HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2020 May 14.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2016 March ; 68(3): 288–291. doi:10.1002/acr.22680.

Exercise Medicine for Osteoarthritis: Research Strategies to Maximize Effectiveness

MARCAS M. BAMMAN[1], **TIMOTHY M. WICK**[2], **CARLOS A. CARMONA MORAN**[3], **S. LOUIS BRIDGES JR.**[2]

[1]University of Alabama at Birmingham Center for Exercise Medicine and Comprehensive Arthritis, Musculoskeletal, Bone, and Autoimmunity Center, and Birmingham VA Medical Center;

[2]University of Alabama at Birmingham Center for Exercise Medicine, BioMatrix Engineering and Regenerative Medicine Center, and Comprehensive Arthritis, Musculoskeletal, Bone, and Autoimmunity Center, Birmingham;

[3]University of Alabama at Birmingham.

Introduction

Osteoarthritis (OA), often called degenerative joint disease, is the most common form of arthritis, with 27 million adult cases of clinical OA reported in the US in 2005 (1). In fact, OA is the second most prevalent chronic condition in community-dwelling adults ages >65 years (2). The term degenerative joint disease is a misnomer, as OA is characterized by abnormal remodeling of joint tissues driven by a host of inflammatory mediators, not simply a process of wear and tear (3). The pathologic changes seen in OA are not limited to the articular cartilage and contiguous bone, but also involve the synovium, ligaments, and periarticular muscles, nerves, and bursae (3).

While there is no cure for OA, accumulating evidence supports prescribed exercise training as an effective form of therapy in the treatment of OA symptoms and associated comorbidities. Exercise as medicine for OA was perhaps best summarized in a 2013 meta-analysis by Uthman et al (4), involving 60 exercise clinical trials. Uthman et al reported clear benefits (e.g., pain relief and improved mobility function) of various exercise prescriptions incorporating endurance training, strength training, flexibility exercises, aquatic exercise, or combination training. Prescriptive exercise and/or increases in leisure time physical activity (LTPA) are now widely promoted by leading organizations (e.g., the Arthritis Foundation [5] and the National Institute of Arthritis and Musculoskeletal and Skin Diseases [6]), strongly recommended for the management of knee and hip OA by the American College of Rheumatology (ACR) 2012 guidelines (7), and promoted more broadly throughout health care by the American College of Sports Medicine via the Exercise is Medicine initiative (8).

Address correspondence to Marcas M. Bamman, PhD, 966 McCallum Building, 1720 Second Avenue South, University of Alabama at Birmingham, Birmingham, AL, 35294-0005. mbamman@uab.edu.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.

The unfortunate irony is that, in every US state (based on the 2009 Centers for Disease Control and Prevention report), a significantly higher percentage of adults with any form of arthritis reported no LTPA (median across states 31.8%) compared to adults without arthritis (median across states 20.7%). In addition, those with arthritis comprised a large portion of all adults reporting no LTPA in each state (mean 35.2%) (9). Approximately half of all women and men with knee OA in the Osteoarthritis Initiative were found via accelerometry to be essentially inactive, and only ~10% met low/moderate aerobic physical activity guidelines (10). There are many factors associated with low physical activity, including joint pain, immobility, fatigue, lack of instruction, logistic issues, and psychological factors, but a review of such factors is beyond the scope of this commentary.

In our view, the high rates of inactivity among persons with OA are troubling and should fuel a robust, multi-tiered research effort with aims of optimizing exercise prescription to improve adherence and effectiveness in OA. Thus, the purpose of this commentary is to describe key knowledge gaps in OA exercise prescription and emphasize opportunities for innovative research (e.g., exercise-drug/device interactions, dose-response research, etc.) that have the potential to impact the treatment and quality of life of persons with OA.

Why is exercise prescription important?

