Osteoarthritis and Cartilage xxx (xxxx) xxx

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Review

Osteoarthritis year in review 2019: epidemiology and therapy

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ARTICLE INFO

Article history:
Received 22 July 2019
Accepted 8 January 2020

Keywords:
Osteoarthritis
Epidemiology
Treatment
Clinical

SUMMARY

Over the past year many studies and clinical trials have been published in the osteoarthritis (OA) field. This review is based on systematic literature review covering the period May 1st, 2018 to April 19th, 2019; the final selection of articles was subjective. Specifically those articles considered to be presenting novel insights and of potential importance for clinical practice, are discussed.

Further evidence has emerged that OA is a serious disease with increasing impact worldwide. Our understanding of development of pain in OA has increased. Detailed studies investigating widely used pharmacological treatments have shown the benefits to be limited, whereas the risks seem higher than expected, suggesting further studies and reconsideration of currently used guidelines. Promising new pharmacological treatments have been developed and published, however subsequent studies are warranted. While waiting for new treatment modalities to appear joint replacement is an effective alternative; new data have become available on how long they might last.

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Introduction

Osteoarthritis (OA) is a highly prevalent Rheumatic Musculoskeletal Disorder, that affected 303 million people globally in 2017[1]. It can affect any joint, but preferentially affects the knee, hands, hip and spine. OA has a considerable impact on the individual patient, resulting in pain and disability, and on society. Also the economic burden of OA on patients and society is considerable. In 2016 the large disease burden has led to the submission by Osteoarthritis Research Society International (OARSI) of a White Paper, describing Osteoarthritis as a Serious Disease[2]. Here, also the lack in treatment that can prevent, stop, or even restrain progression of OA, is discussed. Moreover, the current OA pain medications have a number of risk/benefit considerations.

In this manuscript a subjective overview of the most notable clinical research of the last year in the field of OA is reviewed, with focus on epidemiology, pharmacological and surgical treatment.

Methods

As starting point a PubMed search was performed for articles published between May 1st, 2018 to April 19th, 2019, using the search terms "Osteoarthritis [All fields] AND Epidemiology [All Fields] "and "Osteoarthritis [All Fields] AND Treatment [All Fields]", with the limits: humans and English language. This search resulted in 1419 articles.

In addition, a complimentary search for the same time period was performed for articles published in the New England Journal of Medicine, Annals of Internal Medicine, Lancet, JAMA, BMJ, Annals of the Rheumatic Diseases, Arthritis and Rheumatology, Rheumatology and Osteoarthritis and Cartilage. This resulted in 304 articles. These searched had overlap.

First titles were reviewed and subsequently abstracts. Articles that described OA clinical research and OA pharmacological treatment, with special focus on randomized clinical trials, were selected. Studies on case series, studies on surgical techniques, preclinical studies and clinical trial protocols were excluded. Also studies addressing the other Year in Review topics were not included. Finally, 27 articles were included in the present manuscript. These articles are a subjective selection due to the large number. Inclusion was based on novelty, interest for clinical practice for OA patients and for the OA research field, and impact factor of the journal in which the study was published.

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https://doi.org/10.1016/j.joca.2020.01.002
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Please cite this article as: Kloppenburg M, Berenbaum F, Osteoarthritis year in review 2019: epidemiology and therapy, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2020.01.002

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Results: epidemiology

Disease burden

Musculoskeletal disorders, including OA, are highly prevalent and are expected to increase. *Sebbag et al.* investigated the worldwide burden of musculoskeletal diseases between 2000 and 2015[3]. They extracted Disease-Adjusted life years (DALYs) which combines the years of life lost (YLLs) and the years lived with disability (YLDs) of 183 countries from the WHO Global Health Estimates Database for 23 WHO categories of diseases. Based on these data the worldwide burden of musculoskeletal disorders as quantified using DALYs increased from 2000 to 2015, which was especially due to increase in YLDs. The median proportion of YLDs due to musculoskeletal disorders increased from 11.8% (IQR 25–75 8.3 to 15.1) in 2000–13.5% (9.6–16.6) in 2015. They showed that the burden due to musculoskeletal diseases has increased significantly resulting in being the second cause of YLDs in 2015 (the first being mental and substance use disorders).

