Paediatrics Publications   Paediatrics Department

6-1-2017

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An Official Journal of the American College of Rheumatology
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EDITORIAL

"Weighing in" on the Framingham Osteoarthritis Study: Measuring Biomechanical and Metabolic Contributions to Osteoarthritis

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Thirty years ago, Altman et al told us that osteoarthritis (OA) is not a single disease (1). That 1986 description of OA as "a heterogeneous group of conditions that lead to joint symptoms and signs…" remains true today. But the simple recognition of OA as a group of related but distinct joint disorders among clinicians and researchers is hampered by the lack of a clearly accepted set of criteria to distinguish independent clinical OA phenotypes. Moreover, the description of these clinical OA phenotypes in molecular, anatomic, and physiologic domains remains a formidable, yet fundamental task before us in the field of OA research. Notwithstanding, the blanket term "OA" should no longer be used in isolation to describe the typical joint pathology and symptoms of the most common form of arthritis in humans. An effort should be made in all OA cases to apply accompanying adjectives to at least describe the context in which the joint disease arose. Candidate clinical phenotypes include OA related to joint trauma (posttraumatic OA), advanced age at disease onset (age-related/senescent OA), strong family history (inherited/genetic OA), pain sensitization, inflammatory features, and metabolic syndrome (metabolic OA) (2). Given that ~25% of the world's adult population develops metabolic syndrome (3), the association of metabolic syndrome with OA is especially alarming.

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Submitted for publication January 14, 2017; accepted in revised form March 2, 2017.

Metabolic syndrome consists of 4 core features, variably defined, including hypertension, atherogenic dyslipidemias, visceral obesity, and insulin resistance. The most recent metabolic syndrome definitions from the US National Cholesterol Education Program Adult Treatment Panel III and the International Diabetes Federation were presented in 2005. Regardless of the definition of metabolic syndrome, a clear link between metabolic syndrome and OA has been established in many different studies. Analyses of Third National Health and Nutrition Examination Survey (NHANES-III) data show that metabolic syndrome prevalence is higher among people with OA than those without OA (59% versus 23%, respectively) and that this form of OA occurs in younger age groups (ages 45–65 years) than age-related OA (4). The individual components of metabolic syndrome are also associated with excess OA risk. For example, in the Japanese Research on Osteoarthritis Against Disability (ROAD) study, the risk of OA increased with each additional component of metabolic syndrome (5), although that was a cross-sectional analysis without adjustment for body mass index (BMI).

The nature of the interaction between metabolic syndrome and OA remains unresolved. It is unclear whether the most important link is due to an influence of OA on metabolic syndrome (e.g., decreased mobility due to OA leads to obesity and therefore metabolic syndrome), vice versa (abnormal joint loading—with or without metabolic derangement—fuels OA pathophysiology), or if a common set of risk factors exist which drive both conditions in parallel. A shared etiology in the latter case would suggest that metabolic OA is an underrecognized fifth (or sixth) feature of metabolic syndrome rather than a separate condition per se, as some have suggested (6). As is often the case, the answer may lie in a combination of these possibilities. But the reliance on prevalence data and cross-sectional analyses in most OA/metabolic syndrome studies

makes it difficult to resolve such "chicken-or-the-egg" questions. Nevertheless, the balance of the literature suggests that metabolic syndrome and increased BMI or body weight are each associated with an increased risk of incident knee OA especially. Increased BMI or body weight and metabolic syndrome (given that BMI is a core component) clearly cause increased or abnormal knee joint loading (7). Therefore, the fundamental question that remains is whether metabolic syndrome increases incident OA risk purely driven by the biomechanical consequences of increased body weight, or if metabolic derangement (e.g., from increased visceral fat–driven systemic inflammation or other mechanisms yet to be confirmed) confers additive risk beyond that explained by biomechanics alone.

