HHS Public Access

Author manuscript

Arthritis Rheumatol. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Arthritis Rheumatol. 2016 August ; 68(8): 1797–1800. doi:10.1002/art.39704.

Shifting gears in osteoarthritis research towards symptomatic osteoarthritis

Yuqing Zhang[1] and **Jingbo Niu**[1]

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

Osteoarthritis (OA) is the most common joint disorder and the leading cause of disability in elders. In 2015, the World Health Organization estimated that 18.0% of women and 9.6% of men 60 years of age or over suffer from symptomatic OA. Among people with symptomatic OA, 80% have some limitation in mobility and 25% are unable to perform their major daily activities (1). Symptomatic OA is one of the most expensive medical conditions treated in the U.S. hospitals in 2008, with a cost of approximately $40 billion in expenditure of the total national inpatient care, mainly incurred by arthroplasty surgery (2). More recently, several studies also found that symptomatic knee or hip OA is associated with an increased risk of all-cause mortality (3–5). All of these findings indicate that the societal burden of symptomatic OA is formidable.

To date, there is no known cure for OA. The main goals of the contemporary management of the disease remain control of pain and improvement in both function and health-related quality of life with avoidance of therapeutic toxicity (6). However, the predilection for pharmacologic treatment of symptoms has various side effects. In particular, the frequent use of non-steroidal anti-inflammatory drugs for symptomatic OA patients has been questioned because of their high risk for gastrointestinal and cardiovascular toxicities (7, 8). While arthroplasty surgery greatly improves symptoms, physical function and quality of life among the majority of patients with end-stage symptomatic OA, the surgical procedure itself is neither inexpensive nor risk-free. Approximately 0.5% to 1% of patients died within 90 days after surgery, and the risk of venous thromboembolism increased by almost 6–fold over one year after the surgery in comparison with subjects with similar OA severity who did not have surgery (9). Therefore, identifying risk factors, especially potentially modifiable ones, for symptomatic OA and implementing appropriate measures to prevent its occurrence have significant public health implications.

Although pain from OA is a major factor leading to the decision to seek medical care and an important antecedent to disability, most previous studies have focused on the risk factors for structural lesions detected by various imaging modalities, such as radiographs or MRI (6). Only a few population-based observational studies have been conducted to describe the pattern of incident symptomatic or clinical OA at three major joints (i.e., hip, knee and hand) (10–12), and to identify their risk factors (11, 13). The mismatch between the sparseness of

Corresponding author: Yuqing Zhang, D.Sc, Professor of Medicine & Epidemiology, Boston University School of Medicine, Boston, MA 02118. Tel. 617-6385183; Fax: 617-6385239.

previous studies on symptomatic OA and the actual needs of patients is stark. First, structural lesions detected by radiographs or other imaging modalities are not strongly correlated with symptoms. For example, in the Framingham OA Study, more than two thirds of subjects with radiographic knee OA do not have knee pain (14). Second, besides structural lesions in joints, many other risk factors (e.g., genetic predisposition, prior experience, current mood, expectations, and social/cultural environment) may play important roles in the development of joint symptoms; thus, it is unsurprising that risk factors for radiographic OA may not be good predictors of the symptomatic disease (6). As a result, the underlying causes of symptomatic OA are still not well understood, and there is urgent need to shift OA research towards patient-centered outcomes, i.e., symptomatic or clinical OA and its sequelae (15).

In this issue of Arthritis and Rheumatology, Reyes and colleagues reported that overweight and obese subjects in the Sistema d'Informacio per al Desenvolupament de l'Investigacio en Atencio Primaria (SIDIAP) study were at much higher risk of developing clinically diagnosed OA at the knee, hip and hand joints than those with normal weight. Compared with those of normal body mass index (BMI <25 kg/m^2), the adjusted hazard ratios of clinically diagnosed OA were 1.5, 2.0 and 2.5, for subjects with overweight (BMI: 25-<30 kg/m^2), grade I obesity (BMI: 30-<35 kg/m^2) and grade II obesity (BMI ≥35 kg/m^2), respectively. Similar results were observed when the effect of overweight and obesity on the risk of clinically diagnosed OA was evaluated at knee, hip and hand separately.

Several characteristics of the study are worth commenting. First, the SIDIAP study is one of the largest population-based cohort studies that described the incidence of clinically diagnosed OA at three major joints (i.e., knee, hip and hand). The study consisted of approximately 1.7 million participants aged ≥40 years who were registered in the SIDIAP database. During the 4.5 years of follow-up period, over 83,000 subjects developed clinically diagnosed OA in the knee, 27,000 in the hip, and 31,000 in the hand joint; therefore, the investigators were able to describe the patterns of OA occurrence in each joint by age and BMI categories, and to estimate the effect of BMI categories on disease occurrence.