While both prescriptive exercise and LTPA are likely beneficial for managing symptoms of OA (e.g., pain reduction, reduced fatigue, and mobility improvement) and may slow the loss of tissue and joint function (4,11), the 2 are clearly distinct. As demonstrated in a recent meta-analysis, including nearly 800,000 participants (12), sedentary time confers an alarmingly elevated risk of multiple morbidities (e.g., relative risk [RR] 2.12 for diabetes mellitus, RR 2.47 for cardiovascular events), cardiovascular mortality (hazard ratio [HR] 1.90), and all-cause mortality (HR 1.49); thus, less sitting and more LTPA is recommended for all. Prescriptive exercise, on the other hand, is a structured, well-defined weekly exercise program that yields physiologic and fitness benefits well beyond LTPA (13,14). Community-dwelling older adults (ages >65 years) are more likely to adopt an exercise program and realize its greater fitness benefits when physicians provide an actual prescription versus general physical activity counseling (15). In addition to encouraging more LTPA, we therefore see a great need to establish evidence-based guidelines for prescriptive exercise that will yield maximum benefit in OA patients. Consequently, we have chosen to focus this commentary on prescriptive exercise, and what we perceive as key knowledge gaps and opportunities for innovative research that would drive recommendations for clinical application.

Key knowledge gaps and opportunities for innovative research in OA

While exercise in its various forms profoundly impacts human physiology in health and disease, key knowledge gaps remain, as highlighted recently (13). Here we discuss gaps particularly relevant to OA and exercise that present fertile opportunities for clinical and translational research. By ultimately developing a research agenda that will lead to a base of evidence, we may achieve dramatic improvements in OA outcomes beyond that of

pharmacologic management. Such a base of evidence is essential in order for the medical community to implement prescriptive exercise as a key component of standard care.

Dose-response relationships and interindividual heterogeneity.

For exercise to be prescribed optimally, it must be approached as any other medicine, with the goal of establishing a complete understanding of optimal dosing for maximum effectiveness and safety in a disease-specific and population-specific manner. In exercise prescription terms, dosing is defined by 4 variables: 1) mode (e.g., endurance, resistance, or interval training), 2) intensity, 3) duration or volume of work per session, and 4) frequency (sessions per week). While various modes of exercise benefit the OA patient (4), guidelines for optimal exercise prescription are not yet established, and future goals of wide acceptance and implementation are not within easy reach. Randomized trials investigating modes of exercise (e.g., resistance versus aerobic, continuous versus interval training) in OA are extremely limited. Our literature review revealed no published trials in which variations in dosing variables such as intensity or frequency were directly compared in OA (although one is ongoing) (16). It is well recognized that the prescription dose profoundly influences exercise training adaptations in healthy and diseased individuals, but clearly more definitive trials are needed to both understand and optimize dosing (14). In OA specifically, such studies are important to maximize gains in mobility function, to minimize pain and fatigue, and to alter cellular and molecular processes that may potentially modify the course of disease. While multisite trials are lacking, an encouraging first attempt is the ongoing single-site trial by Messier and colleagues (16) comparing high- versus low-intensity strength training in persons with knee OA (the Strength Training for Arthritis Trial, NCT01489462).

It is equally important to increase our understanding of interindividual exercise response heterogeneity, which is quite substantial and seems to result from both genetic and phenotypic variation (13,17–19). Efforts to understand the basis of wide variability among individuals completing the same exercise prescription (e.g., high versus low responders) is now driving a burgeoning field of exercise genomics (20,21) to reveal the underpinnings, and perhaps develop predictive indices of expected responses. Variability in individual responsiveness is not unique to exercise treatment and is in fact well-established in OA patients attempting to restore function after the ultimate treatment of total joint arthroplasty (22,23). With trials of sufficient scale, one could envision defining the optimal exercise prescription for the majority of OA patients, while also uncovering minority phenotypes and/or genotypes that may gain more benefit from an alternative exercise dose or an entirely different treatment. In this manner, exercise response heterogeneity may become embedded in the fabric of personalized medicine.

Exercise-drug/device interactions.

Research is sorely needed to determine whether and how specific doses of exercise affect the relative efficacy and toxicity of common treatments for OA symptoms (e.g., nonsteroidal antiinflammatory drugs [NSAIDs], opioids, or intraarticular corticosteroids [IACs]). Exercise substantially influences drug pharmacokinetics (24), and it would be of great value to determine whether adjunctive exercise alters the medication needs of OA patients.