The important contribution of musculoskeletal disorders to the disease burden worldwide is also shown by the latest update from 2017 of the *Global Burden of Disease study*, showing that musculoskeletal disorders are the first cause of YLDs in comparison to 21 other cause categories, including 354 diseases and injuries[1]. For this update 68781 data sources from 195 countries and territories, including many new sources, were used. An important notion is, that the musculoskeletal burden is especially high at middle-age. The largest contribution to the YLDs among the musculoskeletal disorders is due to back and neck pain, followed by OA. OA accounts for around 7.1% of this burden and showed a statistically significant increase in comparison to 2007 of 31.4% (95% confidence interval (CI) 30.7 to 32.1). Between 1990 and 2007 a statistically significant increase of 63.1% was seen.

Chua et al. investigated the disease burden in OA in quite a different way[4]. They assessed disease burden at an initial visit to the rheumatology outpatient clinic with questionnaires as RAPID3/MDHAQ (multidimensional health assessment questionnaire/routine assessment of patients index data) and used rheumatoid arthritis (RA) as a benchmark for high disease burden. They showed a similar burden in 149 OA patients as in 203 RA patients. However, at the follow-up visit at 6 months OA patients had improved less than RA patients, most likely due to more effective treatments available for RA.

All these studies underline the impact OA and other musculoskeletal disorders have on the individual and society. These results are crucial for health professionals and policy makers in order to plan the healthcare system of the future[3].

Mortality

Over the years many studies have looked into the association between knee OA and premature mortality, leading to conflicting results. This could be due to differences in knee OA definition, especially whether or not symptoms are part of the definition.

In 2016 *Kluzek et al.* published results based on the Chingford cohort on 821 Caucasian women, showing that knee pain with or without radiographic OA was associated with premature all-cause and cardiovascular (CVD) specific mortality[5].

Recently, *Cleveland et al.* showed similar results in the Johnston County OA project, a community-based cohort including Afro American and Caucasian adults ≥45 years of age[6]. They included 4182 participants with nearly 15 years of follow-up, in which 1822 deaths occurred. An increased all-cause and CVD-specific mortality was seen in those with knee pain alone or with symptomatic radiographic knee OA, but not in those with radiographic OA alone. Risk was especially higher for females, Caucasians, people <65 years of age, and body mass index (BMI) ≥30 kg/m^2 in stratified analysis. These analyses were adjusted for many covariates, including enrolment wave, age, sex, race, education, knee injury, cancer, non-steroidal anti-inflammatory drugs (NSAIDs), hypertension, smoking, liver disease, alcohol use, depression, obesity, diabetes, CVD, and physical activity, defined as whether participants met the CDC guideline for moderate/vigorous physical activity.

However, *Corsi et al.* showed in a substudy in 1709 participants of the Johnston County OA project, where more data on physical activity and performance was available, in univariate analysis, that symptomatic knee OA at baseline was associated with incident CVD risk after nearly 6 years of follow-up. But in multivariate analyses, symptomatic knee OA was not associated, while baseline physical function and worsening in physical function were[7].

Analyses by *Turkiewicz et al.* using a large database from the Swedish Skåne Healthcare Register also showed an increased risk for cardiovascular death for knee and hip OA patients with a doctor-diagnosis (hazard ratio (HR)s 1.19 (95%CI 1.10, 1.28) and 1.13 (1.03, 1.24) during 9–11 years of follow-up, respectively)[8].

This is in accordance with an earlier study by *Hawker et al.* showing that among individuals with hip or knee OA, disability was positively associated with all-cause mortality and CVD events in multivariate analyses[9].

All these studies point into the direction of a contribution of OA to an unfavorable outcome due to limitations in physical function and activity. When these studies will be further confirmed, they call for improved strategies to decrease symptoms and increase physical activity in patients with symptomatic knee OA.