In this issue of *Arthritis & Rheumatology*, Niu et al (8) present longitudinal data from the Framingham OA Study, demonstrating an association of preexisting metabolic syndrome and its components with an increased risk of incident radiographic and symptomatic knee OA over 10 years of follow-up. A dose-response relationship was also seen for the association of the number of metabolic syndrome components with incident radiographic OA. The assessment of metabolic syndrome occurred a year or so before the OA examination. The prospective study design and inclusion of incident OA outcomes allowed for risk factors to be determined, in contrast to previous studies that showed only correlations or associations. The unique statistical approach for examining the various contributions to OA development due to BMI versus body weight versus waist circumference suggested a very high correlation among these measures, which is useful methodologically for future studies.

The incidence data presented by Niu et al are particularly noteworthy, since they show that preexisting metabolic syndrome and its components are risk factors for subsequent symptomatic OA and not just radiographic OA. Their study also provides circumstantial evidence supporting the hypothesis that at least one or more of the metabolic syndrome components may cause OA. Of course, the increased risk may alternately belie the existence of common risk factors for both metabolic syndrome and OA, where OA may be a later-occurring additional component of metabolic syndrome. However, we feel it is most appropriate to consider metabolic OA as a complication of metabolic syndrome, similar to cardiovascular disease.

Understanding how metabolic syndrome underlies the manifestation of metabolic OA is confounded further by the duality of pathobiology and biomechanics impelling OA pathophysiology. Obesity is the only metabolic syndrome component that is consistently associated with OA across most studies, suggesting that increased weight plays a role in OA development through increased joint loading.

However, increased joint loading may not fully explain the effects of metabolic syndrome on all aspects of metabolic OA, since hand OA is also associated with obesity with or without other metabolic syndrome components (9) and is independent of abnormal joint loading. It should be noted, though, that the hypothesis that hand OA is related to obesity remains a subject of controversy, in part due to the cross-sectional design of the studies in which a significant association was found. Nevertheless, failure to adjust for any contribution of increased joint loading in knee OA due to increased body weight in metabolic syndrome will overestimate the contribution of metabolic processes to metabolic OA.

Teasing out the relative contributions of abnormal biomechanics versus metabolic derangement to the development of metabolic OA is an essential step that we must achieve to realize the best approaches to treatment. Niu et al astutely raise this issue in the Framingham OA analysis and attempt to isolate the contribution of metabolic derangement due to metabolic syndrome from abnormal joint loading by adjusting for BMI or body weight. Such adjustment nullified the association between incident radiographic OA and symptomatic OA with metabolic syndrome and each of the metabolic syndrome components, with the exception of diastolic blood pressure, which remained significantly associated with symptomatic OA. Associations between metabolic syndrome components and knee OA after adjustment for BMI were also nullified in the Korean National Health and Nutrition Examination Survey (10), among others.

Unfortunately, BMI and body weight are not ideal surrogates for joint loading, especially in metabolic syndrome, due to a close correlation with central obesity. Indeed, the correlation of BMI and body weight with central obesity is strong (Niu et al calculate a Pearson's correlation coefficient of 0.84–0.88). Measurement of body composition, which better delineates the contribution of fat and muscle to body mass, has led to interesting findings in knee OA. A recent study has suggested that the effect of BMI in asymptomatic knee OA is predominantly mediated by fat mass (and not lean mass), suggesting that differentiating between fat mass and weight may also be beneficial in predicting incident OA (11). Moreover, adjustment for body composition rather than BMI or body weight may be a better approach in future studies, which will be required to determine if a significant contribution to incident OA risk from fat mass–driven metabolic derangement truly does exist beyond biomechanics.

In addition to adding to body weight, central (visceral) obesity is strongly linked to important metabolic functions. For example, beginning with the discovery of leptin in 1994 (12), adipose tissue has been identified as

