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Classification Criteria For Early Knee Osteoarthritis: A Review Article

Klassifikationskriterien für frühe Kniegelenksarthrose: ein Übersichtsartikel

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ABSTRACT

Objective The aim of this systematic review (SR) was to define the "state of the art" on classification criteria for early knee osteoarthritis (EKOA).

Methods A systematic review was performed using MEDLINE (Pubmed), Web of Science, Scopus, EMBASE, PEDro, CINAHL and Google scholar databases. Two independent reviewers conducted the eligibility review. Any type of study that proposed diagnostic criteria of EKOA was included.

Results Seven articles were included according to the inclusion criteria. The evidence presented in this SR shows that there is still no consensus regarding definition and classification of EKOA. At present, there are seven different proposals in the scientific literature, and they only agree on including knee pain and radiographic evaluation in their criteria, but they do not even consider the same situations for including these two factors.

Conclusion There is still no consensus regarding definition and classification of EKOA. Knee pain and radiological assessment seem to be the most commonly used criteria, but due to the variability encountered, it is not possible to reach a consensus on a clear definition and diagnosis of EOKA.

Introduction

Knee Osteoarthritis (KOA) is a major cause of joint pain, resulting in a marked reduction of quality of life and relevant costs to societies worldwide [1]. It is heterogeneous in terms of risk factors and rates of progression. This poses the challenge of stratifying patients with KOA, and proper classification criteria are essential [1]. Altman and colleagues developed the "ACR criteria" for KOA, used as diagnostic outcome criteria in Osteoarthritis (OA) research [2]. However, patients who meet the ACR criteria, already have significant structural joint damage. Subsequently, EULAR and also the National Institute for Health and Care Excellence (NICE) published diagnostic criteria for KOA [3, 4].

Kanamoto et al. highlight that a shift in focus towards early diagnosis is needed, suggesting that KOA progression may be delayed through early diagnosis before the joint is irreversibly destroyed [5]. Therefore, early diagnosis of KOA could be of significant importance for both healthcare and research purposes. It has been suggested that treatments such as Chondroitin sulfate or regenerative medicine for early knee OA (EKOA) could help in delaying the progression of OA and in pain reduction [6, 7]. However, regenerative treatments seem to yield better results when the joint damage is minimal, hence the importance of defining a reliable diagnosis of EKOA [7].

In the last few years several diagnostic criteria and a specific definition of EKOA have been proposed for diagnosing patients with EKOA [8, 9]. Knee pain is one of the established criteria. Nevertheless, it is important to acknowledge that knee pain can arise from various causes apart from OA. Therefore, exclusion criteria such as generalized pain, inflammatory joint disease and recent trauma or injury were proposed by Migliore et al.[10]. The aim of this systematic review (SR) was to define the ''state of the art'' on classification criteria for EKOA.

Methods

This SR was performed in accordance with a predefined protocol based in the PRISMA statement [11]. The PRISMA statement is composed of a 27-item checklist and a four-phase flow diagram, which assists in reporting systematic reviews [11].

Inclusion Criteria of the Studies

The selection criteria used in this review are based on methodological aspects as follows:

Population: Patients with early knee OA.

Outcomes: Only articles that presented diagnostic criteria or specific aspects for EKOA classification were included. These criteria could refer to clinical and radiological aspects, as well as any other type of measurement that facilitates the diagnosis of these patients.

Study design: Any type of study that proposed diagnostic criteria was included. Studies without language restriction were included, and articles published in the last 10 years were selected.

Search Strategy

Two independent reviewers conducted a search of scientific articles generating an agreement for the initial selection of the studies, after which the concordances were searched. The search of scientific articles was performed using the Medline (Pubmed), Web of Science, Scopus, Embase, Pedro, Cinahl and Google scholar databases. This search phase was concluded on April, 2021.

In these databases we used the following search terms and combinations: "Early osteoarthritis" AND "Classification", "Early osteoarthritis" AND "diagnose", "Early osteoarthritis" AND "criteria", "Early osteoarthritis".