Second, the SIDIAP study used ICD-10 Codes entered by the health care providers to identify patients with clinical OA. This approach appeared highly correlated with self-reported OA, with sensitivity of 0.71 and specificity of 0.94 (16). The investigators also validated OA diagnosis by reviewing the free text and radiographic reports from 150 randomly selected subjects with newly registered OA code; however, no measure of validity was reported in terms of sensitivity, specificity and positive predictive value from the study (12). Thus, it is unclear to what extent that misclassification of OA diagnosis could affect the incidence of OA, and its impact on the relation of overweight and obese to the risk of incident clinically diagnosed OA. Nevertheless, the incidence rate of clinically diagnosed OA among participants in the SIDIAP study appeared to be compatible to those reported in other population-based cohort studies (12). Interestingly, while patterns of clinically diagnosed OA according to age, sex and joint involvement among participants in the SIDIAP in 2006–2010 were similar to those among members of the Fallon Community Health Plan (FCHP) reported by Oliveria et al. in the early 1990's (10), the incidence rate of the disease was higher among subjects in the SIDIAP study (6.5 per 1000 person-years) than

that among members of the FCHP (4.3 per 1000 person-years). Such a difference may be accounted for by an increase in the prevalence of overweight and obesity over the last 20 years.

Third, approximately 46% of eligible subjects from the SIDIAP database were excluded from the current study because of missing information on BMI, and the incidence rate of clinically diagnosed OA appeared to be different according to the availability of BMI values: 9.1 at knee, 2.9 at hip, and 3.2 at hand per 1000 person-years among subjects with BMI data available, and 3.0 at knee, 1.0 at hip and 1.3 at hand per 1000 person-years among subjects with BMI information missing. The difference in the incidence rate of OA is unlikely to be explained by sex and age difference between subjects with and subjects without BMI information (women: 54.2% vs. 49.0%, mean age: 64.1 vs. 60.4 years). Therefore, the sample used in the current study not only limits its generalizability of the incidence rate of clinically diagnosed OA to the general population, but it may also jeopardize the validity of the effect estimates of BMI categories on risk of OA. It is not unreasonable to speculate that overweight and obese subjects were more likely to use primary health care resources than their counterparts with normal body weight, and thus were more likely to be diagnosed with OA. If that is the case, potential selection bias may lead to an overestimation of the association between BMI categories and risk of OA.

Finally, the study also examined whether the effect of obesity on the development of clinically diagnosed OA varied by age, and showed that the hazard ratios of obesity on incidence of clinically diagnosed knee OA were greater among subjects around 60 years of age. The investigators stated that “By identifying the age at which obesity would more seriously influence the risk of OA, health care providers could focus prevention strategies on a narrower target population (i.e., middle adulthood).” In general, the effect measures on a relative scale (e.g., hazard ratio, rate ratio or risk ratio) are more pertinent in making a causal inference regarding the etiology of the disease, whereas the effect measures on an absolute scale (e.g., rate difference or risk difference) are more appropriate for public health implications. In the current study, the largest rate difference in clinically diagnosed knee OA between obese and normal-weight subjects was observed around age 70’s (Figure 1), indicating that weight-loss intervention implementing during a relevant time period (may not be around age 70’s) to affect the risk of symptomatic OA around age 70’s may be more cost effective if the cost of weight-loss intervention per subject is the same across different age categories. Nevertheless, OA is a chronic disease and exposure to overweight or obesity during the entire adulthood confers risk of symptomatic OA; thus weight control throughout life should be considered as primary prevention of the disease. Despite a few potential limitations of the study, results from the SIDIAP study provided further convincing evidence that overweight/obesity is a strong risk factor for symptomatic OA.

Over the past three decades the global prevalence of obesity almost doubled. During the same time period the prevalence of symptomatic knee OA almost doubled in women and tripled in men (17). One would expect that the population attributable risk of symptomatic OA from overweight or obese would likely increase in the near future. The consistent findings of being overweight or obese on the risk of both radiographic and symptomatic OA in observational studies beg the questions of whether weight loss may reduce the risk of OA,

and if it does, what kind of intervention programs of weight loss may reduce the risk of symptomatic OA.

In the early 1990's, the results from the Framingham OA Study reported that weight loss of approximately 10 pounds in women was associated with a roughly 50% reduction in the risk of symptomatic knee OA, and the effect was even stronger among women whose baseline BMI was high (18). However, the study did not specify what factors lead to subjects' weight loss. Weight is a biological measure and does not change by itself. People can lose their weight either intentionally (e.g., calorie restriction, exercise, medication use or surgery) or unintentionally (e.g., nutritional deficiency or preexisting medical conditions) and the cost-effectiveness of these various interventions varies markedly (19). The effect of weight loss from each of these measures on the development of symptomatic OA may vary because different approaches of changing weight may themselves have different direct effect on the risk of the disease. To our knowledge, few, if any, observational studies have specifically evaluated the effect of a particular weight-loss measure on the risk of developing symptomatic OA owing to formidable cost of conducting such a study. In a post-hoc analysis of data collected from the Prevention of Knee Osteoarthritis in Overweight Female (PROOF), a moderate amount of weight-loss (i.e., 5 kg or 5% of body weight) mainly through either diet or exercise was associated with a reduced risk of symptomatic knee OA defined by ACR criteria; however, the association was not statistically significant (OR=0.34, 95% CI: 0.09–1.32) owing to small sample size (20).

