7,8]. Prevalence of OA increases with age; 13.9% of adults age 25 and older have clinical OA of at least one joint, while 33.6% of adults age 65 and older have OA[9].

In large epidemiologic studies, OA is often defined on the basis of standard radiographic assessments, such as the Kellgren and Lawrence grade. Symptomatic OA indicates the presence of both radiographic OA and symptoms (i.e., pain, aching, stiffness) in the same joint attributable to OA; as such, its prevalence is generally lower than that of radiographic OA (i.e., regardless of symptoms). For example, the prevalence of *radiographic* knee OA was 19% and 28% among adults age ≥45 years in the Framingham study and Johnston County Osteoarthritis Project, respectively, while the prevalence of *symptomatic* knee OA was 7% in Framingham and 17% in the Johnston County Osteoarthritis Project[10,11]. The prevalence of symptomatic knee OA in two UK studies ranged from 11 to 19%, and estimates of 5–15% were noted in surveys undertaken in other countries[12].

Symptomatic hip OA has been reported to be 9% in the Johnston County Osteoarthritis Project, with lower prevalence estimates of 0.7–4.4% in the UK[13,14]. The prevalence of symptomatic hand OA is higher, with the age-standardized prevalence of symptomatic hand OA being 14.4% and 6.9% in women and men, respectively, in younger Framingham cohorts[15], increasing to 26.2% and 13.4%, respectively, among those age ≥71 in an older Framingham cohort[16]. Another study reported an estimate of 8% among adults age 60 and older[17]. Incidence of symptomatic hand OA was reported to be 9.7% for women and 4% for men over a 9-year period[15].

The lifetime risk of developing symptomatic knee OA is estimated to be ~45% (40% in men and 47% in women) based upon Johnston County Osteoarthritis Project data, with risks increasing to 60.5% among persons who are obese, which is approximately double the risk of those who are of normal weight or are underweight[18]. With aging of the population and increasing obesity, the prevalence of OA is expected to rise. Indeed, an increase in prevalence of symptomatic knee OA over the past 20 years has been noted in the Framingham cohort, rising by 4.1% and 6% among women and men, respectively, intriguingly without a concomitant parallel rise in prevalence of radiographic OA[19]. Based upon National Health Interview Survey (NHIS) data, the estimated number of US adults with doctor-diagnosed arthritis, the majority of which is related to OA and likely symptomatic if it has had medical attention, is projected to increase to nearly 67 million by 2030[20].

* Address correspondence and reprint requests to: T. Neogi, 650 Albany Street, Suite X200, Clinical Epidemiology Research and Training Unit, Boston, MA 02118, USA. Tel: 1-617-638-5180; Fax: 1-617-638-5239.
E-mail address: tneogi@bu.edu.

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Clearly a substantial proportion of adults experience pain related to OA during their lifetime. Further, individuals with OA in one joint will often have OA in another joint(s), with resulting greater symptomatic burden of the disease.

The pain experience in OA

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[21] It is a complex subjective phenomenon, with each individual having a unique perception of it, influenced by biological, psychological and social factors[22]. Under normal circumstances, pain is a warning that something is wrong: pain from touching a hot stove, having injured a joint, or chest pain due to ischemia, for example. In these instances, pain plays a protective role, signaling to the individual to withdraw from the threat, rest to allow tissue healing, or seek help, etc. However, once its warning role is over, persistence or continued pain, i.e., chronic pain, is considered maladaptive.

Unlike many other pain conditions in which the underlying injury typically heals or resolves, OA is a disease that does not resolve. Thus, OA is typically accompanied by chronic pain. Whether, and to what degree, this ongoing chronic pain (i) plays an important nociceptive role, (ii) represents maladaptive pain, or (iii) reflects other aspects of the pain experience is not clear.

The pain experience among persons with OA has been evaluated through a number of qualitative research efforts. In the first qualitative study to focus explicitly on pain and related distress as well as changes in pain over time by Hawker *et al.*, individuals with hip and knee OA identified two distinct types of OA pain: one that was intermittent but generally severe or intense, and another that was a persistent background pain or aching[23]. Stages of OA-related pain could be discerned, with early stages characterized by activity-related pain, becoming more constant over time and punctuated by intermittent intense pain. A decrease in participation subsequently occurs in an attempt to avoid triggering such episodes. The more intense but less frequent pain that comes and goes (i.e., intermittent), particularly when unpredictable, had greater impact on quality of life than the 'background' (i.e., constant) pain. The pain had negative effects on mood, participation in social and recreational activities, and sleep. Similar findings were noted in another study of individuals who had a recent diagnosis of knee OA or were symptomatic but undiagnosed (i.e., "prediagnostic knee OA")[24]. The significance of intermittent knee symptoms was not clear for several years before participants became aware of development of chronic knee symptoms. They then altered activities to avoid more symptoms, until symptoms affected participation, at which time they sought medical care.