Selection Criteria and Data Extraction

First, an analysis of information was carried out by two independent reviewers who evaluated the relevance of the studies in relation to the question and the objective of the investigation. This first analysis was made based on the information of the title, summary, and keywords of each study. In case there was no consensus, or the abstracts did not contain the necessary information, the full text was accessed. In a second phase of analysis, considering the full text, it was checked whether the studies met the inclusion criteria. The differences between reviewers were resolved by moderate consensus by a third reviewer. The data described in the results were extracted by means of the structured protocol that guarantees obtaining the most relevant information of each study [12].

Results

The study search strategy is shown in the form of a flow chart (▶ **Fig. 1**). Seven articles that met the inclusion criteria were selected.

Characteristics of the included studies

All seven studies proposed diagnostic classifications of EKOA or criteria for its diagnosis. The main characteristics of the studies are explained in ▶ **Table 1**.

First, two of the most recognized are those of Luyten et al., 2012 and 2018. In these studies, the authors carried out teamwork through workshops in multidisciplinary teams of physicians, physiotherapists, and surgeons, making diagnostic criteria based on the consensus. Furthermore, Mahmoudian et al., 2021 performed an analysis of the Luyten criteria using data from the Osteoarthritis Initiative. In addition, these authors performed a logistic regression analysis to evaluate the predictive performance of the criteria set for structural as well as clinical progression. On the other hand, Runhaar et al., 2020 conducted a CHECK study based on the screening of patients by experts in the field through a cohort study, which was subsequently used to create predictive models. Migliore and his group of collaborators conducted in 2015 a systematic review and definition of EKOA from a committee of experts. Subsequently, in 2017 they conducted an in-depth analysis using three focus groups, including expert clinicians, researchers, and patients; a systematic literature review and two discussion groups followed by a Delphi survey. Finally, Emery et al. performed a narrative review with consensus expert criteria.

Clinical criteria

Luyten et al. included the criteria "pain in the knee" defined as at least two episodes of pain for more than 10 days in the last year, in their 2012 criteria, and then in 2018 criteria they made a wider clinical approach through the patient-based questionnaires, Knee Injury and Osteoarthritis Outcome score (KOOS), needing to score

"positive" (≤ 85 %) 2 out of the 4 KOOS subscales (Pain, Symptoms, Function or Knee-related quality of life), and patients should present joint line tenderness (JLT) or crepitus in the clinical examination. Mahmoudian et al, in their review of Luyten's 2018 criteria, proposed changing the assessment of KOOS to use a single KOOS4 score (the average of four of the five KOOS subscales: pain, symptoms, ADL and quality of life) as well as 5 scores below and above the known threshold (≤ 80, ≤ 85, and ≤ 90), finding the best predictive performance for structural progression and clinical progression in KOOS4 ≤ 90 % and KOOS4 ≤ 80 %, respectively. Also, they examined the predictive ability of two more clinical variables, the presence of "effusion" and "Heberden's nodes". Migliore et al. on their paper in 2015 identified two major signs/symptoms: knee pain and very short joint stiffness when starting a movement lasting for less than 6 months. Early symptomatic knee OA (ESKOA) was then defined 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. They integrated 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". In 2017 the authors refined these criteria defining ESKOA when (a) two mandatory symptoms (knee pain in the absence of any recent trauma or injury and very short joint stiffness, lasting for less than 10 min, when starting movement) even in the absence of risk factors, or (b) knee pain, and 1 or 2 risk factors or (c) three or more risk factors in the presence of at least one mandatory symptom, with symptoms lasting less than 6 months. Runhaar et al. identified different sets of factors related to the onset of EKOA including questionnaires (WOMAC pain—stairs, WOMAC pain—night, WOMAC function—rising, WOMAC function—descending, WOMAC morning stiffness), sex (female), age, JLT, effusion, BMI and crepitus. Emery et al. included in their suggestions of outcome measures for clinical practice and research settings the use of KOOS and the Intermittent and Constant Assessment of Pain (ICOAP) as patient-reported measures. They also suggested the assessment of the JLT in subjects with new-onset symptoms of knee pain, stiffness, crepitus, or a feeling of 'giving way'. These authors also included in their proposal physical function and modifiable lifestyle-related outcomes, such as the single leg hop test, the 30-second chair sit-to-stand test, the star excursion balance test, and measures of quadriceps strength in the first group, and the assessment of adiposity (through dual-energy X-ray absorptiometry or bioelectrical impedance analysis if available, or BMI other case) and levels of physical activity (through a validated physical activity monitor or a validated questionnaire) in the second one.

