THE CHALLENGE OF EARLY KNEE OSTEOARTHRITIS

IZAZOV RANOG OSTEOARTRITISA KOLJENA

Alberto Migliore, Emanuele Bizzi

Rheumatology, S. Pietro Fatebenefratelli Hospital, Rome, Italy

Correspondence to:
Emanuele Bizzi, MD
via Cassia 600, 00189 Rome, Italy
Tel. +393488882220
E-mail: bizzi.emanuele@gmail.com

Abstract

The identification of early stages of osteoarthritis, like the pre-radiological stage characterized by few and mild symptoms, would allow early preventive interventions, with the aim of modifying the course of the disease. This could improve the prognosis of patients affected by osteoarthritis and lead to a significant reduction of the costs associated with the management of this disease. To date, a clear clinical definition of the early stages of osteoarthritis is still missing. The OARSI initiative and the CHECK study are two ongoing prospective studies among whose objectives is the identification of early stages of osteoarthritis and the risk factors associated with its development. The Italian Society for Rheumatology recently promoted an international consensus for the definition of early knee osteoarthritis. As a first step, a systematic literature review was performed for the identification of possible definitions of early osteoarthritis in scientific literature. As a second step, an international panel of experts in the field of osteoarthritis conceived, in several evaluation steps, a definition of early symptomatic knee osteoarthritis.

Keywords: osteoarthritis, early, definition, knee

Sažetak

Otkrivanje osteoartritisa u ranom stadiju, tj. u preradiološkoj fazi obilježenoj malim brojem blagih simptoma, omogućilo bi rane prevencijske intervencije radi promjene tijeka bolesti. To bi moglo poboljšati prognozu bolesnika s osteoartritisom te dovesti do znatnog smanjenja troškova povezanih sa skrbi za te bolesnike. Za sada još nedostaje jasna definicija ranih stadija osteoartritisa. OARSI inicijativa i CHECK studija dvije su prospektivne studije u tijeku kojima je, između ostalog, svrha identificirati rane stadije osteoartritisa, kao i čimbenike rizika povezanih s njegovim razvojem. Talijansko društvo reumatologa nedavno je predstavilo međunarodni konsenzus za definiciju ranog osteoartritisa koljena. Kao prvi korak učinjen je sustavni pregled literature radi identifikacije ranog osteoartritisa u znanstvenoj literaturi. U drugom je koraku međunarodni panel stručnjaka za područje osteoartritisa s pomoću nekoliko stupnjeva evaluacije prihvatio definiciju ranoga simptomatskog osteoartritisa koljena.

Ključne riječi: osteoartritis, rani, definicija, koljeno

Introduction

Osteoarthritis (OA) is one of the most common degenerative diseases in the world and its incidence is on the increase due to the aging of the world's population (1). OA is a leading cause of disability in western countries, burdened by high costs for national health and health insurance systems. Patients with advanced-stage OA suffer from chronic pain and functional impairment of the limbs and spine, and generally have a poor quality of life.

The understanding of the pathogenesis of OA has made great strides in recent decades. To date, the evolutionary stage of OA may be classified from both a radiological and a clinical point of view (2). The risk factors associated with the development of OA have been clarified (3), thus making it possible to prevent the worsening of OA to a certain extent. Unfortunately, it is now possible to identify only patients suffering from a clinically and radiographically established OA, while it is not possible to identify those patients who are suffering from the early stages of OA (EOA) in the pre-radiological stage.

The identification of patients with early stages of the disease, like the pre-radiological stage characterized by few and mild symptoms, would allow early preventive interventions, which might modify the course of the disease, stopping or slowing it down.

To date, a clear clinical definition of EOA is still missing. In its agenda EULAR proposed to develop diagnostic criteria for an early identification of patients with knee OA (KOA) through prospective studies (4). Several previous studies have investigated patients in the early stages of OA, but the definitions used by authors lack uniformity.

At present, two large cohort studies are being implemented, the OARSI initiative and the CHECK study.

Also, the Italian Society for Rheumatology recently promoted an international consensus for the definition of Early Symptomatic Knee Osteoarthritis (ESKOA) by a multi-methodological approach, including a systematic literature review, focus groups, discussion groups, Delphi surveys, and face-to-face meetings.