In addition to the concepts of "intermittent" and "constant" pain, the intensity of daily pain varies widely[25], although the underlying reasons for such variation are not well-understood. The quality of pain in OA also varies, with approximately one-third of individuals with knee OA using descriptors such as burning, tingling, numbness, and pins and needles to characterize their knee symptoms[26]. Such descriptors suggest that neuropathic pain may contribute to the OA pain experience, although specific nerve lesions have not been identified in OA.

Pain assessment in OA

Given the variation in pain intensity, frequency, pattern, and quality in OA, a single, simple question about pain is unlikely to adequately capture the full pain experience. Some of the variation in reported prevalence of symptomatic OA is related to differences in study design and populations examined, but importantly, it is also due to the way in which questions about knee pain were formulated. Differences in descriptors used to assess pain (e.g., "pain" vs "pain, aching, or stiffness") may elicit different responses. Duration over which pain is being assessed (e.g., "pain on most days of a month in the past year" vs "pain on most days of the past month") can be prone to recall bias. Ideally, uniform, standardized, and valid questionnaires should be used to evaluate pain, particularly to enable more precise pain phenotyping and facilitate cross-study comparisons, genetic association studies, and drug trial protocol development.

In OA cohort studies and trials, a number of approaches are typically used to assess pain. For evaluation of knee OA pain, the most common are a visual analog scale (VAS) or numerical rating scale (NRS) assessment of pain intensity; a single question about presence of "pain, aching of stiffness in or around the knee" over a specified period of time; and/or the pain subscale of the Western Ontario and McMaster Universities Arthritis Index (WOMAC)[27] or the Knee injury and Osteoarthritis Outcome Score (KOOS)[28]. The pain subscales of these latter two instruments assess pain experienced with specific activities. As a result, the pain and function subscale scores are highly correlated. Nonetheless, these validated instruments are responsive and are used in assessing efficacy of interventions. A number of additional validated generic pain instruments are available that are also appropriate for use in OA[29]. A meta-analysis concluded that different patient-reported outcome measures of pain severity have generally comparable responsiveness to treatment, with the single-item pain assessments with the VAS or NRS resulting in effect estimates comparable to the WOMAC pain subscale, although their mean standardized effect sizes were lower[30]. To enable meaningful interpretation of response to therapy rather than relying on mean group responses, the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) set of responder criteria were developed and validated for use in clinical trials[31]. To be considered a responder, at least a minimum threshold of relative and absolute improvement in pain or a lesser degree of absolute and relative improvement in at least two out of three domains (pain, function, patient global assessment) is required. Many of these same questions and instruments (e.g., WOMAC) can be used for hip OA; the Hip disability and Osteoarthritis Outcome Score (HOOS) is specific for hip OA[32]. To assess pain, stiffness and physical functioning in hand OA, the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) is commonly used[33].

Despite widespread use of these pain assessments, the complex pain experience of those living with OA is not adequately captured by existing measures. To address this issue, a multicenter international Osteoarthritis Research Society International/Outcome Measures in Rheumatology (OARSI/OMERACT) initiative led to development of a new measure informed by qualitative research findings that was subsequently validated. This new instrument, Intermittent and Constant OA Pain (ICOAP), assesses various facets regarding both intermittent and constant pain for the knee and hip separately, including frequency (for intermittent pain), intensity, effects on sleep and quality of life, degree of frustration or annoyance and upset or worried feelings associated with the pain, as well as whether the intermittent pain occurs without warning or after a trigger[34]. The ICOAP has recently been demonstrated to be responsive to change in intervention studies[35].

In keeping with the acknowledgment of the multidimensional nature of pain, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recommended six core domains and associated measures that should be considered when studying any type of chronic pain in clinical trials: pain (intensity and use of rescue medications), physical functioning (with a focus on pain interference), emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and