Imaging criteria

Luyten et al. 2012 criteria included two imaging aspects: standard radiographs Kellgren and Lawrence (KL) grade 0 or 1 or 2 (osteophytes only), and at least one of two structural criteria (Arthroscopic findings of cartilage lesions (ICRS grade I-IV in at least two compartments or grade II-IV in one compartment with surrounding softening and swelling) or at least two MRI findings demonstrating articular cartilage degeneration, and/or meniscal degeneration, and/or subchondral BMLs: Cartilage morphology WORMS 3–6, Cartilage BLOKS grade 2 and 3, Meniscus BLOKS grade 3 and 4, BMLs WORMS 2 and 3). In the 2018 criteria, the authors simplified this point to KL grade 0–1, gaining more importance the clinical aspects. Mahmoudian et al. proposed to limit these criteria to including only subjects with KL grade 1. Migliore et al. established in 2015 an applicability criterion for the presence of KL grade 0, and maintained it the same in their 2017 version of the criteria. Runhaar et al. included the radiographic factors lateral joint space narrowing (JSN), bony swelling, medial JSN, and patellofemoral JSN for consideration. Emery et al. considered that standardized measures of plain radiography does not reach the same degree of sensitivity to change in knee OA as MRI, and that the radiographic features are associated with late-stage OA and are detected earlier by MRI. Sukerkar et al. advocate the advantages of MRI in both detecting EKOA and in research. Also, Lee et al. argue that MRI is the most precise imaging modality for KOA as it can even differentiate between patients at risk of knee OA and those who are not.

However, they do not consider the use of MRI for routine clinical care appropriate because of its high cost, long scanning times, limited availability and potential risk of over-diagnosis, given the high prevalence of MRI findings in asymptomatic patients. Although, it could be useful in a research setting.

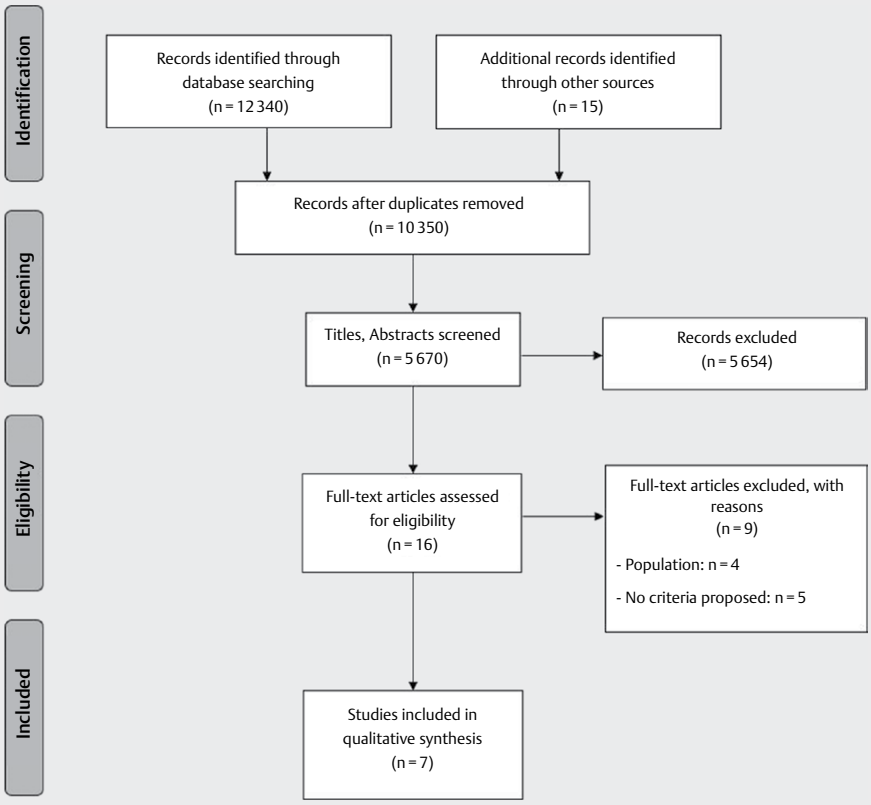
Other criteria

Runhaar et al. also included the hsCRP in one of their models, but they stated it did not add much value. Emery et al. suggested, for the research setting only, the use of biomechanical and biomarkers outcomes, although the last ones would need further validation. The rest of the authors did not include laboratory or biomechanical tests in their criteria.