Pain

Pain is one of the most important symptoms of knee OA. Studies performed in the past have shown that a wide variety of factors such as sex, age, BMI, education, psychological factors, genetic factors, and local structural pathology are associated with knee pain. Also peripheral and central sensitization contributes to pain in knee OA[10]. However, it is still not clear what drives pain in knee OA and why some people develop pain and others do not.

Therefore, *Carlesso et al.* set up a study, within the Multicenter Osteoarthritis Study (MOST), to identify pain susceptibility phenotypes, meaning the development of incident persistent knee pain after 2 years of follow-up in patients with or at risk of knee OA, but without persistent knee pain at baseline[11]. They used Latent Class Analysis -an agnostic approach-to identify distinct classes or phenotypes based on a large variety of determinants. They were especially interested in sensitization measures as assessed with quantitative sensory testing and psychosocial factors. They could distinguish four phenotypes, characterized mainly on the presence of signs of sensitization, being pressure pain thresholds and temporal summation, and not of psychological factors or sleep. Radiographic OA, based on Kellgren–Lawrence grade, obesity, comorbidities and education was similar across the phenotypes. The phenotype (23% of participants) defined by a high proportion of pressure pain sensitivity and moderate proportion of facilitated temporal summation had an increased risk of 1.98 (95%CI 1.07 to 3.68) to develop incident persistent knee pain, when compared to the phenotype with low proportion of sensitization on both tests. Other phenotypes did not have an increased risk for incident persistent knee pain. These results suggest that sensitization might be a target for therapy.

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Please cite this article as: Kloppenburg M, Berenbaum F, Osteoarthritis year in review 2019: epidemiology and therapy, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2020.01.002

Results: treatment

Current pharmacological treatments: risks and benefits

Paracetamol, NSAIDs, corticosteroid injections and tramadol are prescribed to many patients with OA for symptom alleviation in clinical practice, supported by guidelines[12]. Recent research have focussed in more detail on their efficacy, and potential risks, and showed the shortcomings of this medication.

Paracetamol is first choice in many guidelines (i.e., https://www.nice.org.uk/guidance/cg177/chapter/1-Recommendations#pharmacological-management), however recent network meta-analyses indicated that its efficacy is rather limited[13,14]. In 2019, a Cochrane review has been published on the benefits and harms of paracetamol in 3541 patients with knee or hip OA in 10 randomised placebo-controlled trials[15]. The paracetamol dose varied between 1.95 g/day to 4 g/day, and the majority of trials followed patients for 3 months only. The authors conclude that based on high-quality evidence paracetamol provides only minimal improvements in pain and function, with no increased risk of adverse events. Subgroup analyses did not show a difference between doses. Due to the small number of events, the authors are less certain if paracetamol use increases the risk of serious adverse events, withdrawals due to adverse events, and rate of abnormal liver function tests. This study further indicates that the place of paracetamol in OA symptom alleviation needs reconsideration.

Pharmacological treatments are generally studied in short-term clinical trials, whereas the disease is chronic. Therefore many patients ask for pharmacological treatments for a longer time period. *Gregori et al.* performed a systematic review with Bayesian random effects network meta-analysis[16]. They included 31 placebo- and active-controlled randomized controlled trials with at least 12 months of follow-up in patients with knee OA. The primary outcome was pain, as assessed with a WOMAC or VAS pain. In 42 trials 31 interventions, including among others conventional NSAIDs and coxibs, intra-articular hyaluronate and corticosteroids injections, paracetamol, and nutraceuticals, were studied. In 43 trials without high risk of bias, no or only a small pain alleviating effect on pain was seen, which did not exceed the minimal clinical important difference set by the authors on 5 to 10 on a 0 to 100 scale for a difference between placebo and active medication. However, the study had limitations as also pointed out by the authors, especially the large uncertainty regarding all the estimates, the relatively low number of studies for many interventions and the small sample size of many studies. Therefore, large randomized high-quality controlled trials are needed to understand the efficacy of current used pharmacological treatments in knee OA.

