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Multiple Joint Osteoarthritis (MJOA): what's in a name?

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Abstract

Objective: To summarize the current state of the literature regarding multi-joint osteoarthritis (MJOA) and discuss important future directions.

Design: Narrative review of the author's work and other key references on this topic with a focus on the Johnston County studies, definitions of MJOA and their impact, multi-site pain in OA, genetics and biomarkers in MJOA, and perspectives on future work.

Results: MJOA is variably defined and lacks a clear consensus definition, making comprehensive study challenging. Involvement of both symptoms and structural changes of OA in multiple joints in an individual is common, but patterns vary by sex, race/ethnicity, and other factors. Outcomes (e.g., general health, function, falls, mortality) are negatively impacted by greater whole body OA burden. Recent genetic and biomarker studies including whole body OA assessments have begun to shed some light on potentially unique factors in the MJOA population.

Conclusions: Consideration of MJOA is essential for ongoing study of OA phenotypes, epidemiology, risk factors, genetics, biomarkers, and outcomes, to fully understand and eventually limit the negative impact of OA burden on health.

Keywords

Multi-joint osteoarthritis; generalized osteoarthritis; epidemiology; biomarkers

Early in my career, I was struck by a simple truth. All my clinical patients had osteoarthritis (OA) in more than one joint, but the literature was focused only on index knees. I searched the literature on "generalized OA," only to find that there was no consistent definition for this entity, and worse, that it had not been systematically studied and was poorly understood.[1] Therefore, the study of the whole-body burden of OA has become a focus of my research career.

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It is clear that OA often affects multiple joints[2] (Figure 1) and that many, if not most, individuals affected by OA have multiple painful joint sites.[3] Also obvious but rarely addressed is the fact that most risk factors, including modifiable and non-modifiable ones, are systemic in nature. Sex, race/ethnicity, age, body mass index, socioeconomic status, psychosocial factors, and so on, do not impact only the index knee, but the overall burden of OA on the patient. Similarly, serum and urine biomarkers are inherently systemic, but are frequently used to assess a single joint site for OA presence or progression. Even common outcomes in OA, such as standardized pain and function questionnaires, are strongly influenced by the overall burden of OA and multiple site pain[4]. As the field moves toward identification of phenotypes and endotypes within OA[5], a renewed appreciation for multiple joint involvement becomes even more essential.

The synthesis of evidence in this area is made incredibly challenging by the lack of consensus definitions. It is necessary to search for numerous terms (e.g., generalized, polyarticular, multiple, multi-joint, polyOA) to identify relevant studies, but even this strategy will still miss some studies that have considered multiple joint sites separately or together[1]. Every study assesses different body areas, joints/joint sites, risk factors, covariates, and outcomes, making summary statements challenging, and obfuscating critical research gaps. Improved understanding of the patterns of multiple joint OA (MJOA) is crucial to inform future therapies, whether these are designed to affect only one joint (but have potential impact on others[6]), or are meant to reduce the overall OA burden for an individual[7].

This narrative review will summarize the literature to date, including some of my own work, while also highlighting some important gaps and future directions in the area of MJOA.

Results/Summary of key findings

I. The Johnston County Osteoarthritis Project (JoCoOA)

The JoCoOA was a prospective, population-based cohort study that began enrollment of non-institutionalized adults aged 45 years and older in 1991[8]. There was a unique focus on inclusion of rural, minority, and low socioeconomic status populations, allowing this study to be more generalizable to these groups. JoCoOA involved more than 4000 Black and White men and women from Johnston County, North Carolina over its 30-year span, all of whom provided extensive data via questionnaires, clinical examinations, biospecimens, and multiple joint radiographs at multiple time points. The resulting rich longitudinal dataset has provided numerous insights into population prevalence, sex and race differences, and aspects of MJOA described below.

Since the JoCoOA was always focused on multiple joints, and given the population-based design, it has been able to provide estimates of population prevalence for knee[8, 9], hip[10, 11], and hand[12] OA, as well as insights on spine OA[13–15] and femoroacetabular impingement[16, 17]. The longitudinal follow-up also allowed estimates of the lifetime risk, i.e., the risk of developing symptomatic OA in several sites by age 85. At the knee, the overall lifetime risk was about 45%, but was higher among participants with obesity or prior injury.[18] Lifetime risk of hip OA was slightly lower at 1 in 4, and was not substantially affected by any of the

covariates.[19] The risk of symptomatic hand OA was in between at 40%, and as expected was higher for women and White participants[20].