Similarities and different between criteria

Analyzing the similarities between the different criteria, we find pain is the most constant factor, being included by all the authors, although in different ways, as ▶ **Table 2** summarizes. Questionnaires are present in Luyten's 2018 and Mahmoudian modification as KOOS, and in Runhaar's criteria as WOMAC. Emery et al. also include the KOOS, and add the ICOAP. Crepitus and effusion appear in Mahmoudian and Runhaar's, being the first one also present in Luyten's 2018 and Emery's. Joint stiffness is included in both Migliore's 2015 and 2017, and Emery's proposals, and BMI is present in Migliore's 2015, Runhaar's and Emery's criteria (▶ **Table 2**).

Regarding imaging criteria, all authors except Emery et al. agree in including radiograph features in their criteria, specifically 5 authors include the KL index, although they differ in the grade to consider. Runhaar et al. do not take into account KL as such, but some specific radiographic features. Only Luyten's 2012 include structural criteria through one of two of arthoscopic or MRI findings. Emery et al. only consider the use of MRI for research (▶ **Table 3**). And finally, Runhaar et al. consider a laboratory factor, and Emery et al. include biomarkers and biomechanical outcomes for research, as commented before.



▶ **Fig. 1** Study Flow chart.

Discussion

The evidence presented in this SR shows that there is still lacking a consensus regarding definition and classification of EKOA. In this review there are seven different proposals in scientific literature, and they only agree on including knee pain and radiographic evaluation in their criteria, but they do not even consider the same situations for including these two factors.

The main objective in defining the criteria for EKOA diagnosis is to be able to stop the evolution of this process. In addition, assessing EKOA is mandatory for OA reseach and is important as a clear-cut inclusion criteria for research to identify potential study participants.

However, if we consider that radiological findings should be included in the diagnosis, these are probably of limited use as EKOA progression has most likely already begun and it could be too late to carry out preventive measures for EKOA evolution. Therefore, we need to find a consensus between subjective symptoms such as pain, physical examination findings and a more objective criteria which could add reliability to the diagnosis of EKOA.

Regarding the therapeutic consequences, it is known that the initial treatment of symptoms of EKOA does not differ from other causes of knee pain as it is based on analgesic medication. However, an increasing number of studies suggest more specific treatments for knee pain secondary to OA, such as Chondroitin sulfate of non-animal origin or regenerative medicine [6, 7]. This again underlines the importance of identifying patients whose knee pain is caused by EKOA, as there are many other causes of knee pain where treatment differs. For instance, patellar tendinopathy could be treated with extra corporeal shock wave therapy [13], or knee pain due to anserine bursitis can be treated with aspiration, and corticosteroid injection [14]. In conclusion, for successful treatment of knee pain a specific diagnosis and course of treatment is required.

Clinical features

Experts agree that pain is the primary criteria for the classification of symptomatic EKOA [10, 15–17], despite pain and radiographic severity are not synonymous as there are subsets of OA patients with severe pain and mild radiographic changes, and those with mild or no pain despite severe radiographic changes [18, 19]. Joint line tenderness and crepitus are clinical features easy to examine, in clinical practice as well as for research purposes, and they might be associated with the development of OA in the future, even in the absence of radiological findings of OA [15–18].Effusion has also been considered by some authors, based on a study of the OAI cohort showing the association of joint effusion at baseline with future cartilage volume loss, progression of radiographic OA, and risk of total knee replacement over 4 years [16–18].

A systematic review showed a moderate level of evidence supporting a relationship between obesity (increasing weight, BMI or total body fat mass) and the presence of BMLs in the knee in individuals with OA [20], and total fat mass is also associated with the

presence of BMLs in healthy individuals and with knee cartilage defects [17, 21].