Review paper   Pregledni rad

Migliore A. et al. The challenge of early knee osteoarthritis

The OARSI initiative

The OARSI initiative (OAI) comprises a multi-center, longitudinal, prospective, observational study on patients with KOA. The objective of the OAI was the development of a public domain research resource aimed to help the scientific evaluation of biomarkers of OA onset and progression. The principal objectives of the OAI were the development of an ethnically diverse cohort of patients suitable for studying the risk factors and natural history of onset and progression of OA, and to determine the validity of radiographic means such as X-Ray and MRI, as well as biochemical and genetic assays as biomarkers for OA. Within the included patients there is a subgroup of patients at risk of developing KOA. This subgroup is characterized by specific inclusion criteria and is used for the study of incident cases. The inclusion criteria for this patient subgroup include previous knee surgery or injury, the presence of Heberden's nodes at the distal interphalangeal joints, and overweight. The patients included in this subgroup did not necessarily have to report knee pain. The patients in the "high risk" subgroup were stratified by age and presence of pain and/or risk factors. Several papers were published following different evaluations of the OAI cohort of patients. Eckstein et al. (5) reported how in the OAI progression subcohort, the greatest rate of knee cartilage loss, at the medial femoral condyle level as evaluated by X-ray, was observed in patients with a high weight-bearing knee. Obese patients showed trends towards higher rates of cartilage loss, although such trends did not reach statistical significance. Using MRI, Lo et al. (6) evaluated bone marrow lesions and joint effusions and their association with weight-bearing pain, finding that bone marrow lesions and effusions were independently associated with weight-bearing pain. Stehling et al. (7) also found that higher physical activity induced more severe focal knee lesions, as diagnosed by 3T MRI, in a non-symptomatic cohort of OAI. In addition, two studies performed by Joseph et al. (8, 9), reporting on the relevance of MRI in the diagnosis of early stages of KOA, demonstrated that subjects at risk of KOA had more heterogeneous cartilage T2 values in respect to controls, and that certain T2 parameters were associated with future morphologic degenerations. Similarly, Urish et al. (10) found how T2 cartilage texture can predict early KOA progression, reporting how baseline heterogeneity in the T2 cartilage TIC index was able to predict and differentiate patients who would develop worsening in their WOMAC scores on a 3-year follow up. In the following studies it was reported that a history of knee surgery, knee flexion contracture, and pain represented predictor factors for a rapid progression to knee arthroplasty, while valgus malalignment and meniscus injuries represented a risk factor for knee OA incidence (11, 12). In 2014 Hensor et al. (13), in an effort towards a first clinical definition of early OA, found that patients reporting the occurrence of knee pain as a first symptom emerging during weight-bearing activities, such as climbing stairs, may represent a group of patients affected by an early stage of OA and thus suitable for early interventions.

The CHECK study

The other study currently under way is the CHECK study, a prospective study conducted in the Netherlands. Its aim is to identify patients with early stages of hip and knee OA, involving subjects with ages between 45 and 65 who reported knee and/or hip joint pain or stiffness for which they had not visited a GP for more than 6 months. Exclusion criteria are previous meniscus or ligament injuries.

The CHECK study produced several papers aimed to identify the early stages of hip and knee OA and their clinical, laboratory, and radiological features. Regarding biomarkers, in a study from van Spil et al. (14), an association was observed between adipokine levels, other biochemical markers of systemic joint metabolism, and radiographic progression in early-stage KOA, while Vos et al. (15) reported that skin pentosidine did not perform better than uCTXII in predicting radiographic progression on a 5-year follow up. Recently, van Spil et al. (16) found that multiple cartilage and synovial markers, such as uCTXII and sCOMP, showed positive associations with the presence and eventual progression of knee and hip OA. Regarding activity limitations in early symptomatic KOA, Holla et al. (17) reported how three subgroups of patients with different trajectories of activity limitations may be identified. The two subgroups of patients with "poor outome" and "moderate outcome" in terms of activity limitations were characterized by younger age, higher body mass index, greater pain, bony tenderness, reduced knee flexion, hip pain, osteophitosis, presence of 3 or more comorbidities, lower vitality, and avoidance of activities in comparison to the "good outcome" subgroup, thus indicating the above characteristics as predicting factors of a worse prognosis in terms of activity limitation on a 5-year follow up. Similarly, Wesseling et al. (18) reported how three trajectories of pain may be identified in patients with symptomatic knee OA on a 5-year follow up. In the subgroups of patients characterized by a "mild" or "moderate" pain trajectory, in respect to the subgroup of "marginal" pain trajectory, certain characteristics may be identified, such as a BMI>25, having at least 3 comorbidities, a low education level, and additional hip pain.

