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Review

Osteoarthritis year in review 2018: clinical

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SUMMARY

Osteoarthritis (OA) is the most common joint disease in the world, with an age-associated increase in both incidence and prevalence. Clinical and epidemiologic research is crucial to better understand risk factors for disease, find the best treatments for symptoms, and identify therapies to slow down or even prevent disease progression. This paper is based on a systematic review of the osteoarthritis literature published in English between 2017/05/01 and 2018/04/25, with a focus on papers which have the potential to improve patient care, or which suggest novel areas for future research.

Introduction

Osteoarthritis (OA) is a leading cause of disability in the United States with over 22.7 million people reporting arthritis-attributable activity limitations[1,2]. Only depression and alcohol misuse result in more years lost to disability[3]. Already high, the incidence and prevalence of OA is predicted to skyrocket over the coming decades due to the aging population, rising obesity rates and high rates of traumatic knee injuries[4–7]. This is a public health crisis, and there is a pressing need for rigorous high-quality OA clinical research to ensure patients receive safe and effective treatments. This paper is a subjective overview of some of the most notable osteoarthritis clinical research studies published in the last year.

Methods

A PubMed search was performed for articles published between 2017/05/01 and 2018/04/25. Search terms were (osteoarthritis AND treatment) OR (osteoarthritis AND therapy) OR (osteoarthritis AND epidemiology), with results limited to English language studies evaluating human subjects. Including articles listed as [Epub ahead of print], this resulted in 1673 references. In addition, a complementary PubMed search was performed for the same date range for articles which were published in the New England Journal of Medicine, Annals of Internal Medicine, Osteoarthritis and Cartilage, Arthritis and Rheumatology, Arthritis Care and Research, Annals of the Rheumatic Disease and The Journal of Rheumatology and contained the search term “osteoarthritis”. This resulted in 171 articles, with some overlap. Titles were reviewed, and papers excluded if their primary focus was non-clinical, a case-series, a description of a study protocol, or were best aligned with one of the other Year-in-Review content areas. Reference lists of select articles were hand searched for additional potential articles of interest.

It is of course impossible in this brief review to discuss every important osteoarthritis manuscript published in the last year. The choice of which articles to highlight was based on the journal impact factor, the potential impact of the study on patient care, the impact on the study on furthering novel areas of research, and opinions solicited from experts in the field of osteoarthritis clinical research.

Incidence, prevalence and progression of OA

The associations between older age, obesity and increased rates of knee OA are well understood. However a study performed by Wallace *et al.* suggests that these major risk factors are insufficient to explain the exponential increase in the prevalence of knee OA[8]. This group utilized skeletal samples of adults over age 50 who lived in urban areas in the United States. They compared skeletons from people who died between 1905 and 1940, (early industrial; N = 1,581) and those who died between 1976 and 2015, (post-industrial; N = 819). They also included a comparator group of prehistoric skeletons from archeologic sites in North America, (N = 176). They found that prehistoric and early industrial skeletons did exhibit evidence of knee osteoarthritis. However, since the mid-twentieth century, the prevalence of knee osteoarthritis has

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doubled compared to early industrial rates, even after controlling for age and body mass index, (BMI). This finding suggests interactions with the modern environment may play a pathogenic role in the development of osteoarthritis. These authors hypothesize decreased physical activity could be one important factor, as it can a result in chronically underloaded joints with lower proteoglycan content, and weaker muscles which are unable protect and stabilized joints. One potential bias is that It BMI was measured at death. If there was systematic weight loss prior to death, using end-of-life BMI would not accurately control for lifetime BMI, and thus potentially underestimate the contribution of obesity to the development of osteoarthritis in the modern age. Regardless, these data underscore that knee osteoarthritis may be more modifiable than previously assumed and suggests that environmental or ecologic risk factors are novel areas for ongoing research.

Investigators used subjects from the Osteoarthritis Initiative (OAI) who did not have evidence of radiographic knee OA but were at high risk for developing knee OA, to evaluate whether evidence of the tissue lesions were predictive of developing incident radiographic osteoarthritis[9]. Sharma *et al.* found that abnormalities such as bone marrow lesions, meniscal extrusion, meniscal tears and cartilage damage increased the probability of developing incident knee radiographic knee OA over the following 7 years, over and above standard known risk factors. These data suggest there may be a "window of opportunity" to intervene in certain high-risk patients before the development of clinical or standard radiographic evidence of knee OA.

