Review Article

Early osteoarthritis—definition, pathogenesis, diagnosis, management and prevention: management

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Abstract: The concept of early knee osteoarthritis (EKOA) is herein discussed in order to detect and intervene in patients who are at risk of developing definitive KOA. In particular, EKOA should be suspected in the differential diagnosis of patients having knee pain without radiographic KOA, such as Kellgren-Lawrence (KL) grade 0 or 1. The current review discusses the evidence on non-surgical and surgical management for early KOA. We reviewed 22 papers on non-surgical management of early KOA; the majority of studies were case-controls or case series, with a paucity of randomized control trials having been conducted. Strong evidence is still lacking about how to manage the EKOA patient most effectively.

Keywords: Knee osteoarthritis (KOA); early; management

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Introduction

The knee is the most common joint of the lower extremity affected by osteoarthritis. Knee osteoarthritis (KOA) is associated with pain and deteriorating function of knee joint. Aging is the primary factor associated with the development of KOA. With an aging population in nearly all developed countries, the health, social, and economical burdens derived from KOA are increasing (1). KOA is traditionally diagnosed by the classifications of the American College of Rheumatology and radiographic grading scales such as the Kellgren-Lawrence (KL) grading scale (2). However, considerable degeneration in the knee joint has almost always occurred prior to diagnosing definitive KOA on the basis of radiographic evaluation, such as KL grade 2 or more severe (3,4). At present, clinical practices and the research aimed at treating KOA disproportionately focus on patients who have established radiographic osteoarthritis, especially those at terminal stages of the disease for which arthroplasty remains the last therapeutic option . At such advanced disease stages, therapies are palliative. That said, a paradigm shift from palliation to early identification and intervention, with the intention of preventing progression or reversing OA, is underway (5).

During the last two decades, the term of "early osteoarthritis" emerged in the literature, with scientific papers on early osteoarthritis increasingly published. In more clearly defining early knee osteoarthritis (EKOA), parallel work on its diagnosis and treatment can be pursued (6). According to Luyten's criteria, EKOA necessitates the absence of definitive radiographic KOA (i.e., KL grade 0 or 1). Unfortunately, recent work has liberally used the term "EKOA" even in the presence of definitive radiographic KOA, in turn obscuring presumably distinct patient populations. Nevertheless, even with more rigorous definitions of EKOA, there are few studies on the

management of patients with EKOA. This review focuses on studies examining the management of EKOA, especially those studies in which patients do not have definitive radiographic evidence of KOA.

Methods

We searched PubMed using the terms, "knee osteoarthritis", "early", and "management" from inception up to September 1, 2018. A total of 435 papers were found, of which 85 papers were focused on the "the management of early knee osteoarthritis", as determined by an abstract review. We excluded the applicable papers which included small number of the subjects whose KL grade was 0 or 1. Twenty-two papers of non-surgical management were eligible for the current review. In addition, we reviewed the surgical management of EKOA adding the previous papers which managed the patients whose OA disease stage was early.

Results

Non-surgical management

Weight control

Adequate weight control plays a key role in the non-surgical management of all stages of OA (7). Bastick *et al.* observed the subjects who participated in the CHECK cohort, and found that higher BMI, lower level of education, greater comorbidity, higher activity limitation scores, and joint space tenderness were more often associated with trajectories characterized by pain progression (8). Laberge and colleagues evaluated whether obesity affected cartilage degeneration in knee joints without radiographic KOA during 36-month follow up by using the OAI database. The number of new or worsening cartilage lesions was significantly higher in obese subjects (9). Although the innovative surgeries or regenerative therapies are eligible for the cartilage and meniscal degeneration in the early stage of OA, these therapies are unable to completely overcome the development of osteoarthritic changes without the management of obesity (10). The potential cause which induces such therapeutic failures is the lack of having the approach for how to deal with the overload on the osteoarthritic knee joint. On the basis of the previous evidence, healthcare providers should emphasize weight management as weight-mediated overloading of the joint might otherwise attenuate any benefit of emerging therapies (10).

Pharmacological approaches

Knee pain is the primary problem even for the patients with EKOA, in turn limiting their daily physical activity. Almost 80% of OA patients are estimated to experience residual knee pain, which restricts their daily activity. Pharmaceutical therapies are the most common strategy to improve the quality of life of these patients (11). Hoogeboom and colleagues examined the trend in analgesic use between 2004 and 2006 in EKOA subjects (age, 45–65 years old) included in the CHECK cohort. One third of 414 total subjects constantly used analgesics during two-year follow up; if they had used analgesics or shown worsened knee pain at the baseline, the odds of constant utilization of analgesics was higher (12). Therefore, the therapeutic necessity of analgesics seems to be high, even in the EKOA population. As there are many analgesics for potential use by the patients with KOA, physicians should weigh a particular drug's benefit and risks when prescribing.