II. Definitions of Multiple Joint Osteoarthritis and health outcomes

I was interested in formulating MJOA phenotypes from a very early stage in my career. Initially, we developed these as exclusive permutation subgroups, with each participant in only one category, in a cross-sectional analysis. In over 1400 JoCoOA participants, we found a much lower frequency of radiographic OA (rOA) in the hands (particularly in the distal interphalangeal joints) both alone and in combination with other joint sites among Black compared with White participants (odds ratios [OR] ~0.3). However, Black participants had a higher odds of multiple large joint combinations, especially knee and spine OA (OR 1.77), than White participants[21]. Following this work, we reported exclusive permutations of symptomatic OA phenotypes, which followed a similar pattern. Again, symptomatic hand rOA, alone or in combination, was very infrequent among Black participants, but symptomatic knee rOA, alone or with concomitant spine OA, was more common in Black than White individuals[22]. Men were also less likely to have symptomatic hand rOA alone or in combination. A recent cross-sectional study in 180 Nigerian patients with knee OA (of whom 28 had spine and 2+ other sites involved) found similar patterns, with combinations of large joints being more common than presence of hand OA[23]. *This was a critical finding, as many definitions of "generalized OA" require either hand rOA or nodal changes, which will misclassify many men and Black individuals with multiple joint OA as not having "generalized" disease and miss the large burden of OA faced by these individuals*. Despite our observations and those of others, nodal OA is frequently (and imprecisely) used as a proxy for generalized or MJOA[24, 25].

This work prompted two systematic reviews to better understand the literature around defining MJOA[1], and to attempt to provide an improved set of definitions for this elusive condition[26]. First, we performed a systematic review of 98 papers proposing a definition of OA in more than one joint from 1946 to 2012[1]. We identified 24 unique cohorts including more than 30,000 people across 22 countries and 5 continents, with at least 15 distinct definitions. While these definitions always included the hands, and frequently included the knees, only half considered the spine or feet. We returned to update this review up to 2017 and attempt to provide a smaller set of operationalized definitions for use in MJOA research (Table 1)[26]. We also sought to assess the frequency (Table 1) and impact of MJOA by these various definitions within the JoCoOA cohort. We found a median frequency of 50% across radiographic MJOA definitions, and of 24% across symptomatic MJOA definitions in this community-based cohort. All symptomatic MJOA definitions were associated with poorer general health physical function in affected versus unaffected individuals[26].

As this was a cross-sectional analysis, we subsequently sought to determine the influence of symptomatic MJOA on self-reported physical function after an average of 3.5 years of follow up. We found that among 586 individuals with available data, the frequency of symptomatic MJOA was up to 50%, and that PROMIS-PF (Patient Reported Outcomes Measurement Information System Physical Function Scale, Short Form 10a version 1.0[27]) scores worsened among the majority of these individuals, with differences among the MJOA

definitions and by sex and race.[28] In a separate analysis, we found that an increasing number of lower extremity joints (hips or knees) with symptomatic OA resulted in higher odds of falls over 6 years of follow-up in the JoCoOA, such that those with one symptomatic joint had 50% higher odds of falling, but those with 3–4 symptomatic joints had 85% higher odds of falling, than those with no affected knee or hip joints, independent of multiple other risk factors for falls[29]. A recent study using claims data from Germany reported that WOMAC scores were reflective of body burden of OA, not just an index joint, and that burden of MJOA resulted in poorer WOMAC, affected work and personal life, increased medication use including opioids, especially when both the hip and knee were affected[4]. *Taken together, these studies highlight the importance of assessing multiple body sites, particularly multiple lower extremity body sites, for OA and pain, as this burden is strongly related to general health, physical function, morbidity and mortality in affected individuals*.

III. Multi-site pain

There is substantial literature to suggest that the presence of symptoms in multiple joints (whether there is evidence of structural OA or not), may be contributing to, or even driving, observed associations between MJOA and outcomes such as pain, function, falls, and mortality. In a cohort of 201 adults over 50 years of age, chronic multi-site pain was noted to be frequent, with a median number of painful joints of 6 (most commonly knee, lower back, and shoulder), almost all had OA and 85% had MJOA[30]. We have applied factor analysis to multiple joint radiographic and symptom data, with the goal of identifying phenotypes of MJOA. However, what emerged were distinct factors around radiographic OA in various sites (i.e., interphalangeal/carpometacarpal [CMC], metacarpophalangeal, knee, and spine)[31] and a single factor including symptoms at all sites[32]. This separate symptom factor was also most strongly associated with functional impairments as assessed by health assessment questionnaire and gait speed[32]. A few other studies focused on knee OA have assessed the presence of pain at other sites. Carlesso et. al noted that severity and bilaterality of knee pain, but not radiographic knee OA, increased the risk of widespread pain in the Multicenter OA Study (MOST)[33].