having an important endocrine function through the secretion of adipokines. In the Invecchiare in Chianti (Aging in the Chianti area; InCHIANTI) study, high leptin levels were associated with metabolic syndrome in obese and nonobese patients (13), and high levels of leptin were associated with incident radiographic knee OA in the American Study of Women's Health Across the Nation (SWAN) (14). Central obesity is also tied to the development of metabolic syndrome components, including dyslipidemia and insulin resistance. So, while central obesity contributes to abnormal joint loading via increased body weight, it may also influence joint homeostasis via systemic metabolic derangements. Since BMI/weight (which captures central obesity) encompasses both metabolic and mechanical loading variables, it follows that adjustment for BMI or body weight in studies may simultaneously adjust for both joint loading and metabolic factors associated with central obesity. Even though the intention is to adjust for abnormal joint loading in isolation, this strategy limits the ability to draw conclusions about the relative contributions of abnormal joint loading versus metabolic syndrome (or its components) with incident OA. Inventively, Niu et al try to address this issue with residuals of waist circumference after removing variation caused by BMI and body weight, but this also negated any associations with incident OA.

What is needed is an alternative factor for adjustment that more precisely estimates the magnitude of abnormal joint loading without encompassing any metabolic effects of adipose tissue. An ideal measure would be to quantify knee joint load directly, but this is quite difficult to measure externally, and force-measuring joint implants are expensive, are invasive, and would not be feasible for incident radiographic OA or symptomatic OA studies. Knee adduction moment (KAM) is a close surrogate of medial tibiofemoral compartment force, especially components of KAM such as peak KAM. Changes in peak KAM in obese patients are due to weight and not obesity distribution, making this a suitable alternative measure to use for adjustment of joint loading (7). Future studies exploring associations between metabolic syndrome and OA could include and adjust for KAM and compare with adjustment for BMI and body weight.

There are some limitations to the study by Niu et al. Despite the large sample size, incident OA was rare, so the borderline effect of blood pressure on incident OA may have been due to the study not having adequate power to detect a more robust effect. Moreover, all knee OA was combined (medial, lateral, and patellofemoral). The latter may have been a limitation since perhaps medial OA is affected more by metabolic syndrome than patellofemoral OA. The numbers of different subsets with incident OA were too small to allow for subset calculations for robust answers regarding associations with metabolic syndrome. The date of onset of OA could not be precisely determined since subjects were only examined at fixed dates. Since OA symptoms might motivate participants to make lifestyle changes (e.g., to lose weight), future studies need to carefully consider how to take such prior exposures into account for adjustment. There was a protective effect of glucose (after adjustment for BMI), which warrants further research since this could be real or spurious due to the use of numerous statistical tests.

Considering the likely confounding of body weight between mechanical and metabolic processes, the fact that any component of metabolic syndrome remained significantly associated with symptomatic OA after adjusting for BMI and body weight argues strongly for a metabolic driver of OA pathophysiology. A 2012 cross-sectional study in 352 OA patients showed that 60% of patients with prevalent OA had hypertension after correcting for age and BMI (15). In NHANES-III, 77% of subjects with OA had hypertension versus 30% of those without OA (4). Again, this does not help us to sort out whether it's the chicken (OA-related loss of mobility causing hypertension) or the egg (hypertension leading to OA). Mechanistically, subchondral ischemia is the best described hypothesis for hypertension contributing directly to OA pathogenesis. Narrowing of subchondral vessels may reduce nutrient exchange and devitalize the overlying articular cartilage (16) or stimulate apoptosis of osteocytes and subsequent osteoclast activation and subchondral bone remodeling (17). Much work is left to be done in this area to delineate the mechanisms involved, but clinical studies investigating the impact of antihypertensive therapy in patients with hypertension and comorbid metabolic OA would offer insights.

Metabolic OA should be considered and studied separately from other types of OA. The development or updating of classification criteria would aid significantly in defining metabolic OA. While such a task is best suited to a classification criteria committee, possible minimum criteria to consider might include a) the presence of metabolic syndrome according to an accepted definition, b) symptomatic OA and/or radiographic OA, and c) exclusion of alternative etiologies such as prior joint trauma, family history of genetic OA, advanced age at onset (e.g., >75 years), and underlying comorbid risks (e.g., inflammatory arthritis, hemochromatosis, calcium pyrophosphate deposition disease, etc.). Adjustment for confounders is a key issue in clinical studies, but biomechanics are especially important in OA and musculoskeletal diseases. Thus, working with our expert colleagues in OA biomechanics research continues to be a vital collaboration in our field. OA and metabolic syndrome are complex diseases with an unresolved

etiology, but the work presented by Niu et al further emphasizes the link between these conditions.