The SIR systematic literature review

The SIR carried out an updated systematic review on both PubMed and Embase databases, searching for all the studies published in medical literature in the last 30 years addressing the issue of early osteoarthritis definition and diagnosis before starting the attempt at an international consensus for the definition. This review found a number of articles varying between 209 and 307 (published from 1973 to 2013), when searching on PubMed and Embase databases, respectively.

In the systematic literature review we found 6 observational studies; 1 RCT and 2 expert opinion papers were selected among 1522 records captured. All the studies defined different types of established OA, such as OA onset in young patients, incident OA, recently diagnosed early OA, or MRI-detected early stages of OA. 4 studies used MRI, with or without arthroscopy findings, while 5 studies used the Kellgren-Lawrence and Ahlback X-ray criteria.

Only 1 article (Luyten et al., 2011) (19) explicitly addressed the issue of a definition of EOA (only in the knee), although that instance should be considered only an "expert opinion" (lowest level of evidence), as the authors did not perform a systematic review of the literature. All the other researches were mainly focused on the early stage of radiological OA damage (grades I-II of the Kellgren and Lawrence classification), and on onset at younger ages, treatment options, and prompt diagnosis.

Despite its limitations, the study by Luyten et al. refers to the American College of Rheumatology (ACR) criteria for

Review paper   Pregledni rad

Migliore A. et al. The challenge of early knee osteoarthritis

knee OA, which combines clinical and radiological findings with a 91% sensitivity and an 86 % specificity (20). According to the ACR criteria, a diagnosis of knee OA is confirmed if objective findings (i.e., osteophytes and radiologically detectable joint space narrowing corresponding to grade 2 of the Kellgren and Lawrence classification) are concurrently present together with one of the following conditions: age <50 years old, joint stiffness (<30 min), or crepitus. In addition to that, some authors have suggested that the presence of at least one osteophyte and joint space narrowing is needed to establish a diagnosis of KOA (21). However, as remarked by Luyten et al. in their paper, the definition of early osteoarthritis implies that patients suffering from this condition do not fulfill the ACR criteria for the diagnosis of OA. Therefore, the authors propose the following specific criteria for the identification of EOA patients: (1) knee pain (at least two episodes of pain for more than 10 days in the past year); (2) possible radiological evidence of osteophytes (Kellgren–Lawrence grades 0, I, or II); (3a) arthroscopic findings of cartilage lesions (ICRS classification grades I-IV at least in two compartments or grades II-IV in one compartment with softening and swelling of the surrounding cartilage as reported at www.cartilage.org/_files/contentmanagement/ICRS_evaluation.pdf); or (3b) Magnetic Resonance Imaging (MRI) evidence of cartilage alterations, meniscus and/or subchondral bone marrow lesions (BMLs), as assessed according to the WORMS and BLOKS scores (22). It should be noted that all three criteria should be present for the diagnosis of knee EOA, as proposed by the authors (19). We have to note that risk factors were not taken into account.

No similar studies or expert opinions have been published in the literature concerning the definition of early osteoarthritis affecting other joints (i.e., the hip joint).

The SIR Early Symptomatic Knee Osteoarthritis Definition project

A multi-methodological approach, including a systematic literature review, focus groups, discussion groups, Delphi surveys, and a final face-to-face meeting, was implemented in order to achieve this goal. A first focus group was held with the participation of five patients affected by OA and characterized by different ages and clinical profiles. The second focus group involved six researchers in basic sciences sampled on the basis of recent publications in the area of OA. The third focus group comprised six expert clinicians selected on the basis of publications of clinical studies involving OA. The results of both the systematic literature review and the three focus groups were collated and submitted to an international panel of OA experts, coming from the following European countries: Albania, Belarus, Bulgaria, Croatia, France, Italy, Portugal, Romania, Russia, Serbia, Spain, and Turkey. During the discussion session, the following topics were analyzed: the strengths and possible limitations of existing criteria, as well as items to be included in a new definition of early OA and in referral recommendations. The panel elaborated a total of 38 propositions to be potentially included in the definition of ESKOA, ranging from primary and specialist care to barriers for referral and problems of assessment. These were sent to all the participants of the two Delphi rounds of survey. After the first survey, the categories of signs and symptoms were collated, and the ten propositions that reached an agreement of over 7 were resubmitted to the second Delphi round. Regarding risk factors, 10 items reached a sufficient consensus and were resubmitted for the second Delphi round. During the second Delphi round, the signs and symptoms were ranked. Then a face-to-face meeting was held to establish a definition of ESKOA.