Among the many available analgesics, acetaminophen is recommended to prescribe as the first choice due to its low cost, few adverse effects, and potential for long-term use. This oral analgesic acts by downregulating the production of cyclooxygenase 3 and by inhibiting nitric oxide signaling (11,13). Acetaminophen has one of the safest risk profiles, but has the potential to cause some adverse effects.. The half-life of warfarin can be prolonged by acetaminophen and the international normalized ratio (INR) of warfarin users should be monitored carefully. Physicians should pay attention to the prescription of acetaminophen for those with a history of hepatic diseases and excessive alcohol consumption (11). In addition, more recent evidence reported that acetaminophen had the higher risk of gastrointestinal problems and multiple organ failure with prolonged use. Physicians are encouraged to prescribe acetaminophen with caution as the long-term safety of this drug is still being elucidated (13).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used analgesics to treat the knee pain of OA. Several previous studies showed that the inflammation and immunological responses in the knee joint of EKOA patients are related to the onset and development of advanced OA. While acetaminophen is principally used to mitigate pain, NSAIDs are used to control both pain and inflammation in the knee joint. Many studies confirmed that NSAIDs are superior to acetaminophen in terms of relief from knee pain, yet the toxicity of NSAIDs is higher (13). Therefore, physicians should prescribe NSAIDs if acetaminophen is insufficient to control the patient's knee

pain. The main pharmacological mechanism of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX), in turn reducing downstream synthesis of prostaglandin. Non-selective NSAIDs, as most commonly used, inhibit both COX-1 and COX-2. Of note, COX-1 is constitutively expressed in the normal tissues (11), whereas COX-2 is an inducible enzyme upregulated specifically during the inflammatory process. Inhibiting COX-1 in gastric epithelial cells reduces the synthesis of cytoprotective prostaglandin and leads to gastrointestinal bleeding and ulceration (13). Although all type of NSAIDs have similar therapeutic effect, physicians are advised against prescribing this analgesic to patients at risk for upper gastrointestinal hemorrhage. A combination of non-selective NSAIDs and gastroprotective drugs is likely a cost-effective means to reduce the risk of gastrointestinal hemorrhage (11,13). Non-selective NSAIDs also induce adverse effect on the renal and cardiovascular systems.

COX-2 selective inhibitors were developed to obviate these adverse effects, theoretically permitting long-term pharmaceutical therapy. COX-2 selective inhibitors show similar therapeutic effects as non-selective NSAIDs with much fewer adverse event of gastrointestinal hemorrhage (11). However, COX-2 inhibitors were found to induce prothrombotic states; those having a history of ischemic heart disease and/or cerebral infarction should be prescribed COX-2 inhibitors with extreme caution. Finally, two different NSAIDs should not be combined because therapeutic effects are unlikely to be synergistic, yet adverse effects may be (11,13).

Topical NSAIDs have more recently been employed to provide similar therapeutic effect as their oral counterparts without systemic pharmacological exposure and adverse effects. Topical NSAIDs penetrate the skin and are absorbed into the circulation or subcutaneous tissue to bring its pharmaceutical effect (11,13). Absorbed topical NSAIDs may not be able to penetrate the complete depth of cartilage, but the emerging studies are exploring novel transportation molecules to aid drug penetration (11). Topical NSAIDs may be safer and better tolerated than oral NSAIDs despite adverse effects of skin.

Pharmaceutical therapy which focuses on controlling the joint inflammation is not always successful in reducing knee pain of OA patients. Opioids may be consider when the other analgesics are insufficient to control knee pain due to its severity, and alternative pharmaceutical and/or surgical therapies are contraindicated (11,13). However, opioids other than tramadol are not clinically superior to placebo in terms of reducing knee pain or improving physical function; yet adverse effects such as drowsiness, dizziness, and respiratory depression are common (13). Therefore, opioids other than tramadol should be considered only after exhausting all other treatment options.

