European Geriatric Medicine xxx (2017) xxx–xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Hot topic in geriatric medicine

Early osteoarthritis: How to define, diagnose, and manage. A systematic review

G. Iolascon [a,*], F. Gimigliano [b], A. Moretti [a], A. de Sire [a], A. Migliore [c], M.L. Brandi [d], P. Piscitelli [e]

[a] Department of Medical and Surgical Specialties and Dentistry, University of Campania "Luigi Vanvitelli", Naples, Italy
[b] Department of Mental and Physical Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[c] Fatebenefratelli St. Peter's Hospital, Rome, Italy
[d] Department of Surgery and Translational Medicine, University of Florence, 50139 Florence, Italy
[e] Southern Italy Hospital Institute, IOS/Coleman Ltd., Naples, Italy

ARTICLE INFO

Article history:
Received 16 March 2017
Accepted 7 July 2017
Available online xxx

Keywords:
Early osteoarthritis
Systematic review
Osteoarthritis
Hip osteoarthritis
Knee osteoarthritis

ABSTRACT

Since a clear definition of early osteoarthritis (EOA) has not been set up, some critical questions concern its diagnosis and treatment. The upcoming of newly available drugs and innovative therapeutic approaches, such as regenerative medicine, foster a better knowledge of the problem by medical community. We have carried out an updated systematic review on both PubMed and Embase databases, searching for all the studies and researches published in medical literature in the last 32 years, addressing the issue of EOA definition, diagnosis, and treatment, with a special focus on EOA at hip and knee. Our review found out 211 and 447 (published from 1973 to 2015) articles, when searching on PubMed and Embase database, respectively. Among the 132 papers that met our inclusion criteria, only 1 article explicitly addressed the issue of EOA definition, but it was only an expert opinion, while all the other researches were focused on diagnosis or management of EOA. EOA has been defined with regards to the younger age of osteoarthritis onset and radiological damage (grade I–II of the Kellgren and Lawrence classification). A more clear classification of EOA, based on characteristics and symptoms of affected patients, should be delivered by scientific community in order to better identify subjects who might benefit from new expensive drugs and innovative therapeutic approaches.

1. Introduction

Osteoarthritis (OA) is a major cause of joint pain and impaired mobility resulting in a marked reduction of quality of life (QoL) and relevant costs to individuals and societies worldwide [1]. The disease is often progressive, with evolving radiological damages [2]. The prevalence of OA increases indefinitely with age, because the condition is not spontaneously reversible [3]. Almost 9.6% of men and 18.0% of women aged $\geq$ 60 years old all over the world are thought to be affected by symptomatic OA [1]. Hip and knee are the joints most commonly involved in OA, but many other skeletal sites (i.e. hands, feet, spine) may be affected by this condition [4]. According to the World Health Organization (WHO), OA is the sixth leading cause of disability in the world, accounting for 3% of the total global years lived with disability (YLDs) [5,6]. Limitations to job activities are relevant in people affected by OA if compared with healthy age and sex matched population causing a reduction of working hours, problems in applying for a job or early retirement due to the illness [7]. This condition is expected to result in a progressively higher number of people affected with unaffordable costs for healthcare systems or insurance companies [8,9]. Since OA is a very common disease, it would be of crucial importance to have a clear definition of early osteoarthritis (EOA) in order to adopt proper preventive measures that might result in better long-term quality of life of affected patients and reduce or delay the need of joint replacement interventions, with the related implications in terms of economic impact on healthcare services.

The aim of this systematic review (SR) was to define the "state of the art" on definition, diagnosis, and management of EOA.

* Corresponding author.
E-mail addresses: giovanni.iolascon@gmail.com (G. Iolascon), francescagimigliano@gmail.com (F. Gimigliano), antimomor83@hotmail.it (A. Moretti), alessandro.desire@gmail.com (A. de Sire), migliore.alberto60@gmail.com (A. Migliore), m.brandi@dmi.unifi.it (M.L. Brandi), prisco.piscitelli@tiscali.it (P. Piscitelli).

http://dx.doi.org/10.1016/j.eurger.2017.07.008
1878-7649/

2. Materials and methods

We carried out an updated systematic review on both PubMed and Embase databases searching for all the studies and researches published in literature – up to the 31st December 2015 – which were addressing the issues of EOA definition, diagnosis, and management. The systematic review has been carried out following the 5 steps summarized by Khan and colleagues in 2003 [10]. As inclusion criteria, we have decided to initially consider (with the possibility of defining specific exclusion criteria after the analysis of the characteristics and quality of the studies) all the papers indexed in PubMed and Embase databases, which were addressing the issue of EOA. The search on PubMed database has been performed by using the following keywords and Boolean operators: "early osteoarthritis" [TIAB] and osteoarthritis [Mesh]. The search on Embase database has been performed by using the following keywords and Boolean operators: 'early osteoarthritis': ab, ti and [embase]/lim. Methodological quality of studies was evaluated according to the Levels of Evidence defined by the Centre for Evidence Based Medicine (CEBM) [11] as reported in Table 1. After methodological quality assessment, we excluded from our analysis studies on cadavers. In vitro studies and all the basic researches and animal studies on new molecules or treatments for OA (presenting laboratory research data) were included in the present systematic review – after examining the methods and results sections of each study – only if they could add any relevant information to current knowledge about definition, diagnosis, management of EOA. Articles written in languages other than English, single case reports as well as papers describing improvements in surgical techniques to prevent iatrogenic-induced OA have been systematically excluded from our analysis. Exploration of heterogeneity of the studies has been performed by assessing their quality (i.e. level of evidence), in order to properly consider the suitability of a meta-analysis (overall or per subgroups of studies). Interpretation of the findings has been conducted in the frame of current medical knowledge about OA diagnosis and management.