Combining data from MOST and the Osteoarthritis Initiative (OAI), individuals with or at risk for KOA who developed new knee pain (especially bilateral) had more sites of pain outside the knee, both at baseline and developing over time, versus those without new knee pain[34]. MJOA and multi-site pain have also been shown to contribute to poorer outcomes at knee and hip arthroplasty[35, 36], as well as spinal decompression surgery[37]. Additionally, good outcomes from knee arthroplasty have been estimated to be 20% less likely for every additional joint (hip/knee) involved[38]. Work from our group has demonstrated that associations between OA and mortality are strongest for symptomatic joints (whether radiographic OA is present or not)[39–41]. *While MJOA is an important construct, the overall burden of disease is reflected in the symptoms experienced by the patient, which may or may not be evident through available structural assessments*.

IV. MJOA and genetics

A familial pattern of MJOA, initially observed in clinical settings, has also been identified in research studies[42, 43], particularly in relation to nodal hand OA[44–47]. In twin studies,

hand OA (involving the distal [DIP] and proximal interphalangeal [PIP] joints and CMC joints) was highly heritable at >50% (65% DIP, 53% PIP, 68% CMC), much more than either hip or knee OA (heritability 28% and 37%, respectively), but there was essentially no genetic correlation between hand and hip/knee OA[48]. Valdes et. al studied individuals with either nodal or non-nodal hand OA who underwent hip or knee replacement for OA[49]. They found that patients with nodal OA were more likely than those with non-nodal OA to need both hip and knee replacement, and bilateral knee (but not hip) replacement. Associations between joint replacement and known risk factors such as age and female sex were stronger among nodal vs non-nodal patients, while the association with BMI was stronger in those with non-nodal OA. GDF5 risk alleles were associated with knee replacement regardless of nodal status[49]. In the most recent and largest OA GWAS to date, Boer et. al reported several single nucleotide variants (SNVs) that were associated with various OA phenotypes including 4 SNVs for combinations of hand and knee/hip OA[50]. Further work including study of numerous specific phenotypes in large consortia is underway, such as the Genetics of Osteoarthritis (GO) consortium (https://www.genetics-osteoarthritis.com), which has an active workgroup around GWAS of endophenotypes in OA. *Importantly, these large consortia can include sufficient numbers of individuals from diverse ancestry to provide some insight regarding OA in historically underrepresented groups; continued study of large, diverse cohorts with a focus on MJOA is needed*.

V. MJOA and biomarkers

Biomarkers from serum or urine are by their nature systemic, and even synovial fluid biomarkers are affected by the systemic milieu. Studies of a single index joint often (but surprisingly not always) adjust for OA or pain in other joints, but only those for which data are available in each study. In contrast, it may be of more interest to consider biomarkers in the context of the body burden of OA as outlined in the BIPED criteria[51]. For example, joint counts (by various methods) have been correlated with elevated levels of urinary type II collagen C-telopeptide (uCTX-II); cartilage oligomeric matrix protein (COMP); and hyaluronic acid (HA)[52], while PIIANP[53] is negatively correlated with higher burden. More recently, cartilage acidic protein 1 (CRTAC1) was identified in a large proteomic analysis and found to be strongly associated with OA of the knee, hip, and hand individually; a cursory analysis by number of affected joint types indicated a possible association with MJOA[54]. This promising marker (along with COMP) was also associated with OA burden (summed KL grades at the bilateral knees, hips, and hands) and severity in over 3500 participants in the population-based Rotterdam study[55].

Beyond summed scores of joints or features, radionuclide scanning can quantify body burden of OA, and has been associated with serum and synovial fluid cartilage oligomeric matrix protein (COMP)[56]. A recent study incorporating etarfolatide imaging to quantify inflammation (related to activated macrophages and neutrophils) in the knees and 30 other joints found that while c-reactive protein was associated with osteophyte scores, CRPM (a neoepitope of CRP generated by matrix metalloproteinase cleavage) was associated with inflammation in the knees and with a summed multiple joint score[57]. Finally, using JoCoOA data with a focus on symptomatic sites (rather than rOA), we found that higher serum osteoprotegerin (OPG) and C-X-C Motif Chemokine Ligand 6 (CXCL-6) were associated

with 70% higher odds of multiple painful sites (versus none), while higher serum HA was associated with 50% higher odds of having multiple painful sites versus none or only one site of pain[58]. *Consideration of the body burden of OA, both symptomatic and structural, is important for understanding of mechanisms and potential surrogate markers of OA that may lead to improved treatments*.