Whether metabolic OA should be considered a component of metabolic syndrome is still open for debate, but Niu et al have provided data on incident OA in the setting of preexisting metabolic syndrome, the Framingham OA Study, suggesting that OA may be a consequence of metabolic syndrome rather than the reverse. Carefully designed future studies are still required to determine the relative impact of increased body mass in metabolic syndrome on joint loading versus metabolic derangements (including systemic inflammation). Such future studies should be a top priority for our field. Studies employing a life course approach including past history of elevated BMI (e.g., obesity during childhood and early adulthood) are also needed. Ruling in or out a clinically important impact of altered metabolism on incident OA risk independent of biomechanics would be a significant breakthrough in our understanding of metabolic OA and other OA phenotypes. It would also provide a strong foundation for the development of rational treatment approaches for this pervasive and disabling disease.

AUTHOR CONTRIBUTIONS

REFERENCES

1. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
2. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011;377:2115–26.
3. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415–28.
4. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgrad Med 2009;121:9–20.
5. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Association of knee osteoarthritis with the accumulation of metabolic risk factors such as overweight, hypertension, dyslipidemia, and impaired glucose tolerance in Japanese men and women: the ROAD study. J Rheumatol 2011;38: 921–30.
6. Velasquez MT, Katz JD. Osteoarthritis: another component of metabolic syndrome? Metab Syndr Relat Disord 2010;8:295–305.
7. Segal NA, Yack HJ, Khole P. Weight, rather than obesity distribution, explains peak external knee adduction moment during level gait. Am J Phys Med Rehabil 2009;88:180–8.
8. Niu J, Clancy M, Aliabadi P, Vasan R, Felson DT. Metabolic syndrome, its components, and knee osteoarthritis: the Framingham Osteoarthritis Study. Arthritis Rheumatol 2017;69:1194–1203.
9. Dahaghin S, Bierma-Zeinstra SM, Koes BW, Hazes JM, Pols HA. Do metabolic factors add to the effect of overweight on hand osteoarthritis? The Rotterdam Study. Ann Rheum Dis 2007;66:916–20.
10. Han C, Yang I, Lee W, Park Y, Park K. Correlation between metabolic syndrome and knee osteoarthritis: data from the Korean National Health and Nutrition Examination Survey (KNHANES). BMC Public Health 2013;13:603.
11. Ho-Pham LT, Lai TQ, Mai LD, Doan MC, Nguyen TV. Body composition in individuals with asymptomatic osteoarthritis of the knee. Calcif Tissue Int 2016;98:165–71.
12. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425–32.
13. Stenholm S, Koster A, Alley DE, Visser M, Maggio M, Harris TB, et al. Adipocytokines and the metabolic syndrome among older persons with and without obesity: the InCHIANTI Study. Clin Endocrinol (Oxford) 2010;73:55–65.
14. Karvonen-Gutierrez CA, Harlow SD, Mancuso P, Jacobson J, de Leon CF, Nan B. Association of leptin levels with radiographic knee osteoarthritis among a cohort of midlife women. Arthritis Care Res (Hoboken) 2013;65:936–44.
15. Morović-Vergles J, Šalamon L, Marasović-Krstulović D, Kehler T, Šakić D, Badovinac O, et al. Is the prevalence of arterial hypertension in rheumatoid arthritis and osteoarthritis associated with disease? Rheumatol Int 2013;33:1185–92.
16. Imhof H, Sulzbacher I, Grampp S, Czerny C, Youssefzadeh S, Kainberger F. Subchondral bone and cartilage disease: a rediscovered functional unit. Invest Radiol 2000;35:581–8.
17. Aguirre IJ, Plotkin LI, Stewart SA, Weinstein RS, Parfitt MA, Manolagas SC, et al. Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. J Bone Miner Res 2006;21:605–15.