From COX-2 selective inhibitors it is known that they are associated with an increased cardiovascular risk. However, diclofenac, a frequently used traditional NSAID, has also been associated with an increased cardiovascular risk[17]. Two studies have been performed in the past year to further elucidate the cardiovascular risk of diclofenac. The first study by *Schmidt et al.* used data from Danish, nationwide, population based health registries to obtain data on health care in general practice and hospitals, on prescriptions, and on mortality and migration and performed an emulated trial within the database[18]. Focus was on cardiovascular adverse events within 30 days of initiation of diclofenac compared to other traditional NSAIDs, paracetamol and no-use. To reduce confounding by indication adjustment for propensity score was performed. Diclofenac initiators had a 50% increased risk for a major adverse cardiovascular event compared to non-initiators, a 20% increased risk compared to paracetamol initiators and 30% compared to naproxen initiators.

The results are in accordance with the second study by *Dubreuil et al.* using data from The Health Improvement Network (THIN) database with data from over 600 general practitioners practices in the UK[19]. This study was a nested-case control (6287 cases, 25164 controls), with myocardial infarction as outcome in patients that had prescribed ≥1 NSAID and no history of myocardial infarction. Use of diclofenac, naproxen or other NSAIDs initiated less than 180 days before the myocardial infarction, was compared to reference NSAID use more than 365 days ago. This design was chosen to control for confounding by indication.

Diclofenac performed worse (adjusted Odds Ratio (OR) 1.26 (95% CI 1.14 to 1.39) than naproxen (adjusted OR 0.98 (0.85–1.13). The latter not posing an increased risk for myocardial infarction compared to remote NSAID use. Interestingly, the risk for myocardial infarction with diclofenac use was lower in OA than in spondyloarthritis.

These results support the notion by European Medicines Agency that diclofenac poses the same cardiovascular risk as selective COX-2 inhibitors and that similar precautions should be taken (https://www.ema.europa.eu/en/medicines/human/referrals/diclofenac-containing-medicines). Further studies are needed, to confirm these data, especially whether naproxen and other conventional NSAIDS have a lower risk than diclofenac.

Recent it was shown in a randomized double-blind clinical trial that repeated intraarticular corticosteroids in knee OA were associated with greater cartilage loss on MR images after 2 years than intraarticular saline injections[20]. To further increase insight into the effects of intraarticular corticosteroid injections in knee OA an observational study was set up by *Zeng et al.* using the 0–48 months radiographic data of the OA Initiative[21]. Knees with radiographic OA of 148 participants that had initiated a corticosteroid injection were compared to osteoarthritic knees from 536 propensity-matched participants that did not receive such an injection. The incidence of radiographic worsening, as assessed with Kellgren–Lawrence scores, was greater in the knees initiating a corticosteroid injection than in the controls. The HR was 3.02 (95% CI 2.25 to 4.05). For continuous injections the HR was even higher (4.67 (2.92–7.47). Also an effect on joint space narrowing was seen. Since this is an observational study potential residual confounding by indication cannot be ruled out. However, intraarticular injections with corticosteroids are frequently administered, therefore further investigations are warranted.

An alternative for an intraarticular injection with corticosteroids might be an intramuscular injection. This was investigated by *Dorleijn et al.*, especially because in hip OA intraarticular injections cannot easily be done, and require imaging support[22]. Therefore, in this randomized controlled trial the efficacy of an intramuscular injection with triamcinolone 40 mg was investigated in 52 patients with painful radiographic hip OA, in comparison to an intramuscular injection with saline as placebo in 54 patients. The primary outcome was hip pain at rest, during walking (0–10), and hip pain measured with the Western Ontario and McMaster Universities OA Index (WOMAC), all 2 weeks post-injection. Hip pain at rest was alleviated in comparison to placebo after 2 weeks (difference between groups, −1.3 (95%CI -2.3 to −0.3) and maintained up to 12 weeks, the duration of the trial. The other outcomes were also significantly better compared to placebo after 6 and 12 weeks. Adverse effects were mild. Whether intramuscular injections can pose a risk for cartilage loss has to be investigated.