Most radiographic studies of knee OA evaluate the tibiofemoral joint, although the patellofemoral compartment can also be affected. A study by Lankhorst *et al.* utilizing The Cohort Hip and Knee Study found that subjects with mild symptoms of early knee OA are most likely to have involvement of the patellofemoral joint first, and then progress to combined patellofemoral and tibiofemoral osteoarthritis[10]. These data suggest clinicians should routinely evaluate the patellofemoral joint in patients complaining of knee pain, especially in the absence of tibiofemoral joint space narrowing on plain radiographs. Identifying this anatomic variant of OA is clinically important, as there are manual and targeted physical therapy approaches specifically designed for patients with patellofemoral OA.[11]

Two papers by Davis *et al.* suggest that certain patients are at risk for accelerated osteoarthritis, and that these patients are more likely to have knees replacements. Using the data from the OAI, these investigators identified patients who progressed from having no radiographic evidence osteoarthritis to having Kellgren and Lawrence grade 3 or 4 osteoarthritis within 48 months-quite a dramatic change[12]. Subjects who developed "accelerated" knee OA had a specific constellation of symptoms noted at the index visit 1-year prior compared with those who did not have rapidly accelerating osteoarthritis. These subjects had more trouble lying down, more pain when they straightened their knee, and more pain with walking. These subjects also reported more frequent pain, more frequent knee swelling, and were more likely to restrict their activities due to pain. Having accelerated OA was not benign, as these patients were approximately 25 times more likely to have a knee replacement within 9 years compared to patients with radiographic knee OA which was not rapidly progressive[13]. Whether screening for patients in clinical practice who present with this constellation of symptoms would identify patients at high risk of OA progression is unknown. In addition, further research would be needed to determine if knowing they were at high risk for rapidly progressive OA would motivate patients to aggressive pursue effective interventions to retard OA progression such as physical therapy to strengthen articular musculature, or weight loss.

Therapies for OA

Probably the highest impact clinical OA paper this past year was a paper by McAlindon *et al.* evaluating intra-articular corticosteroids for the treatment of knee osteoarthritis[14]. This paper was ranked as the fifth top article published in JAMA in 2017. In this blinded randomized controlled trial subjects with knee OA were administered intra-articular triamcinolone or saline placebo every 3 months for 2 years. Given that synovitis in known to be associated with worsening of structural damage in knee OA, it was hypothesized that local treatment of synovitis may retard disease progression. Although knee pain and function improved in both groups, there was no difference in pain between the groups at the end of the 2-year study period. However, cartilage thickness as measured by magnetic resonance imaging (MRI) was slightly decreased in patients receiving the intra-articular triamcinolone, with a between-group difference of −0.11 mm (95% CI, −0.20 to −0.03). These results suggest that rather than retard cartilage destruction, intra-articular triamcinolone may accelerate cartilage destruction, and that the anti-inflammatory effects of steroids, (at least in the short-term), are not operating as a disease modifying agent. This difference is unlikely to be clinically meaningful, however, as this is similar to the degree of cartilage loss seen in patients who do not show any progression of clinical or radiographic OA, (mean change of -0.12 ± 0.28)[43]. These findings contrast with those from a previous similarly designed study which did not show any negative structural impact of steroid injections[15]. However, this earlier study used plain radiographs to evaluate structural outcomes, and it is likely radiographs are not sensitive enough to pick up very small changes in cartilage volume. Although these data suggest that regularly scheduled use of intra-articular steroids may be detrimental to cartilage health, it is important for clinicians to realize that these data do *not* suggest that periodic use of intra-articular corticosteroids for flares of OA pain is either contraindicated or ineffective.

Another study evaluated a new extended-release formulation of triamcinolone acetonide in which the steroid is delivered inside microspheres which are designed to maintain prolonged concentration of the steroid within the joint[16]. This double-blind phase 11b trial evaluated the effect of one injection of this steroid preparation on mean average daily pain over 12 weeks in patients with moderate to severe knee OA. Although the extended-release steroid formulation did not lead to better pain control at 3 months, the results suggested it may provide patients with more rapid onset of pain relief. This medication holds promise for patients for whom systemic absorption of corticosteroids could be particularly detrimental. Further studies are needed to evaluate whether this medication can maximize analgesia and minimize steroid side effects in high risk population such as diabetics or the elderly.

There were several papers evaluating therapies which were borrowed from other musculoskeletal conditions.