Determining whether exercise reduces NSAID dosing would be particularly valuable, since NSAIDs are widely used to treat OA symptoms and long-term usage carries a number of risks for side effects (stomach bleeding or ulcer, hypertension, kidney problems, rashes, etc.). Interestingly, long-term NSAID consumption in relatively healthy older adults appears to augment resistance exercise training adaptations in both skeletal muscle (25) and tendon (26). This fact raises the possibility that, among persons with OA, NSAID usage may have influenced the exercise adaptations summarized by Uthman et al (4). Oral corticosteroids have been shown to reduce pain and inflammation in persons with knee OA (27), but for a variety of reasons are not clinically indicated for the treatment of OA. IACs are conditionally recommended by the ACR for the initial treatment of knee OA and other joints (7). IACs injected inside the joint capsule are assumed to largely remain in this confined space and to not be absorbed systemically. However, many effects attributed to such injections are likely due to systemic absorption (28), including a blunted cortisol response to adrenocorticotropic hormone stimulation in some patients (29). Thus, there remain many unanswered issues related to IACs in OA (30), including the systemic effect of IACs delivered into the joint capsule relative to those administered in the periarticular tissues. While IACS are known to be efficacious in OA, chronically elevated serum corticosteroid levels have profound negative effects on skeletal muscle (31) and bone (32). There are no high-quality data addressing the effects of IAC injections on muscle or bone. Furthermore, the effects of combined systemic or IAC therapy and adjunctive exercise training in humans with OA are not yet known. Assessing their interactive effects seems important, as potentially exercise training might attenuate the deleterious drug effects. Opioids are conditionally recommended for patients refractory to initial therapies (7) and are sometimes prescribed to those who experience pain in multiple joints (33). It would therefore be beneficial to determine whether a prescribed exercise program can be tolerated and affects opioid-associated fatigue (33).

The risks of hip and knee OA are thought to increase with low-grade systemic inflammation coupled to obesity, metabolic syndrome, and aging (34). On the other hand, the inflammatory burden within the diseased joint (34–36), including the proinflammatory complement system (37), is emerging as a likely, central contributor to OA pathogenesis. Thus, a logical approach to improving exercise adherence and potentially training adaptability would be directed delivery of antiinflammatory medications (e.g., NSAIDs or corticosteroids) to the diseased joints in a targeted fashion. An alternative to systemic dosing is transdermal drug delivery (TDD) directly to the site of pain. We speculate that prescriptive exercise in conjunction with novel interventions such as chemical and physical approaches currently under investigation may lead to improved outcomes in OA. The idea of investigating chemical and physical approaches to improve the permeation of drugs through the skin and overcome the barrier function of the stratum corneum (38) is not new (e.g., iontopheresis (39), electroporation (40), sonopheresis (41), microneedles (42), and the use of chemically modified drugs or chemical enhancers (43)). On the other hand, exercise trials incorporating novel TDD formulations would be particularly innovative, as local drug delivery at the sites of pain may improve both exercise adherence and effectiveness. Overall, research to more fully understand the interactions between exercise training and current antiinflammatory, analgesic therapies would significantly advance the field.

Summary and recommendations: research to inform exercise prescription guidelines for OA

Treatment guidelines have been proposed for many diseases, including OA, as summarized in the ACR 2012 consensus statement (7), in which the expert panel strongly recommended aerobic, aquatic, and/or resistance exercises for the management of knee OA. We fully support this recommendation but also recognize that it falls short of a well-defined exercise prescription because data from randomized, controlled trials comparing doses are sorely lacking. Rigorous, large-scale trials are needed to provide the evidence base that should incentivize both clinicians and patients to adhere to prescribed exercise regimens. We suggest that this research should aim to: 1) optimize both dose-response effectiveness and adherence, 2) identify genetic and phenotypic determinants of responsiveness, and 3) better understand the interactive effects (e.g., synergism and antagonism) between exercise and both common and novel drug/device treatments. Overall, these gaps present rich opportunities for innovative research that would provide the solid base of evidence needed to drive better implementation, enable the creation of prescription guidelines tailored to the site of arthritis and patient characteristics, and improve OA outcomes and ultimately the quality of life for those experiencing this common, chronic disease.

Acknowledgments

Drs. Bamman and Bridges' work was supported by the NIH (grant RO1-HD-084124).