Finally tramadol, a weak opioid agonist, was investigated for risk on all-cause mortality by *Zeng et al.*[23]. This cohort study also made use of the THIN database. However, in this study propensity-score matching was chosen instead of a nested case–control design as by *Dubreuil et al.* to reduce confounding by indication[19]. Although there are serious concerns whether this can be totally ruled out

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	Total hip replacement			Total knee replacement			Unicondylar knee replacement		
	CPRD	Case series	Registries	CPRD	Case series	Registries	CPRD	Case series	Registries
Follow-up									
−15 years	91.0# (90.3,91.6)	87.9 (87.2,88.5)	*89.4 (89.2,89.6)	92.9 (92.2,93.6)	96.3 (95.7,96.9)	*93.0 (92.8,93.1)	–	85.5 (82.2,88.7)	**76.5 (75.2,77.7)
−20 years	85.0 (83.2,86.6)	78.9 (77.9,80.0)	**70.2 (69.7,70.7)	89.7 (87.5,91.5)	94.8 (92.5,97.1)	**90.1 (89.7,90.4)	–	81.9 (77.9,85.9)	**71.6 (69.6,73.6)
−25 years	–	76.6 (75.1,78.2)	**57.9 (57.1,58.7)	–	–	**82.3 (81.3,83.2)	–	72.0 (58.0,95.0)	**69.8 (67.6,72.1)

CPRD = Clinical Practice Research Datalink.
#Percentage (95% confidence interval).
*Australian and Finnish data, ** Finnish data.

Table I Implant survival rate based on data from Clinical Practice Research Datalink[37] and pooled all-cause construct survival of joint replacement based on case series and Australian Orthopaedic Association National Joint Replacement Registry Annual report 2017 and Finnish Arthroplasty Report November 2017[38,39]

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with this study design and as a consequence will result in a high likelihood of bias[24]. 88902 patients were included in the study, in which 278 deaths occurred after 1-year follow-up. 44451 initiated tramadol. The authors showed that tramadol was associated with increased all-cause mortality when compared to naproxen (HR 1.71 (95%CI 1.41 to 2.07) and diclofenac (1.88 (1.51−22.35), and also celecoxib and etoricoxib. No difference was seen between tramadol and codeine. Since there are serious limitations in the study design, additional studies are warranted to understand the mortality risk of tramadol.

Novel treatments

Capsaicin is an agonist for the transient receptor potential cation channel subfamily V member 1 (TRPV1), and is used as topical analgesic treatment. *Stevens et al.* investigated whether a highly purified trans-capsaicin in injectable form, CNTX-4975, is effective and safe in patients with knee OA[25]. In a multicentre randomized, double-blind, placebo-controlled, phase 2 study 172 pts with painful radiographic knee OA received a single intraarticular injection with 0.5 or 1 mg CNTX-4975 or placebo after 45 min of cooling of the knee and a lidocaine 2% injection. Primary outcome was change between baseline through week 12 on the question from the WOMAC: pain with walking (range 0−10) (Area Under the Curve). CNTX-4975 1 mg alleviates pain more than placebo (difference with placebo −1.5 (95% CI -2.2 to −0.8), which is more than a minimal clinical important difference. Also, a beneficial effect of 1 mg on stiffness and function were seen. Beneficial effects are maintained up to 24 weeks (difference with placebo −0.9 (−1.6 to −0.1)). Safety profile was comparable to placebo, although procedural pain was higher with CNTX-4975. Further studies investigating the pain alleviating effects of CNTX-4975 are warranted.

Several studies investigating biologicals have been performed.

Pre-clinical studies have suggested a role for interleukin (IL)-1α and IL-1β. Lutikizumab, a humanized IL-1α/β dual variable domain immunoglobulin. blocks IL-1α/β simultaneously.