Three studies evaluated therapies routinely used in inflammatory arthritis as potential therapies for erosive hand osteoarthritis. Two randomized double-blind, placebo-controlled trials evaluated hydroxychloroquine[17,18]. Both trials were negative, providing no evidence that hydroxychloroquine is effective in improving pain in this patient population. These studies did not use MRI to evaluate synovitis, which would have allowed them to stratify patients by degree of inflammation. Therefore, these studies did not rule out the possibility that patients with erosive osteoarthritis and high levels of synovitis may preferentially benefit from hydroxychloroquine. This patient subset could be the focus of a future randomized trial. A third randomized double-blind placebo-controlled crossover trial evaluated whether adalimumab was effective in treating the pain associated with erosive hand

osteoarthritis. Adalimumab or identical placebo was given subcutaneously every 2 weeks for a total of 12 weeks[19]. This was followed by an 8-week washout period, at which time patients crossed over to the other treatment arm for 12 weeks. All subjects had to have an index joint which showed signs of active synovitis on MRI , so as to enrich the sample with patients who had active inflammation and thus might be more likely to respond to adalimumab. However, results showed no improvement in pain, synovitis or bone marrow lesions suggesting that regardeless of the presence of active synovitis this tumor necrosis factor inhibitor is not an effective treatment for erosive hand OA.

Three studies evaluated whether bisphosphonates, standard treatments for osteoporosis, might be beneficial to patients with OA. Since subchondral bone remodeling and bone turnover underlies both the pathogenesis of and pain associated with osteoarthritis, it's possible that bisphosphonates could both prevent osteoarthritis progression and potentially treat its associated pain. Two studies used large cohorts to evaluate the effect of bisphosphonates on knee OA, using total knee replacement, (TKR) as a proxy for severe symptomatic knee OA. Neogi *et al.* evaluated older women in the UK who started bisphosphonates after being diagnosed with knee OA. After controlling for potential confounders, patients starting bisphosphates were 24% less likely to have a TKR over a 3-year period, compared to similar patients who did not start a bisphosphonate[20]. Fu *et al.* utilized a large national insurance database in Taiwan to ask a similar question[21]. These investigators evaluated rates of TKR in osteoporotic patients with knee OA, comparing rates between those who did and did not start a bisphosphonate. Over 2 years, patients who were adherence with taking bisphosphonate had a 44% reduction in TKR compared to bisphosphonate non–users. In addition, patients who used bisphosphonates had significantly less pain medication. In contrast, a systematic review and meta-analysis of randomized controlled trials evaluated over 3000 subjects who received oral bisphosphonates and found that bisphosphonates neither improved pain nor prevented radiographic progression of knee OA[22]. However, they could not rule out a potential benefit in patients with bone marrow lesions, as such patients have higher rates of subchondral bone turnover which may put them at higher risk for OA. Whether the contradictory findings between articles are due to unmeasured confounders, confounding by indication or differential patient selection is not clear; however, at a minimum it does not appear bisphosphonates are harmful to patients with OA-at least in the short term. Perhaps larger cohort studies with longer follow-up or future randomized controlled trials will resolve this issue.

An intriguing new therapy for the treatment of painful knee osteoarthritis, borrowed from interventional radiology, is geniculate artery embolization, (GEA). GAE is used to treat recurrent hemarthrosis after TKR. Excessive post-operative bleeding is believed to be due to synovial neoangiogenesis[23]. Embolization of the geniculate arteries supplying blood to the areas of pathologic hypervascularity “devascularize” the synovium and thus stop the intra-articular bleeding. Since there is clear evidence that synovial inflammation is associated with pain in knee OA[24], Okuno *et al.* hypothesized that targeted infarction of synovium may therefore decrease pain in subjects with knee OA. An open label cohort study of 72 subjects with painful knee OA underwent GEA. Subjects had a significant and clinically meaningful improvement in pain relief 24 months after the procedure, with no significant adverse events[25]. Whether this procedure is safe and effective in more heterogeneous groups of patients, and whether it could decrease the rate of knee OA progression, remains to be proven in randomized controlled trials.

Internet based therapies

There are significant barriers to accessing osteoarthritis care based on geography, cost, mobility limitation or a dearth of qualified providers. A number of studies this year investigated whether internet-based interventions, which could be used to overcome such barriers, are effective in patients with OA.