3. Results

Our initial review found out 211 and 447 (published from 1973 to 2015), when searching on PubMed and Embase database, respectively. According to the predefined exclusion criteria, a total of 78 papers from PubMed and 315 articles from Embase have been excluded from the analysis. Among the 132 papers that met our inclusion criteria, only 1 article explicitly addressed the issue of EOA definition (particularly for knee EOA), although it should be considered only an "expert opinion" (lowest level of evidence) [12]. All the other studies included in our analysis were focused on the early stage of radiological OA damage [grades 1–2 of the Kellgren and Lawrence (KL) classification], on the age of onset, prompt diagnosis, and treatment options. In Table 1, it was resumed the number of studies included in our analysis according to their Level of Evidence. Table 2 reported the authors of the papers, the study design and Level of Evidence, with number of enrolled patients and the main findings.

3.1. Definition of EOA

Despite its limitations, the study from Luyten et al. (the only one addressing the issue of EOA definition based on experts' opinion) [12] refers to the American College of Rheumatology (ACR) criteria for knee OA (KOA), which combines clinical and radiological findings high sensitivity and specificity [144]. According to ACR criteria, diagnosis of OA is confirmed if objective findings (i.e. osteophytes and radiologically detectable joint space narrowing, JSN, corresponding to grade 2 of KL 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 JSN is needed to establish a diagnosis of KOA [144]. However, as remarked by Luyten et al. in their paper, the definition of EOA implies that patient suffering from this condition do not fulfill the ACR criteria for the diagnosis of KOA [144]. Therefore, specific criteria for the identification of EOA patients were proposed: (1) knee pain (at least 2 episodes of pain for more than 10 days in the last year), (2) possible radiological evidence of osteophytes (KL grades 0-2), (3a) arthroscopic findings of cartilage lesions (International Cartilage Repair Society, ICRS, classification grade I–IV at least in 2 compartments or grade II–IV in 1 compartment with softening and swelling of the surrounding cartilage) [145] (3b) Magnetic Resonance Imaging (MRI) evidence of cartilage alterations, meniscus and/or subchondral bone marrow lesions (BMLs), as assessed according to the Whole Organ Magnetic Resonance Imaging Score (WORMS) [146] and Boston Leeds Osteoarthritis Knee Score (BLOKS) scales [147]. No similar studies or experts opinion have been published in the literature concerning the definition of EOA in other joints (i.e. hip joint).

3.2. Diagnosis of EOA

Karachalios et al. carried out a diagnostic survey among patients with a clinical and radiological diagnosis of EOA of the knee by MRI on 70 patients (82 knees) with a mean age of 59 years (range: 40–71 years) with chronic knee pain, clinical diagnosis of EOA, and knee radiographs corresponding to the first grades of the KL scale [70]. Actually, authors described EOA as a condition corresponding to grade 1 and 2 on the KL scale on conventional knee radiographs. They found a variety of different structural alterations in knees affected by EOA: degenerative meniscal lesions, rupture of the anterior cruciate ligament, osteonecrosis of femoral and tibial condyles, osteophytes and degenerative articular cartilage lesions, transient osteoporosis, benign neoplasms, and cysts. These findings might justify a modern MRI approach to get a proper clinical diagnosis of knee EOA [70,148]. The delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) technique has shown promising results in pilot clinical studies of EOA [149]. The clinical utility and diagnostic performance of MRI for the identification of early and advanced KOA have been confirmed by a SR carried out by Quatman et al., although with huge between-studies differences in the specificity and accuracy rates (50–100% and 49–94%, respectively), and in the sensitivity for identifying articular cartilage abnormalities (26–96%) [13]. Stahl et al., in their MRI studies, suggested that T1rho and T2 could be a parameter suited to identify active healthy subjects at higher risk for developing cartilage pathology [46]. As water distribution is detectable by MRI, cartilage homogeneity visualized through the water distribution (bone edema) by MRI has been proposed as a potential very early marker for knee EOA [48].

3.3. Biomarkers of EOA

Very few studies have investigated the role of serum biomarkers in EOA. Chronic inflammatory changes with production of pro-inflammatory cytokines are a feature of synovial membranes from patients with EOA, with the most severe changes observed at the time of joint replacement surgery resembling those seen in rheumatoid arthritis (RA). This low-grade synovitis results in the production of cytokines that may contribute to the pathogenesis of OA [56]. C-reactive Protein (CRP) is modestly but significantly increased in women with early KOA, and higher levels predict disease progression over 4 years, suggesting that low-grade

Please cite this article in press as: Iolascon G, et al. Early osteoarthritis: How to define, diagnose, and manage. A systematic review. Eur Geriatr Med (2017), http://dx.doi.org/10.1016/j.eurger.2017.07.008