Two double-blind randomized placebo-controlled trials have been set up in inflammatory (with signs of synovitis on MRI or ultrasonography) knee and erosive hand OA to investigate the efficacy of lutikizumab 25−200 mg subcutaneously every 2 weeks. Primary end point was change in pain at 16 weeks. The first trial randomized 350 knee OA patients[26]. Only for one dose (100 mg) of lutikizumab a small statistical significant effect was seen at 16 weeks, but not at later time points. The second trial randomized 132 hand OA patients to 200 mg lutikizumab or placebo every 2 weeks; no symptomatic effect was seen[27]. In both trials no effect was seen on imaging end-points of synovitis. Patients on lutikizumab had more injection site reactions and neutropenia as safety signals. So, IL-1 inhibition does not seem to be a relevant target in symptomatic OA treatment.

TNF blockade is efficacious in many inflammatory rheumatic diseases. Etanercept 50 mg/weekly (25 mg/weekly after 24weeks subcutaneously) was investigated in a 1-year multicentre randomized, double-blind placebo-controlled trial in 90 patients with erosive inflammatory hand OA[28]. The primary outcome, being change in VAS pain after 24 weeks, was not met. However, in prespecified per-protocol analyses of completers with pain and inflammation at baseline a beneficial effect on VAS pain was seen at 1 year. Moreover, etanercept-treated joints showed more radiographic remodeling; this was more pronounced in joints with baseline inflammation. Studies investigating treatment strategies specifically inflammation with anti-inflammatory treatment are warranted.

Galcanezumab, a humanized monoclonal antibody, blocks calcitonin gene-related peptide (CGRP), that plays a role in pain in OA, and has been shown to be efficacious in migraine. In a double-blind, placebo- and celecoxib-controlled randomized trial galcanezumab (doses 5 up to 300 mg subcutaneously every 4 weeks, twice), was investigated in 266 patients with painful knee OA[29]. Primary outcome was change in WOMAC pain after 8 weeks. The planned interim analysis suggested inadequate efficacy and therefore the study was terminated.

Low dose radiation therapy (LDRT) is popular in many counties, although evidence is lacking[30]. Therefore, two randomized double-blind clinical trials have been performed. The first published by *Mahler et al.*[31], in radiographic painful knee OA. Fifty-five patients were randomised to 6 times LDRT (1 Gay per fraction) or sham during 2 weeks. Primary outcome was the proportion of OMERACT-OARSI responders after 3 months. More than 40% responded in either group. No statistical significant difference was seen between the groups.

A second comparable trial was performed in patients with painful hand OA with ≥1 inflammatory hand joint on ultrasonography[32]. 29% and 36% responders were seen in the LDRT and sham groups, respectively, with no statistical significant difference between the groups. Although small differences between the groups could not be ruled out given the limited sample size, substantial beneficial effects on symptoms are unlikely. Due to potential long-term severe adverse effects, the risk benefit ratio of such an intervention is probably unfavourable.

Please cite this article as: Kloppenburg M, Berenbaum F, Osteoarthritis year in review 2019: epidemiology and therapy, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2020.01.002

Regenerative medicine

Regenerative medicine methods are increasingly popular, as reflected by wide availability in clinical practice and by publications of many case series and clinical trials. One approach is mesenchymal stem cell injections. However, its efficacy is still unclear, with controversial conclusions of earlier systematic reviews. *Xing et al.* performed a systematic overview of overlapping systematic reviews[33], to synthesize the current evidence qualitatively, using the Confidence in the Evidence from Reviews of Qualitative Research (CERQual) tool. The methodological quality and risk of bias were assessed by several tools, being the AMSTAR (Assessment of Multiple Systematic Reviews) and ROBIS (tool for assessing the risk of bias in systematic review). Four systematic reviews were included, of which one with low risk of bias[34]. The authors concluded that there is moderate confidence in safety of mesenchymal stem cell therapy for knee OA, but low confidence in efficacy outcomes due to limitations of current evidence. Studies are hampered in methodological quality, with regard to blinding of patients or assessors, and randomization. Another limitation is generalizability, since often surgical co-interventions have been applied and there is a heterogeneity among inclusion/exclusion criteria. Finally, sources of cells differ between studies, procedures of detaching, processing, storage and delivery of cells vary, and phenotypes of the cells are unclear[33].