Conversely, tramadol is a type of opioid commonly prescribed for OA patients. This analgesic is weak opioid and inhibits reuptake of norepinephrine and serotonin; tramadol has minimal potential to induce drug abuse and is associated with fewer adverse risks as compared to other opioids. In summary, opioids should not be routinely prescribed for chronic knee pain. Physicians should carefully prescribe tramadol to the elderly patients so as to minimize the risk of adverse events; combining tramadol and standard conservative treatment is recommended to reduce the effective dosage needed (11,13).

Pharmaceutical therapy available to EKOA patients is essentially the same as that used for moderate to severe KOA (11). In general, acetaminophen and topical NSAIDs should be prescribed prior to oral NSAIDs. Physicians must take the indication of oral NSAIDs into account due to its side effects and should the addition of a gastroprotective drug. Opioids are an alternative pharmaceutical option if other analgesics are ineffective or contraindicated (11). In theory, and in comparison to patients with advanced KOA, EKOA patients should be treated with pharmaceutical agents that can both alleviate knee pain but also avoid negative effects on articular cartilage. There is not any evidence that acetaminophen, tramadol, or opioids have an adverse effect on articular cartilage (13). On the other hand, limited medical evidence has already reported that the chronic use of non-selective NSAIDs adversely affects articular cartilage, including loss of cartilage volume. In contrast, COX-2 inhibitors may provide some chondroprotection (11). Therefore, oral analgesics should be prescribed on the basis of their pharmacological properties such as efficacy, susceptibility, interaction, and complications. Both patients and physicians should have realistic expectations when beginning pharmaceutical therapy. Furthermore, pharmaceutical therapies should be implemented in combination with other conservative strategies, such as physical therapy and/or other physical modalities (11,13).

Intra-articular injections

Intra-articular injection of hyaluronic acid (HA) and platelet-rich plasma (PRP) have been increasingly studied as therapies for EKOA. Sugimoto *et al.* measured the synovial

concentration of catabolic biomarkers [e.g., chondroitin-6-sulfate (C6S), chondroitin-4-sulfate (C4S), aggrecan], following injection of HA. Subjects in whom biomarker concentrations were higher showed the better improvement of Japan Orthopaedic Association (JOA) score after 1 month following injection. In addition, HA was equally effective regardless of OA stages, although most patients possessed advanced disease (14). One review paper suggested that low molecular weight HA (LMWHA) was effective for pain relief (15), yet a recent systematic review reported that the effect of HA was modest in the early to moderate stages of. In particular, there modest therapeutic effect 6 to 8 weeks following injection, but this effect was attenuated at six months (16). Ishijima *et al.* compared the improvement of clinical scores (JKOM, VAS score) between HA and oral analgesics in KOA patients. Both therapies had similar effects in improving clinical scores. Regarding the use of HA, the therapeutic effect was attenuated gradually, while the HA had significant effect. Notably, those who used NSAIDs showed the side effect and interruption of study (17). Regarding trends in HA utilization, Rosen *et al.* reviewed that 117 orthopaedic surgeons and physicians were interviewed about how they administered HA. Many clinicians (83%) prescribed HA in early to mid-stage KOA, while it was less frequently used in the later stages (57%). In this review, it was still unclear how the molecular weight, cross-link, and product process affect the therapeutic efficacy (18).

Regarding with the intra-articular injection of PRP, Kon *et al.* compared PRP against (LMWHA) and high-molecular weight HA (HMWHA) up to 6-months. PRP showed better clinical outcomes in both EQ VAS and International Knee Documentation Committee (IKDC) scores as compared to HA, especially in the subjects who had KL grade 0. Additionally, younger subjects (<50 years) who had received PRP also showed better outcomes than LMWHA (19).

Görmeli and colleagues also compared the efficacy of intra-articular injection of PRP or HA. Especially in the population with EKOA, three-time weekly PRP injections showed a significant improvement of clinical outcomes (EQ-VAS and IKDC score) at six months after injection, compared with HA or single-time PRP injection (20). Lee *et al.* reported the efficacy of PRP for the middle-age patients who concomitantly received microfracture for focal cartilage defects in the context of early stages of cartilage degeneration. As compared to those who underwent microfracture alone, the combination of microfracture and PRP showed better improvements of VAS scale and IKDC scores (21). Lastly, Jang *et al.* evaluated the efficacy of PRP in patients with patellofemoral EKOA. The intra-articular injection of PRP remained effective for up to 9 months. Although mean IKDC and VAS scores were improved, patients who were younger and possessed less severe radiographic grades showed more significant improvement, compared with the older patients or those with more severe radiographic grades (22). Taken together, these early studies suggest that intra-articular injection of both HA and PRP may provide a therapeutic effect in EKOA patients. At this point, compared with HA, intra-articular injection of PRP seems to show better clinical outcomes. However, long-term studies must be performed and greater attention must be given to defining the composition of PRP for a given patient, in a given study.