Functional features

It has been suggested that symptoms of EKOA might be not only pain but also the disturbance of ADLs because of a functional impairment [22]. This and the fact that early pre-radiographic OA is associated with intermittent symptoms and adaptive physical behavior support the incorporation of measures of physical function in the clinical evaluation of these patients. But no consensus exists regarding which measures are the most relevant for this end [17], being simple tests such as walking speed, chair rise, and simple muscle strength tests, among others, some of the suggested measures [15, 23].

Decary et al. made a SR on the reliability of physical examination tests for knee disorders. All OA tests demonstrated moderate intra-rater reliability, but tests that reached moderate inter-rater reliability came from low-quality evidence [23]. Due to the challenge of performing objective functional tests in primary care, and this low reliability of physical examination, the use of patient-reported outcomes, such as KOOS, WOMAC and ICOAP, has been suggested to assess functional features [15–18]. These patient-reported outcomes have been the subject of previous reviews in OA population, showing an acceptable reliability, validity, and ability to detect change. Although it should be taken into account that these tests seem to be responsive to change in patients with a variety of conditions, not only knee OA, and their ability to detect change has not been tested for healthy subjects in risk of developing OA or in EKOA [24, 25].

Imaging features

OA is a whole-joint disease involving multiple tissue pathologies. A number of different imaging modalities have been used to characterize the various structural components involved in OA, being radiography, and MRI the most used [17]. Almost all authors agree that radiography remains the primary imaging modality in OA research and in daily clinical practice, despite their known limitations, such as the detection of changes in a late-stage OA and a lower sensitivity than MRI [12, 15, 16, 18].Radiographic features of OA are generally classified using the KL grading system which includes JSN, osteophyte formation, sclerosis and deformity of bony contours [26]. But there is a serious lack of consensus regarding the KL grade to consider for early OA classification. Luyten et al. 2018 considered the variability of scoring of grade 2 across different centers and cohorts, and they agreed that, in the absence of obvious alternatives with significantly better performance, a KL grade of 0 or 1 should be used in the classification criteria [13]. Mahmoudian et al. limited these classification criteria to only subjects with KL grade 1, based on previous reports showing a strong association between this KL grade 1 and an increased risk of developing radiographic knee OA [16]. Migliore et al., for their part, established that any radiographic changes, in symptomatic patients, should be considered as an established disease rather than an early radiographic disease, and exclude the KL > 0 of their criteria [12].

On the other hand, preradiographic joint changes detectable on MRI may predict incident radiographic knee OA by several years, but MRI shows lesions in the tibiofemoral joint in most middle-aged and older people with no evidence of radiographic OA, regardless of pain [16]. Defining what changes are pathological and what changes are part of a normally ageing joint to avoid over-diagnosis because of incidental MRI findings, remains a challenge [17]. Luy-

▶ **Table 1** Main characteristics of the included studies.

Study	Type	Criteria
Luyten FP., 2018	Group of experts	Luyten's criteria for classifying EOA patients: (a) Patient-based questionnaires:Knee Injury and Osteoarthritis Outcome score: 2 out of the 4 KOOS subscales (Pain, Symptoms, Function or Knee-related quality of life) need to score "positive" (≤ 85 %); (b) Patients should present joint line tenderness or crepitus in the clinical examination; (c) X-rays: Kellgren and Lawrence (KL) grade 0–1 standing, weight bearing (at least 2 projections: PA fixed flexion and skyline for patellofemoral OA)
Luyten FP., 2012	Group of experts	1. Pain in the knee (at least two episodes of pain for more than 10 days in the last year) 2. Standard radiographs Kellgren–Lawrence grade 0 or I or II (osteophytes only). 3. 3. At least one of the two following structural criteria ▪ Arthroscopic findings of cartilage lesions (ICRS grade I-IV in at least two compartments or grade II-IV in one compartment with surrounding softening and swelling) ▪ MRI findings demonstrating articular cartilage degeneration and/or meniscal degeneration, and/or subchondral BMLs. At least two: Cartilage morphology WORMS 3–6 Cartilage BLOKS grade 2 and 3 Meniscus BLOKS grade 3 and 4 BMLs WORMS 2 and 3

▶ **Table 1** Continued.