Allen *et al.* published a pragmatic randomized controlled trial that enrolled physically inactive patients with symptomatic radiographic knee OA, and compared the effects of a standardized in-person course of physical therapy sessions with an internet-based exercise program which could be accessed from home, and used patients placed on a wait list as controls[26]. The primary outcome was total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at 4 months. Neither the internet-based exercise program nor the in-person physical therapy was superior to the wait list in improving knee OA symptoms. These results were a little surprising given the known benefit of both exercise and physical therapy for the pain of knee OA. The null result may have been because there was only moderate uptake of the internet intervention. Only 80% of the internet group logged on to the study website, with mean number of days logged on being only 20.7 over the entire 4-month study period.

Another randomized controlled trial by O'Moore *et al.* evaluated an internet administered program of cognitive behavioral therapy (CBT) for depression in subjects with knee OA[27]. In this unblinded study of subjects with major depressive disorder and knee OA, subjects were randomized to six on-line sessions of a validated CBT program vs usual care. Primary outcomes were self-reported depression severity and the general psychologic distress at 3 months. Secondary outcomes included pain, function and arthritis self -efficacy. At 3 months, 84% of subjects receiving CBT no longer met diagnostic criteria for depression vs 50% of usual care. In addition, WOMAC subscales and arthritis self-efficacy also improved. This study was encouraging, as it suggests CBT can be effectively administered on-line to depressed patients with knee OA, and that both mental and physical benefits can be maintained for at least 3 months. The fact that CBT was effective in this population is heartening, as depression can be a deterrent to positive behaviors such as increasing physical activity and weight loss, which are known to improve knee OA pain. There was however no attention control in this unblinded study, so a significant placebo effect cannot be ruled out.

Is intriguing to hypothesize why an internet-based CBT program was effective but an internet-based exercise program was not. Allen at al hypothesize their aggressive case finding strategies may have resulted in subjects enrolling in their study who were not motivated to comply with the exercise intervention[26]. In their study subjects only logged on to the study website for approximately 17% of the study period. By contrast, 84% of the CBT subjects completed all online lessons and 40% of the CBT patients were already on antidepressant when they entered the trial. This suggests that a large portion of the CBT subjects were already in the “action” phase of the “readiness for change model.”[28] Perhaps subjects in studies of internet-based interventions need to be specifically screened for motivation to engage with an intervention when it is being administered remotely. This will be crucial to future studies of osteoarthritis interventions, as lack of trained providers and geographic remove between patients and providers limits real life access to many potentially helpful interventions. Understanding psychosocial attributes which influence engagement will be an important aspect of future population-based internet trials.

Regenerative medicine

The use of regenerative medicine therapies to treat osteoarthritis is an area of tremendous interest, as is evidenced by the surge of publications evaluating therapies such stem cell treatments and platelet rich plasma (PRP) injections. Systematic reviews are therefore helpful to make sense of the multiplicity of publications. Amongst many recent systematic reviews of stem cell therapy for OA, only one, by Pas *et al.*, was identified as having low risk of bias[29,30]. This systematic review evaluated randomized and non-randomized controlled trials (RCTs) of different stem cell therapy for knee OA The authors identified five RCTs, each of which reported positive results of stem cell therapies. However, each of these studies was at high risk of bias for multiple reasons, including inadequate blinding, high risk of selection bias, and no intention to treat analyses, casting serious doubts their efficacy claims. A narrative overview by Bennell *et al.* identified RCTs evaluating the effects of PRP, 15 in knee OA and 3 in hip OA. Most studies found a benefit of PRP. However there were multiple issues with quality in all the PRP studies, including questionable blinding, failure to conceal allocation, selective reporting, inappropriate statistical analyses as well as heterogeneous patient populations, outcome measures and PRP preparation[31]. Although the "brave new world" aspect of regenerative medicine is appealing, especially to patients desperate for pain relief, the best quality reviews suggest we don't yet have strong enough data to support recommending these therapies for our patients with OA.

Opioids in OA

How to best treat the pain of OA, especially knee OA, remains a major public health challenge, especially with the projected increased rates of knee OA. Opioids are effective treatments for knee OA pain, and given the known gastrointestinal and cardiovascular risks of nonsteroidal anti-inflammatories it has been argued there should be a role for opioid medication in the treatment algorithm of OA[33]. However, there are little rigorous data to help guide treatment decisions. Krebs *et al.* performed a pragmatic randomized trial among Veterans Administration patients, to evaluate the best strategy for managing chronic back pain or pain due to hip and knee osteoarthritis[34]. Patients were randomized to a flexible treat-to-target strategy of sequential opioid medications or sequential non-opioid medications, and were followed for 12 months. The investigators found that the opioid medication strategy was not superior to the non-opioid approach for either pain-related function or pain interference, and that there were significantly more adverse events in the opioid group. Since only 35% of their subjects had hip or knee OA, the investigators were not powered to look at OA patients separately; however, a *post hoc* sensitivity analyses did not show any significant differences in outcomes between the back pain and OA groups. Although results from this Veterans Administration cohort should be replicated in other populations, this well-done trial suggests no clinical advantage to utilizing narcotics in the treatment of painful hip or knee OA.