Physical therapy

Physical or exercise therapy has been consistently found to improve pain and function of KOA patients, and is recommended by clinical guidelines (23). However, Farr and colleagues reported that even in the early stage of knee OA, the ability to perform all activities of dialing living can be compromised (24). Actually, compared with the population of definitive radiographic KOA, EKOA subjects showed a significant decrease of quadriceps strength (25); otherwise, their gait pattern, loading stress, and hamstring strength were not different (26). The loss of quadriceps strength has the potential to accelerate the onset of definitive KOA. Based on previous studies, it is recommended that the clinician develop a strategy to enhance or maintain the EKOA patient's physical activity level as early as possible. Farr *et al.* also reported that physical impairment was significantly improved when an organized resistance-training program was assigned for EKOA patients, as compared to self-management (27). McKnight and colleagues also evaluated how strength training affected the functional and symptomatic outcomes in 201 middle-age adults (35 to 64 years old) whose radiographic OA severity was KL grade 0 to 2. They divided the subjects into three groups: strength-training, self-management, or combined program. At 24-month follow up, the study's participants improved leg press power, range of motion, work capacity (ERGOS work simulator), balance, stair climbing capacity, self-reported pain, and disability scores. Participation compliance was modest (56% to 69 %) in each group. The improvement of functional and symptomatic outcomes was not significantly different among the three

groups. Although these limited studies showed the efficacy of strength training to improve the physical activity and performance in EKOA patients, the efficacy of physical therapy in the early stage of OA requires further research. Bennell and Messier found that most studies evaluating the utility of strength training in EKOA patients lacked a control group, were not assessed by a blinded evaluator, and often suffered from modest patient compliance. Obviously, low adherence can compromise the conclusions drawn from clinical studies evaluating the therapeutic effect of strength training (23). Future research will be needed to deal address these shortcomings.

Surgical treatment for EKOA

If EKOA patients with symptomatic knee pain derive inadequate benefit from conservative treatment, and after careful consideration of patient background, pathology, and the alignment of the lower extremity, surgical treatment may be considered. Since EKOA patients are usually relatively younger, the surgical treatment should be aimed not only to relieve pain and restore function, but also to return the patient to high level activities.

Most symptomatic EKOA patients have multiple pathologies such as synovitis, meniscus injury, and cartilage defects without radiographic findings. Arthroscopic treatment for the patients who have mechanical symptoms due to a meniscal lesion or free bodies, including articular cartilage fragments, may not only experience relief of symptoms but also the indirect benefit of delaying reconstructive surgery.

Arthroscopic lavage and debridement

The purpose of lavage and debridement is to resect hyperproliferated synovium and/or intra-articular debris, and trim the irregular tissue surfaces. Arthroscopic debridement is still widely performed as a treatment for OA patients. However, Moseley *et al.* conducted a randomized, placebo-controlled study including a large number of OA subjects, and revealed that outcomes following arthroscopic lavage or debridement were no better than those after sham surgery (28). On the other hand, Jackson *et al.* claimed that arthroscopic lavage and debridement provide benefits to EKOA patients by washing out and diluting inflammatory mediators in the synovial fluid (29). Although these procedures are beneficial for temporary symptomatic relief, the benefits might be limited in the long term. The orthopedic surgeon should apply these methods cautiously after making efforts to clarify the cause of the symptoms of EKOA patients.

Treatment for the meniscus

With increasing knowledge of the biology and function of the meniscus, there is now consensus that the meniscus should be preserved whenever possible (30). Degenerative meniscal tears have a high prevalence in EKOA patients (31), and meniscal surgery can be applied with the proper indication even in these cases (32). Although there are several studies that support the benefit of meniscus repair for preventing OA progression (33,34), few studies have been reported on the clinical outcomes following meniscus repair explicitly in EKOA patients. On the other hand, several studies with EKOA patients revealed that meniscectomy often failed to prevent OA progression. Han *et al.* investigated the effect of a posterior medial meniscus meniscectomy on EKOA patients, and showed that only one-half of the patients had symptomatic improvement while one-third developed definitive radiographic OA changes (35). Roemer *et al.* studied 355 knees from the dataset of an ongoing longitudinal cohort study and concluded that partial meniscectomy is strongly associated with incident radiographic OA development within 1 year (36). It is important to limit the meniscectomy just to the unstable tissue, without sacrificing the intact and stable tissue so as to mitigate the risk of OA progression due to a decrease in tibiofemoral contact area with an associated increase in peak contact pressure (37).