Study	Type	Criteria
Mahmoudian, 2021	Test previous criteria using regression analysis	▪ X-ray examination: limiting inclusion to only subjects with KL grade 1. ▪ Clinical examination: examined the predictive ability of two more variables, the presence of "effusion" and "Heberden's nodes" ▪ Patient-based questionnaires: using a single KOOS4 score (the average of four of the five KOOS subscales: pain, symptoms, ADL and QoL) as well as 5 scores below and above the known threshold (≤ 80, ≤ 85, and ≤ 90)
		Ninety different combinations of the criteria, studying the best predictive performance for clinical and structural progression separately: ▪ Structural progression: the best predictive performance for the criteria set of: KL 1-only, KOOS4 ≤ 90 % and inclusion of (presence of) Heberden's nodes in the combination of clinical examinations (sensitivity of 42.0–43.9 and specificity of 84.0–84.6). (AUCs) for all prediction models ranged from 0.70 to 0.73 [CI, 0.700.75]. ▪ Clinical progression: the best predictive performance was found for KL 0–1, KOOS4 ≤ 80 % and presence of Heberden's nodes in addition to other clinical examinations. (AUCs) for all prediction models ranged from 0.66 to 0.69 [CI, 0.660.71].
Runhaar, 2020	Cohort Knee (CHECK) + Expert diagnosis	Questionnaire and physical examination items at baseline Odds ratio (95 % CI) WOMAC pain—stairs 1.99 (1.36, 2.92) WOMAC pain—night 1.52 (1.06, 2.20) WOMAC function—rising 1.61 (1.08, 2.39) Sex (female) 1.87 (1.20, 2.92) Joint line tenderness 2.36 (1.73, 3.22) Effusion 1.86 (1.09, 3.16) BMI 1.07 (1.03, 1.12) Pooled AUC (pooled S.D.) 0.746 (0.002) Questionnaire, physical examination and radiographic items at baseline Odds ratio (95 % CI) WOMAC pain—stairs 1.98 (1.34, 2.90) WOMAC pain—night 1.53 (1.06, 2.20) WOMAC function—rising 1.58 (1.06, 2.35) Sex (female) 1.81 (1.16, 2.83) Joint line tenderness 2.29 (1.68, 3.13) Effusion 1.85 (1.09, 3.15) BMI 1.07 (1.03, 1.12) Crepitus 1.32 (0.96, 1.81) Lateral JSN 5.32 (1.14, 24.88) Pooled AUC (pooled S.D.) 0.749 (0.002) Questionnaire, physical examination and radiographic items and hsCRP at baseline Odds ratio (95 % CI) WOMAC pain—stairs 2.05 (1.39, 3.03) WOMAC pain—night 1.55 (1.07, 2.24) WOMAC function—rising 1.67 (1.11, 2.49) Sex (female) 1.90 (1.22, 2.97) Joint line tenderness 2.43 (1.78, 3.32) Effusion 1.84 (1.08, 3.13) BMI 1.08 (1.03, 1.13) Lateral JSN 4.66 (1.01, 21.65) hsCRP 0.95 (0.90, 0.99) Pooled AUC (pooled S.D.) 0.756 (0.002

▶ **Table 1** Continued.