Another study from the OAI also suggests there are increased adverse events associated with using opioids[35]. Subjects with or at high risk of developing knee OA had a 22% increased risk of falls compared to patients not receiving opioids. Opioids are also often used for patients with severe knee OA waiting to undergo total knee replacement. A recent cohort study suggests that patients with knee OA who use opioids for pain relief before their surgery have less pain relief 6-months after TKR than those who do not use narcotics[36]. This is an important observation, as while most patients have excellent results after TKR, multiple studies have shown that up to 30% of patients undergoing TKR have chronic pain despite technical success[32,37]. Whether limiting opioids preoperatively can affect long term pain relief remains to be seen.

Diet and OA

Two related papers examined the association between fiber intake and knee OA. The first evaluated knee pain trajectories in subjects enrolled in the OAI[39]. These patients all had or were at risk of developing knee OA. Over 8 years, patients who consumed more dietary total or cereal grain fibers were less likely to have moderate or severe pain. These findings were even more pronounced among the patients with radiographic knee OA. The second paper by the same group evaluated the association between fiber intake and incident radiographic knee OA among subjects in the OAI and the Framingham offspring OA study[40]. In both of these prospective cohorts, even after controlling for confounders, there was a statistically significant dose-dependent inverse relationship between total dietary fiber and developing symptomatic knee OA. Although mechanisms are speculative, these findings could be due anti-inflammatory effects of fiber due to decreased adiposity, or beneficial changes in the microbiome. While these are associations from observational cohorts and thus cannot prove causality, until the definitive RCTs are performed, suggesting patients with knee OA adhere to the recommended average daily fiber intake of 25 g per day is very low risk and may have significant benefits.

Comorbidities and OA

Although physical therapy is known to benefit patients with OA, clinicians may be hesitant to prescribe exercise therapy to patients with OA and significant medical comorbidities, worried about the risk of adverse events. This would preclude a significant number of patients from receiving physical therapy, as between 30 and 50% of people with heart disease, diabetes, and obesity carry a doctor-diagnosis of arthritis[2]. In addition, these patients may particularly benefit from this therapy, as comorbidities are known to be associated with worse pain and physical function in patients who have hip and knee OA[41]. Rooji *et al.* performed a randomized controlled trial to see whether exercise therapy can administered safely and effectively to subjects with knee OA and significant clinical comorbidities[42]. Subjects had knee OA as well as one of coronary heart disease, heart failure, type 2 diabetes, chronic obstructive pulmonary disease (COPD) or a body mass index of over 30 kg/m^2. The comorbidity had to interfere with daily activities, and patients had to be receiving active treatment for the comorbidity. The intervention was a 20 week tailored exercise therapy program, which could be adapted to accommodate specific comorbidities, and was administered by trained physical therapists. Subjects were randomly assigned to receive either the intervention immediately, or be placed on a waiting list after which they would be eligible to receive physical therapy. These investigators found that there were clinically and statistically significant improvements in physical function, which were maintained for 32 weeks, as well as a trend towards less pain. Although underpowered to evaluate adverse events, there were no serious adverse events reported. This is the first study to document that careful administration of a tailored exercise program can be administered safely and effectively to a high-risk knee OA population, and that benefits last beyond program completion.

Conclusions

In conclusion, this review highlights some of the advances in clinical osteoarthritis published over the past 12 months. To ensure ongoing progress, it is vital that innovative clinical investigators continue to be encouraged and supported, to optimize quality of life

for the growing number of patients living with the pain and disability of osteoarthritis.

Author contributions

The author (LAM) was responsible for conception and design of the study, data review and interpretation, drafting and critical revision of the article.

Conflict of interest

LAM is an associate editor at Annals of Internal Medicine for which she receives compensation. She also receives royalties from Wolters Kluwer for contributing to Up-To-Date, the evidence-based online clinical resource.

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