Recently, meniscal replacement utilizing synthetic scaffolds or allograft has been proposed as an option for the patients after meniscectomy or an irreparable meniscus lesion, with the aim of reducing OA development and providing pain relief. Meniscal replacement should be considered in stable and well-aligned knees with no diffuse cartilage lesions. Zaffagnini *et al.* (38) and Monllau *et al.* (39,40) reported the 10-year outcomes after meniscal scaffold transplantation and showed both prevention of OA progression and concurrent improvement in clinical and radiographic outcomes. However, both of these studies suggested minimal maturation of the scaffolds, as evaluated by MRI signal intensity. Moreover, Bulgheroni *et al.* evaluated the MRI appearance of transplanted meniscal scaffolds 5 years after surgery and showed overall size reduction, persistent signal abnormality, and extrusion of the scaffolds (41). In terms of meniscal allograft transplantation (MAT), while the surgical procedures, evaluation methods, patient demographics, and follow-up

periods have varied across studies, most investigations have shown successful outcomes in pain relief and functional restoration. Nevertheless, despite the observed prevention of OA development (42), the survival rate of MAT is less than 50% in long-term follow-up (43).

Treatment for cartilage defects

Microfracture, the method for liberating the stem cells from subchondral bone marrow to the focal articular cartilage defects, has an advantage of minimal invasiveness, technical simplicity, and cost effectiveness. While the repair tissue resulting from microfracture consists mostly of fibrocartilage, which is lower quality than native articular hyaline cartilage, it can be applied easily and in combination with most of other procedures.

Mosaicplasty aims for early restoration of the articular joint surface by transplanting single or multiple osteochondral autografts from non-weight-bearing regions to the osteochondral lesion (44,45). Although several studies reported promising long-term results (46-48), mosaicplasty still has the disadvantage of relatively higher donor-site morbidity (49-51).

Autologous chondrocyte implantation (ACI) can produce hyaline-like repair tissue in articular cartilage defects (52) with sufficient functional restoration in long-term follow-up (53). In terms of EKOA cases, Minas *et al.* conducted a case series including 155 knees with focal chondral defects that received ACI. The symptoms and functions were improved in most patients and 92% of patients avoided further arthroplasty after treatment for at least 5 years (54).

Surgical realignment and arthroplasty

If varus or valgus malalignment is considered the principal cause for unilateral early knee OA, an osteotomy may be a surgical option. High tibial osteotomy (HTO) and distal femoral osteotomy (DFO) alter the mechanical axis in order to reduce the load on the medial or lateral compartment and to distribute the load into the relatively preserved articular cartilage in the other compartment. The advantages of osteotomy are in correcting the malalignment of the lower extremity and preserving the bone stock around knee joint, which allows for future arthroplasty when and if indicated.

There are few clinical studies investigating surgical realignment focused on EKOA patients. Cavallo *et al.* conducted a short-term prospective clinical study of 24 EKOA patients treated with medial open-wedge HTO combined with bone marrow-derived mesenchymal stem cells implantated into the cartilage defect. They reported the safety of cell implantation, and its positive effect on pain relief and restoring knee function (55). As corrective osteotomies for OA due to malalignment, especially in younger patients (56), HTO with or without additional arthroscopic or biological treatment may be appropriate for EKOA patients. However, future research is needed to confirm any additive or synergistic benefit of additional biological augmentation.

Total knee arthroplasty (TKA) and unilateral knee replacement (UKR) for OA patients provides a successful outcome, especially in elderly patients. Moreover, TKA has greater potential than arthroscopic surgery and osteotomy in terms of relieving pain of OA patients (57). However, because of the limited longevity of prostheses and the associated need to restrict certain activities, TKA should be considered the last resort for younger EKOA patients. Due to relative high revision rates, several studies argued that both TKA and UKR are not an ideal surgical option for relatively younger and more physically active patients (58,59). Considering these aspects, these procedures should not be the first choice for younger EKOA patients with no radiographic OA findings.

Conclusions

The current review highlights the emerging evidence on the non-surgical and surgical management of EKOA. At present, nearly all studies are case-control or case series, and few randomized control trials have been conducted. Strong evidence is still lacking about how to manage the EKOA patient properly, however, ongoing research is beginning to offer promising strategies for this challenging clinical problem.

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