Study	Type	Criteria
Migliore, 2015	SR + focus groups + discussion groups + Delphi surveys + face-to-face meetings	**Exclusion criteria:** ▪ presence of generalized pain ▪ active inflammatory joint disease ▪ Kellgren-Lawrence radiologic degree above 0 ▪ any recent trauma or injury of the knee
		Two major signs/symptoms: ▪ knee pain ▪ very short joint stiffness when starting a movement. ▪ Lasting for less than 6 months.
		Applicability criteria: ▪ absence of inflammatory arthritis ▪ age of 50 years or older, or ▪ age of 40 years or older with the presence of at least 1 risk factor ▪ Kellgren Lawrence grade 0
		Definition: ▪ 3 or more symptoms in the absence of risk factors ▪ 2 or more symptoms and 1 risk factor ▪ 2 or more risk factors and 1 or more symptoms Symptom duration of less than 6 months.
		Risk factors: ▪ overweight with a BMI over 25 ▪ family history of OA ▪ previous knee injuries ▪ malalignment ▪ lower limbs dissymmetry ▪ OA in other sites ▪ metabolic syndrome ▪ hypermobility
		Referral criterion for the identification of patients affected by ESKOA: 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.
Migliore, 2017	Expert consensus + review	**Applicability criteria:** ▪ Without active inflammatory arthritis or generalized pain ▪ More than 50 years ▪ More than 40 years if at least one risk factor present ▪ Kellgren and Lawrence = 0 ▪ Absence of any recent trauma or injury
		Definition: ▪ In the absence of risk factors 2 mandatory symptoms are necessary ▪ In the presence of 1 or 2 risk factors, presence of at least mandatory symptom number 1 is necessary ▪ In the presence of three or more risk factors, at least one mandatory symptom is necessary Mandatory (major) symptoms: (1) Any knee pain (in the absence of any recent trauma or injury) i. e. Pain when climbing up and/or down the stairs , Pain increasing with overload (2) Very short joint stiffness (less than 10 min) when starting the movement
		Risk factors: ▪ Overweight (body mass index > 25) ▪ Family history of OA ▪ Previous knee injury ▪ Malalignment ▪ Lower limbs dissymmetry ▪ OA in other sites ▪ Metabolic syndrome ▪ Not being ready to run or walk fast after a period of inactivity
		Symptoms duration: Less than 6 months

▶ **Table 1** Continued.

Study	Type	Criteria
		Referral criterion for the identification of patients affected by ESKOA: Knee pain, in the absence of any recent trauma or injury, with or without very short joint stiffness when starting a movement, with symptoms lasting for less than 6 months
Emery, 2019	Narrative review	**In clinical practice and research settings:** Patient-reported outcomes: ▪ KOOS can be used to measure pain during activity, other symptoms (for example, stiffness, grinding, catching, swelling, knee flexion and extension), function in daily life and during sport and recreational activities, and quality of life across different age and treatment groups. ▪ The Intermittent and Constant Assessment of Pain (ICoAP) questionnaire can be used to evaluate constant and intermittent pain. Clinical features: A clinical assessment including joint line tenderness should be performed in individuals with new-onset symptoms of knee pain, stiffness, crepitus or a feeling of 'giving way'. Physical function outcomes: single leg hop test, the 30-second chair sit-to-stand test, the star excursion balance test and measures of quadriceps strength. Modifiable lifestyle-related outcomes: Adiposity can be assessed by measuring body fat percentage or fat mass index (fat mass in kilograms/height in metres squared) using dual-energy X-ray absorptiometry or bioelectrical impedance analysis if available. BMI is more feasible in the clinical setting, although it has limitations for use in athletes. Levels of physical activity can be assessed using a validated physical activity monitor or a validated questionnaire if objective methods are not available. Nutrition outcomes are not currently suggested for use in routine clinical care; however, the 3-day dietary record provides reliable estimates of nutrient intake.
		In research setting only: Biomechanical outcomes: Measures of biomechanical outcomes require further research and are not currently suggested for use in routine clinical care. However, such outcomes are ideal for informing the underlying mechanisms of OA progression and informing treatment interventions in the research setting.
		Imaging features: The utility of plain radiography in early OA is limited. Although MRI has superior sensitivity to change, has validity in the context of early OA and is hence ideal in the research setting, MRI is not thought appropriate for the routine clinical care setting because of its high cost and potential risk of over-diagnosis.
		Biomarkers: No biomarkers are currently of use in routine clinical care; however, further validation of proteomic, lipidomic and metabolomic tools in the research setting could lead to informative cartilage and synovial fluid profiles and provide important insights into OA progression.

ten et al., who included MRI features in their 2012's criteria, reached the consensus in 2018 that, at present, MRI is not recommended as an aid to identify or define early OA in routine clinical practice or primary care, considering the lack of validated consensus criteria, and the high population prevalence of structural joint changes detected by this method.