Another approach is an injection of platelet rich plasma. *Muchedzi et al.* performed a systematic review included 2328 patients across 17 studies in patients with knee OA or following knee arthroplasty, including 10 randomized and almost half double-blind[35]. There was a lack of high-quality studies. Limitations were due to methodological short-comings in trial design, lack of standardization in methods of platelet rich plasma preparation, differences between frequency and amount of injections, heterogeneity of data, and small study samples. Summary of six studies in knee OA showed no benefits on pain, quality of life and knee function.

To understand the value of these regenerative approaches for clinical care high-quality controlled trials with standardization of product manufacturing, frequency and method delivery, and definition of target patient population is urgently needed[36].

Surgical treatment

For end-stage hip or knee OA a joint replacement is an effective treatment option. However, joint replacements will not survive for ever, and will fail after some time. In that situation a revision is needed. While counselling patients, information about the survival time of joint replacements is very important.

In 2017 a lifetime risk for revision surgery up to 20 years was estimated based on data from primary care medical records from the UK collected in the Clinical Practice Research Datalink; the estimates included participants ≥50 years of age and were adjusted for all-cause mortality[37](Table I).

Evans et al. took a different approach[38,39]. They performed a systematic review and meta-analysis of case series and cohort studies (6490 total knee replacements, 742 unicompartmental knee replacements, 13212 hip replacements), and of Australian and Finnish registries (299,291 total knee replacements, 7714 unicompartmental knee replacements, 215,676 hip replacements). Risk of all-cause construct survival was assessed up to 25 years. Based on the Finnish registries, since registry data seemed least biased, survival of total hip and knee replacement was 58% and 82%, respectively (Table I).

The authors also investigated unicompartmental knee replacement separately, showing a lower survival rate (70%) than for total knee replacement. The latter is also supported by a recent systematic review with meta-analysis investigating 5-year revision rates[40].

Conclusions

The current review discussed the highlights of the past year in clinical OA research. Further epidemiological studies are needed to confirm premature mortality in OA and whether this is inversely associated with the level of physical activity, and could be translated into treatment recommendations. Published studies underscore that high-quality studies are necessary to understand the value of currently used pharmacological treatments, with regards to benefits and risks, and to understand the value of regenerative medicine approaches. Moreover, new treatments need to be developed.

Author contributions

The authors conceived and designed the review, acquired, analyzed and interpreted the data (MK, FB), drafted the article and revised it critically for important intellectual content (MK, FB), approved the version to be submitted (MK, FB), and take full responsibility for the integrity of the work (MK).

Conflict of interest

MK is consultant to Pfizer and Kiniksa. She also receives royalties from Wolters Kluwer for contributing to Up-to-Date, and from Springer Verlag for contributing to “Reumatologie en klinische immunologie”. She has received grant funding from Dutch Arthritis Association, European League Against Rheumatism and IMI/APPROACH.

FB reports personal fees from Boehringer, Bone Therapeutics, Expanscience, Galapagos, Gilead, GSK, Heel, Merck Sereno, MSD, Nordic, Novartis, Pfizer, Regulaxis, Roche, Sandoz, Sanofi, Servier, UCB, Peptinov, TRB Chemedica, 4P Pharma. He also receives royalties from Wolters Kluwer for contributing to Up-to-Date. He has received grant funding from French society of rheumatology, Fondation Arthritis, H2020 and IMI/APPROACH.

Role of the funding source

This work was not supported by any extikernal funding. Q1

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Please cite this article as: Kloppenburg M, Berenbaum F, Osteoarthritis year in review 2019: epidemiology and therapy, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2020.01.002

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