On the other hand, in a randomized clinical trial of Intensive Diet and Exercise for Arthritis (IDEA) (21), a secondary prevention of weight loss on OA, subjects with symptomatic knee OA who were assigned to the intensive diet intervention only group lost more weight than those who were assigned to exercise only group (lost 8.9 vs. 1.8 kg); however, there was no statistically significant difference in the improvement of pain, function and SF-36 physical component subscale. Moreover, subjects assigned to receive both intensive diet and exercise (lost 10.6 kg) had significant improvement in knee pain, function and physical component subscale than those assigned to a single intervention, suggesting that intervention aiming at both weight loss and muscle strength improvement with appropriate exercise program may provide better beneficial effect to patients with symptomatic OA. Assuming that there is a causal relationship between weight loss and risk of the occurrence of symptomatic OA and that an appropriate approach will be taken to reduce the weight, using data from the SIDIAP study, eliminating obesity alone from the population would prevent approximately 30% of symptomatic knee OA, 15% of symptomatic hip OA and 7.0% of symptomatic hand OA, respectively, indicating a tremendous public health impact.

Besides overweight and obesity there are likely other risk factors for the development of symptomatic OA and its sequelae, and the risk factors for OA may vary at different joints. Nevertheless, Reyes and colleagues' study aiming to assess the risk factors for the clinically diagnosed OA is worth applauding. With limited resources, it is time to gear OA research towards patient-centered outcomes: symptomatic OA and its sequelae.

Acknowledgments

Funding: This project was supported in part by the NIH grant P60-AR-047785

References

1. World Health Organization. 2016. [cited 2016 February 5]. Available from: http://www.who.int/chp/topics/rheumatic/en/.
2. United States Bone and Joint Initiative. The Burden of Musculoskeletal Diseases in the United States. 2. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2011.
3. Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ. 2011; 342:d1165. [PubMed: 21385807]
4. Hawker GA, Croxford R, Bierman AS, Harvey PJ, Ravi B, Stanaitis I, et al. All-cause mortality and serious cardiovascular events in people with hip and knee osteoarthritis: a population based cohort study. PLoS One. 2014; 9:e91286. [PubMed: 24608134]
5. Liu Q, Niu J, Huang J, Ke Y, Tang X, Wu X, et al. Knee osteoarthritis and all-cause mortality: the Wuchuan Osteoarthritis Study. Osteoarthritis Cartilage. 2015; 23:1154–7. [PubMed: 25819581]
6. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med. 2000; 133:635–46. [PubMed: 11033593]
7. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011; 342:c7086. [PubMed: 21224324]
8. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. NEJM. 1999; 340:1888–99. [PubMed: 10369853]
9. Lu N, Misra D, Neogi T, Choi HK, Zhang Y. Total joint arthroplasty and the risk of myocardial infarction: a general population, propensity score-matched cohort study. Arthritis Rheum. 2015; 67:2771–9.
10. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum. 1995; 38:1134–41. [PubMed: 7639811]
11. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. BMC Musculoskeletal Disorders. 2008; 9:132. [PubMed: 18831740]
12. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis. 2014; 73:1659–64. [PubMed: 23744977]
13. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology. 1999; 10:161–6. [PubMed: 10069252]
14. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum. 1987; 30:914–8. [PubMed: 3632732]
15. Tallon D, Chard J, Dieppe P. Relation between agendas of the research community and the research consumer. Lancet. 2000; 355:2037–40. [PubMed: 10885355]
16. Prieto-Alhambra D, Nogues X, Javaid MK, Wyman A, Arden NK, Azagra R, et al. An increased rate of falling leads to a rise in fracture risk in postmenopausal women with self-reported osteoarthritis: a prospective multinational cohort study (GLOW). Ann Rheum Dis. 2013; 72:911–7. [PubMed: 22730372]
17. Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. Ann Intern Med. 2011; 155:725–32. [PubMed: 22147711]

18. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study Ann Intern Med. 1992; 116:535–9. [PubMed: 1543306]

19. Gortmaker SL, Swinburn BA, Levy D, Carter R, Mabry PL, Finegood DT, et al. Changing the future of obesity: science, policy, and action. Lancet. 2011; 378:838–47. [PubMed: 21872752]

20. Runhaar J, de Vos BC, van Middelkoop M, Vroegindeweij D, Oei EH, Bierma-Zeinstra SM. Moderate weight loss prevents incident knee osteoarthritis in overweight and obese females. Arthritis Care Res. 2016

21. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA. 2013; 310:1263–73. [PubMed: 24065013]