Unanimous agreement was reached on all exclusion criteria, which were consequently included in the definition: the presence of generalized pain, an inflammatory joint disease, an active inflammatory joint disease, and a Kellgren-Lawrence radiologic degree above 0.

The absence of any recent trauma or injury of the knee was reported among the exclusion criteria. After unifying the two knee pain-related signs/symptoms, two major signs/symptoms were identified: knee pain and very short joint stiffness when starting a movement.

The panelists agreed to consider ESKOA as possible if the condition has lasted for less than 6 months. An algorithm was compiled based on the absence or presence of 1, 2, or more risks factors. Four signs or symptoms, selected from the highest-ranked propositions, plus 8 risk factors which had ranked highest in the second Delphi round, were included in the definition. ESKOA was then defined by the presence of applicability criteria (absence of inflammatory arthritis, age of patients of 50 years or older, or 40 years or older with the presence of at least 1 risk factor, Kellgren Lawrence grade 0) and by the presence of 3 or more symptoms in the absence of risk factors, 2 or more symptoms and 1 risk factor, or 2 or more risk factors and 1 or more symptoms with a symptom duration of less than 6 months. The risk factors included were overweight with a BMI over 25, family history of OA, previous knee injuries, malalignment, lower limbs dissymmetry, OA in other sites, metabolic syndrome, and hypermobility.

Regarding the referral criteria, the panel decided to integrate the signs and symptoms in a single referral criterion in order to improve applicability. "The presence of knee pain, in the absence of any recent trauma or injury, with or without joint stiffness, with symptoms lasting for less than 6 months" was stated as a successful criterion for its applicability and sensitivity.

Discussion

Similarities and differences may be found in our definition of ESKOA when compared with what was established in the OAI and CHECK studies. Similarly to what was established by the CHECK study, pain and stiffness are relevant signs/symptoms for detecting patients affected by ESKOA, while in the OAI study the patients did not necessarily have to report pain in order to be included in the incidence analysis. On the contrary, overweight and previous knee injury/surgery were reported in the OAI study as risk factors, just like in our study. Regarding risk factors, there are similarities between what was established in our definition and the results obtained by the OAI and CHECK studies. In various studies, both CHECK and OAI report how BMI may play a role in the development of OA, while previous episodes of knee surgery were identified as risk factors by the OAI study. Similarly, valgus malalignment was identified as a risk factor by the OAI study.

A more clear classification of EOA, based on the characteristics and symptoms of affected patients, should be delivered by the scientific community in order to better identify subjects who might benefit from new expensive drugs and innovative therapeutic approaches.

Review paper

Migliore A. et al. The challenge of early knee osteoarthritis

Pregledni rad

Conclusions

Until now, EOA has be defined with regards to the younger age of EOA onset and radiological damage (grades I-II of the Kellgren and Lawrence classification).

There is only one definition of EOA, with a very low level of evidence. In addition, there are many other interpretations of EOA in the literature. These interpretations may vary from: initial radiologic degree of OA, such as grades I and II according to the KL radiologic classification, associated or not with classic symptoms; premature onset of OA; initial histopathological or MRI-detected joint changes associated or not with classic symptoms; low-grade symptomatic OA patients diagnosed according to the ACR classification. It is still necessary to achieve an agreement in order to classify every condition explored relative to the different stages or features of OA with a universally accepted nomenclature.

This should present a great opportunity to detect early stages of OA (a combined use of MRI and biomarkers could be useful for this purpose) in order to apply newly available drugs for the treatment of osteoarthritis as well as innovative therapeutic approaches, such as regenerative medicine, in the attempt to delay or to halt the disease progression.

Declaration on conflict of interest: The author declares that there is no conflict of interest.

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