Sukerkar et al. also defend the advantages of MRI in detecting EKOA. MRI is recognized for its exceptional cartilage imaging capabilities and its ability to identify initial biochemical alterations related to OA before any visible morphological changes occur [27]. Also, Lee et al. point out MRI notable specifity (82 %) and moderate sensitivity (61 %) in OA detection. Furthermore, MRI can quantify early degenerative cartilage changes in symptomatic patients [28].

However, there is inadequate evidence that MRI is superior to current diagnostic standards of clinical and radiographic evaluation [27, 28].

The arthroscopic evaluation, included in Luyten et al. 2012's criteria, was discarded in their 2018 review of the criteria. The arthroscopic evaluation remains the gold standard for assessing cartilage defects and their reparability, but it cannot determine the cause of the lesion, and is not generally useful in primary care because of its invasive nature [12, 16, 19].

▶ **Table 2** Clinical features of the EOA diagnosis extracted for the included studies.

	Luyten et al. 2012	Luyten et al. 2018	Mahmoudian et al. 2021	Migliore et al. 2015	Migliore et al. 2017	Runhaar et al. 2020	Emery et al. 2019
Pain	Knee pain ≥ 2 episodes > 10 days in the last year	JLT	JLT	Knee pain < 6 months	Knee pain < 10 min, < 6 months	JLT	JLT
Questionnaires	–	KOOS: 2 out of 4 ≤ 85 %	KOOS4 score ≤ 90 % (SP) and ≤ 80 % (CP)	–	–	WOMAC pain—stairs	KOOS
						WOMAC pain—night	ICOAP
						WOMAC function—rising	
						WOMAC function—descending	
						WOMAC morning stiffness	
Crepitus	–	x	x	–	–	x	x
Effusion	–		x	–	–	x	–
Joint stiffness	–	–	–	< 6 months	< 10 min, < 6 months	–	x
BMI	–	–	–	> 25	–	x	x

▶ **Table 3** Imaging features of the EOA diagnosis extracted for the included studies.

	Luyten et al. 2012	Luyten et al. 2018	Mahmoudian et al. 2021	Migliore et al. 2015	Migliore et al. 2017	Runhaar et al. 2020	Emery et al. 2019
Radiograph	KL grade 0–1–2 (osteophytes only)	KL grade 0–1	KL grade 1	KL grade 0	KL grade 0	Lateral JSN	–
						Bony swelling	
						Medial JSN	
						Patellofemoral JSN	
Arthroscopic	ICRS:	–	–	–	–	–	–
	- grade I-IV in ≥ 2 compartments						
	- grade II-IV in 1 compartment with surrounding softening and swelling						
MRI	≥ 2 of:	–	–	–	–	–	In research setting only
	Cartilage morphology WORMS 3–6						
	Cartilage BLOKS grade 2–3						
	Meniscus BLOKS grade 3–4						
	BMLs WORMS 2–3						

In the light of the above analysis of the current criteria, further efforts on the classification of EKOA are still needed, and maybe it should be considered if the classification in this early stage is even possible, given its nature of pre-radiographic stage and the heterogeneity and intermittence of symptoms.

Limitations

There are several limitations to be considered in the interpretation of the results of this systematic review. First, and although a systematic search strategy was followed, the risk of selection bias might still be present. Secondly, the disparity of criteria among the different proposals prevents us from being able to draw solid conclusions about the diagnosis of EKOA. Finally, most of the included studies made proposals based on expert opinion, but few of them evaluated these proposals in experimental studies. Regarding the importance of obtaining objective criteria to confirm EKOA diagnosis, using biomechanical gait parameters could be a point of interest.

Conclusions

There is still lacking a consensus regarding definition and classification of EKOA. Knee pain and radiological assessment seem to be the most commonly used criteria, but due to the variability encountered, it is not possible to reach a consensus on a clear definition and diagnosis of EKOA. Future experimental studies should evaluate these criteria to assess their clinical relevance, as well as to improve their research validity. In order to make reliable diagnoses of EKOA in our daily practice, several criteria could be established, such as pain and patient-reported outcomes.

Conflict of Interest

The authors declare that they have no conflict of interest.

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