REFERENCES

1. Murphy L, Helmick CG. The impact of osteoarthritis in the United States: a population-health perspective. A population-based review of the fourth most common cause of hospitalization in US adults. Orthop Nurs 2012;31:85–91. [PubMed: 22446800]
2. Egan BA, Mentes JC. Benefits of physical activity for knee osteoarthritis: a brief review. J Gerontol Nurs 2010;36:9–14.
3. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012;64:1697–707. [PubMed: 22392533]
4. Uthman OA, van der Windt DA, Jordan JL, Dziedzic KS, Healey EL, Peat GM, et al. Exercise for lower limb osteoarthritis: systematic review incorporating trial sequential analysis and network meta-analysis. BMJ 2013;347:f5555. [PubMed: 24055922]
5. Arthritis Foundation. 2014 URL: http://www.arthritis.org.
6. National Institute of Arthritis, Musculoskeletal, and Skin Diseases. 2014 URL: http://www.niams.nih.gov.
7. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012;64:465–74. [PubMed: 22563589]
8. American College of Sports Medicine. Exercise is medicine. 2007 URL: http://www.exerciseismedicine.org/.
9. Hootman JM, Watson KB, Harris C, Barbour KE. State-specific prevalence of no leisure-time physical activity among adults with and without doctor-diagnosed arthritis, United States, 2009. MMWR Morb Mortal Wkly Rep 2011; 60:1641–5. [PubMed: 22157882]
10. Dunlop DD, Song J, Semanik PA, Chang RW, Sharma L, Bathon JM, et al. Objective physical activity measurement in the Osteoarthritis Initiative: are guidelines being met? Arthritis Rheum 2011;63:3372–82. [PubMed: 21792835]

11. Simon TM, Jackson DW. Articular cartilage: injury pathways and treatment options. Sports Med Arthrosc 2006;14: 146–54. [PubMed: 17135961]
12. Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. Diabetologia 2012;55: 2895–905. [PubMed: 22890825]
13. Bamman MM, Cooper DM, Booth FW, Chin ER, Neufer PD, Trappe S, et al. Exercise biology and medicine: innovative research to improve global health. Mayo Clin Proc 2014;89: 148–53. [PubMed: 24485128]
14. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand: quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults. Guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334–59. [PubMed: 21694556]
15. Petrella RJ, Koval JJ, Cunningham DA, Paterson DH. Can primary care doctors prescribe exercise to improve fitness? The Step Test Exercise Prescription (STEP) project. Am J Prev Med 2003;24:316–22. [PubMed: 12726869]
16. Messier SP, Mihalko SL, Beavers DP, Nicklas BJ, DeVita P, Carr JJ, et al. Strength Training for Arthritis Trial (START): design and rationale. BMC Musculoskelet Disord 2013;14: 208. [PubMed: 23855596]
17. Thalacker-Mercer A, Stec M, Cui X, Cross J, Windham ST, Bamman MM. Cluster analysis reveals differential transcript profiles associated with resistance training-induced human skeletal muscle hypertrophy. Physiol Genomics 2013;45: 499–507. [PubMed: 23632419]
18. Petrella JK, Kim JS, Mayhew DL, Cross JM, Bamman MM. Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonu-clear addition: a cluster analysis. J Appl Physiol 2008;104: 1736–42. [PubMed: 18436694]
19. Timmons JA, Knudsen S, Rankinen T, Koch LG, Sarzynski M, Jensen T, et al. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. J Appl Physiol (1985) 2010; 108:1487–96. [PubMed: 20133430]
20. Timmons JA. Variability in training-induced skeletal muscle adaptation. J Appl Physiol 2010;110:846–53. [PubMed: 21030666]
21. Bouchard C, Rankinen T, Timmons JA. Genomics and genetics in the biology of adaptation to exercise. Compr Physiol 2011;1:1603–48. [PubMed: 23733655]
22. Singh JA, Lewallen DG. Predictors of activity limitation and dependence on walking aids after primary total hip arthroplasty. J Am Geriatr Soc 2010;58:2387–93. [PubMed: 21143444]
23. Singh JA, Lewallen D. Predictors of pain and use of pain medications following primary total hip arthroplasty (THA): 5,707 THAs at 2-years and 3,289 THAs at 5-years. BMC Musculoskelet Disord 2010;11:90. [PubMed: 20462458]
24. Lenz TL. The effects of high physical activity on pharmacokinetic drug interactions. Expert Opin Drug Metab Toxicol 2011;7:257–66. [PubMed: 21244343]
25. Trappe TA, Carroll CC, Dickinson JM, LeMoine JK, Haus JM, Sullivan BE, et al. Influence of acetaminophen and ibuprofen on skeletal muscle adaptations to resistance exercise in older adults. Am J Physiol Regul Integr Comp Physiol 2010;300:R655–62. [PubMed: 21160058]
26. Carroll CC, Dickinson JM, LeMoine JK, Haus JM, Weinheimer EM, Hollon CJ, et al. Influence of acetaminophen and ibuprofen on in vivo patellar tendon adaptations to knee extensor resistance exercise in older adults. J Appl Physiol (1985) 2011;111:508–15. [PubMed: 21596925]
27. Abou-Raya A, Abou-Raya S, Khadrawi T, Helmii M. Effect of low-dose oral prednisolone on symptoms and systemic inflammation in older adults with moderate to severe knee osteoarthritis: a randomized placebo-controlled trial. J Rheumatol 2014;41:53–9. [PubMed: 24293578]
28. Habib GS. Systemic effects of intra-articular corticosteroids. Clin Rheumatol 2009;28:749–56. [PubMed: 19252817]
29. Mader R, Lavi I, Luboshitzky R. Evaluation of the pituitary–adrenal axis function following single intraarticular injection of methylprednisolone. Arthritis Rheum 2005;52:924–8. [PubMed: 15751089]

30. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006;2:CD005328.
31. Schakman O, Kalista S, Barbe C, Loumaye A, Thissen JP. Glucocorticoid-induced skeletal muscle atrophy. Int J Biochem Cell Biol 2013;45:2163–72. [PubMed: 23806868]
32. Seibel MJ, Cooper MS, Zhou H. Glucocorticoid-induced osteoporosis: mechanisms, management, and future perspectives. Lancet Diabetes Endocrinol 2013;1:59–70. [PubMed: 24622268]
33. Hoogeboom TJ, den Broeder AA, Swierstra BA, de Bie RA, van den Ende CH. Joint-pain comorbidity, health status, and medication use in hip and knee osteoarthritis: a cross-sectional study. Arthritis Care Res (Hoboken) 2012;64:54–8. [PubMed: 21954220]
34. Houard X, Goldring MB, Berenbaum F. Homeostatic mechanisms in articular cartilage and role of inflammation in osteoarthritis. Curr Rheumatol Rep 2013;15:375. [PubMed: 24072604]
35. Benito MJ, Veale DJ, FitzGerald O, van den Berg WB, Bresnihan B. Synovial tissue inflammation in early and late osteoarthritis. Ann Rheum Dis 2005;64:1263–7. [PubMed: 15731292]
36. Wojdasiewicz P, Poniatowski LA, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm 2014;2014: 561459. [PubMed: 24876674]
37. Wang Q, Rozelle AL, Lepus CM, Scanzello CR, Song JJ, Larsen DM, et al. Identification of a central role for complement in osteoarthritis. Nature Med 2011;17:1674–9. [PubMed: 22057346]
38. Subedi RK, Oh SY, Chun MK, Choi HK. Recent advances in transdermal drug delivery. Arch Pharm Res 2010;33:339–51. [PubMed: 20361297]
39. Scheindlin S Transdermal drug delivery: past, present, future. Mol Int 2004;4:308–12.
40. Prausnitz MR, Bose VG, Langer R, Weaver JC. Electroporation of mammalian skin: a mechanism to enhance transdermal drug delivery. Proc Natl Acad Sci U S A 1993;90: 10504–8. [PubMed: 8248137]
41. Mitragotri S, Kost J. Low-frequency sonophoresis: a noninvasive method of drug delivery and diagnostics. Biotechnol Prog 2000;16:488–92. [PubMed: 10835253]
42. Henry S, McAllister DV, Allen MG, Prausnitz MR. Microfabricated microneedles: a novel approach to transdermal drug delivery. J Pharm Sci 1998;87:922–5. [PubMed: 9687334]
43. Sloan KB, Wasdo S. Designing for topical delivery: prodrugs can make the difference. Med Res Rev 2003;23:763–93. [PubMed: 12939791]