VI. The Johnston County Health Study

Active data collection for the JoCoOA ended after the T4 time point in 2018 due to declining numbers in the cohort primarily from age-related mortality and poor health. To continue to leverage the remarkable community infrastructure in Johnston County, we began enrolling a new cohort in 2019, called the Johnston County Health Study (JoCoHS; jocohs.unc.edu). In addition to maintaining the strong infrastructure and population-based nature of the original study, JoCoHS includes somewhat younger individuals (age 35–70 years) and additional diversity through active inclusion of Hispanic individuals in addition to Black and White men and women. We have built on our extraordinary staff to include Spanish-speaking team members and have generated all study materials in both English and Spanish to reflect the changing demographics of the county and the United States. We continue to focus on representation of Black and White men and women from rural and urban areas and all socioeconomic backgrounds. We recently reported preliminary data on MJOA in the first ~400 consecutive participants (31% men, 21% Black, 9% Hispanic, 29% with a college degree or higher), where a surprisingly high number of these younger (mean age 55 years) individuals met criteria for several MJOA phenotypes; about 12% across radiographic and 8% across symptomatic MJOA definitions[59]. *Study of diverse, generalizable population-based cohorts is needed to understand the prevalence and impact of MJOA*.

Perspectives and summary

This review has summarized research from our group and others around the concept of the whole-body burden of OA, which we refer to as multiple joint OA, or MJOA. Since other terms lack clear definitions, MJOA is a reasonable alternative when accompanied by a clear and transparent definition of which joints/joint sites are being assessed (e.g., hands, knees, spine, etc.) and how OA at these sites is being defined (e.g., clinical, symptomatic, radiographic criteria). Despite the challenges around differing definitions, it is abundantly clear that the burden of MJOA is substantial, contributing to loss of quality of life and function in affected individuals, and that its impact is dependent on individual characteristics. It is essential to consider MJOA when studying OA phenotypes and systemic risk factors, particularly genetics and biomarkers, to understand their relation to the individual's overall OA burden. Multi-joint pain, whether related to MJOA or another cause, is also important in the context of patient reported outcomes, pain, and function.

Our ongoing work will consider additional ways in which to define and quantify the burden of MJOA on individuals from diverse backgrounds, the relation among MJOA, biomarkers, and the microbiome (in both humans and in pet dogs who are also frequently affected by MJOA), and consideration of pain mechanisms in MJOA.

Key future directions in MJOA research include:

- Epidemiologic study of MJOA patterns in men and women from diverse populations
- Consideration of body burden of OA for systemic risk factors and outcomes such as biomarkers
- Accounting for body burden of OA and pain in clinical trials, both for efficacy and for safety of the intervention at all joint sites
- Investigation of genetics in single versus multi-joint OA
- Assessment of the relative importance of MJOA vs multi-site pain for patients (e.g., quality of life, functional status) and the impact of these features on the efficacy of management options

An improved understanding of the overall burden of OA on an individual is essential to move the field of OA research forward. Despite decades of study, there are still no highly effective therapies for OA, and no treatments have even been studied in the specific setting of MJOA, despite the obvious burden of this condition. In addition to the study of the whole joint as an organ (not just focusing on a single tissue such as cartilage), it is imperative to study the whole person[60] living with OA and all the aspects of their lived experience with this chronic condition.

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Competing interest statement:

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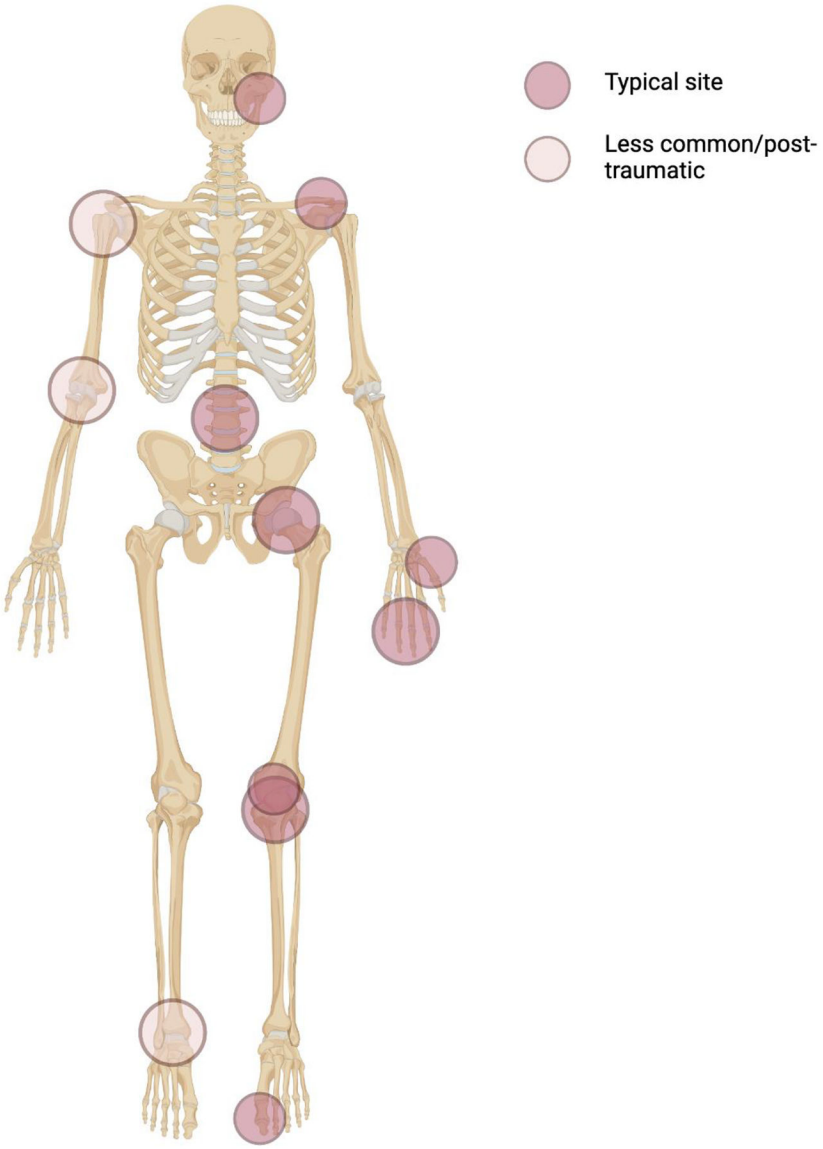

Figure 1.

Sites commonly affected by multiple joint osteoarthritis (MJOA), including the temporomandibular, acromioclavicular, spinal facets, hip, carpometacarpal, interphalangeal, patellofemoral, tibiofemoral, and 1st metatarsophalangeal joints. Less commonly and often with a history of trauma, the glenohumeral, elbow, and ankle joints may be affected. Figure created with biorender.com.

Table 1.

Multiple joint (MJOA) definitions and frequencies of these definitions in the Johnston County Osteoarthritis Project (JoCo OA; 2013–2015 follow-up visit, n=904)*[26]

MJOA-	Joint sites included in definition	JoCo rOA *n (%)*	JoCo sxOA *n (%)*
1	≥1 IP node and ≥2 other sites (hip, knee, spine, ankle, foot)	503 (56)	441 (49)
2	≥2 IP and ≥1 CMC and knee or hip	228 (26)	139 (16)
3	≥5 joint sites (DIP, PIP, CMC, hip, knee, spine, ankle, foot)	230 (26)	165 (18)
4	≥2 lower body joint sites (hip, knee, spine, ankle, foot)	565 (63)	345 (38)
5	Knee or hip and 1 other joint site (spine, ankle, foot)	489 (55)	466 (52)
6	≥3 sites (hip, knee, spine, ankle, foot)	228 (25)	147 (16)
7	Bilateral knees and spine	24 (4)	14 (2)
8	≥3 joint sites (DIP, PIP, CMC, hip, knee, spine, ankle, foot)	606 (67)	390 (43)
9	≥1 CMC and bilateral nodes	289 (32)	120 (13)
10	≥3 IPs or bilateral nodes	663 (74)	135 (15)

rOA = radiographic OA (KLG≥2 except as noted below1); sxOA = symptomatic OA (symptoms + rOA in same site); KLG = Kellgren-Lawrence grade; knee=tibiofemoral joint; ankle=tibiotalar joint; DIP = distal interphalangeal; PIP = proximal interphalangeal; CMC = carpometacarpal; Exceptions: rOA of spine: DSN ≥1 and ≥2 OST together in ≥1 vertebral level; rOA of foot: ≥2 OST or JSN in at least 1 of 5 joints (1st metatarsophalangeal, 1st cuneo-metatarsal, 2nd cuneo-metatarsal, navicular-1st cuneiform, talo-navicular); DSN = disc space narrowing; OST = osteophyte; JSN = joint space narrowing

*Adapted from Seminars in Arthritis and Rheumatism, vol 48, issue 6, Gullo TR et al, Defining multiple joint osteoarthritis, its frequency and impact in a community-based cohort, p 958, 2019, with permission from Elsevier[26].