Early Knee Osteoarthritis Classification and Clinical Evolution: a Longitudinal Observational Study.

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Research Article

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Abstract

Objective: The main objective was to determine the relevance of the diagnosis of early osteoarthritis (EOA) according to the existing criteria. The secondary objective was to evaluate the clinical progression of healthy subjects (HS) at risk for osteoarthritis and with EOA.

Methods: A cross-sectional longitudinal study was performed. 105 participants were classified through difference diagnosis criteria as EOA patients or HS. Measures of disability, pain and disability self-reported variables were assessed. Two follow-ups were performed, reclassifying all the participants to assess their diagnosis and radiological progression, and evaluating the clinical progression by the self-reported measures.

Results: Following the current diagnostic criteria the participants were divided as EOA (n=54) and HS (n=51). Most of the participants did not present changes in their classification, although some subjects were reclassified as EOA or HS in the follow-ups performed. In relation to clinical progression, the ANOVA did not reveal statistically significant differences in time for pain, disability, or psychological variables neither in the HS nor in the EOA.

Conclusion: Current classification criteria for EOA based on self-reported measures could, make it difficult to clearly diagnose of EOA leading to changes in the classification of patients according to their condition at each particular moment.

Introduction

Osteoarthritis (OA) is one of the most significant causes of disability, and specifically Knee OA (KOA) is one of the main problems for the aged-society in terms of incidence, impairment in the quality of daily living (QOL), and economics [1]. KOA is a degenerative disorder including the pathology of a wide range of tissues and includes structural and qualitative abnormalities interfere with joint function, motor function, and physical activity [2]. KOA is an unavoidable disease for human beings linked to ageing, and therefore the early diagnosis, treatment and prevention should be the main focus for our aged-society [3].

During the last two decades, the term of “early osteoarthritis” emerged in the literature, with scientific papers on early osteoarthritis increasingly published, and with an increasing awareness on the importance in identifying early phases of the degenerative processes in KOA [4].It has been suggested that KOA progression may be prevented or delayed through early diagnosis before the joint is irreversibly destroyed. When OA is treated appropriately at an early stage, therapeutic or exercise treatment may be valid to stop progression or even heal KOA. From the prevention and treatment aspects, a clear definition of early OA (EOA) is paramount for diagnosis [2].

Several years have passed since the definition of EOA were started to be discussed globally, and several diagnostic criteria have been proposed to identify healthy subjects at risk of developing osteoarthritis, as well as to recognize patients with EOA [2,5]. Definition of early OA with a combination of “symptoms” of

joint pain, “signs” such as joint stiffness, tenderness, risk factors, and diagnostic imaging such as radiographs have been proposed [2,5]. However, knee EOA definition and identification is complicated as the signs/symptoms may still be limited and sporadic, only becoming manifest under certain conditions [6,7].

For this reason, the main objective of this study was to determine the relevance of the diagnosis of EOA according to the existing criteria. In addition, the secondary objective was to evaluate the clinical progression of healthy subjects at risk for OA, as well as patients with EOA.

Methods

Study design

A cross-sectional longitudinal study with a non-probabilistic sample was performed. The design followed the international recommendations for Strengthening the Reporting of Observational Studies in Epidemiology [8]. All participants received an explanation of the study procedures, which were planned according to the ethical standards of the Declaration of Helsinki and approved by the Ethics Committee on Drug Research of the University and Polytechnic Hospital La Fe (CEIm La Fe 2017/0147). Written informed consent was obtained from all participants before their inclusion.

Participants

Subjects were recruited and followed at Hospital La Fe, Valencia, Spain, within the H2020 project OACTIVE. The design of the data collection protocol started on November 2017, and the recruitment of participants started on October 2018 and the follow-ups lasted until June 2019. 105 participants were divided into two groups: EOA and healthy subjects (HS) in risk of developing OA.

First, we used 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) [9]. For the secondary analysis, the suggestion with the best predictive performance presented by Mahmoudian et al. was used to reclassify the patients with EOA as follows: (a) Patient-based questionnaires: Knee Injury and Osteoarthritis Outcome (KOOS) 4 score: the average of four of the five KOOS subscale averages: pain, symptoms, ADL and QOL (Pain, Symptoms, Function or Knee-related quality of life) need to score “positive” (≤ 80%); (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)

For HS, the inclusion criteria were (a) Patient age greater than or equal to 40 years; (b) Body mass index greater than or equal to 25; (c) KL 0–1. Exclusion criteria were the same for both groups: (a) Any cognitive

disability that hindered viewing of the audio-visual material; (b) Illiteracy; (c) Comprehension or communication difficulties, (d) Insufficient Spanish language comprehension to follow measurement instructions; (e) Presence of any rheumatic, autoimmune or infectious pathology.

Outcome measures

Descriptive, demographic data and control variables

We included in this section general demographic information included in other big databases, and well-established conventional predictors, such as gender, age, educational level, marital status [10,11]. Unhealthy behaviors such as smoking and drinking alcohol were registered. We also registered hormonal status in women. Finally, we collected weight, height, and calculated BMI.

Pain and disability variables

Pain intensity

Visual Analogue Scale (VAS) was used to measure pain intensity. The VAS is a 100-mm line with two endpoints representing the extreme states “no pain” and “the maximal pain imaginable”. It has been shown to have good retest reliability ($r = 0.94$, $p < .001$) and a minimal detectable change of 15.0-mm [12,13]. Pain intensity was measured both at rest and while walking.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

This instrument is the most extensively used for the functional and symptomatic assessment of patients with osteoarthritis. The WOMAC questionnaire is self-administered and is used to assess patients who progress with hip and/or knee osteoarthritis. The questionnaire is a multidimensional scale composed of 24 items divided into 3 aspects: functional pain (consisting of 5 items), stiffness (2 items) and activities of daily life difficulties (17 items). Higher values mean poorer WOMAC subscales scores of pain and physical function. The Spanish version of the WOMAC questionnaire has adequate psychometric properties, presenting an index of internal consistency (a) of 0.82 for pain and 0.93 for physical function subscales [14].

Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is a knee-specific instrument, developed to assess the patients' opinion about their knee and associated problems. The KOOS evaluates both short-term and long-term consequences of knee injury. It holds 42 items in 5 separately scored subscales: Pain, other Symptoms, Function in daily living (ADL), Function in Sport and Recreation (Sport/Rec), and knee-related Quality of Life (QOL). The psychometric properties and the ICC of the Spanish version have shown acceptable properties for both the total score and the subscales [15].

Psychological variables

Anxiety and depression symptoms

The Spanish version of the Hospital Anxiety and Depression Scale was used to assess the presence of depression and anxiety symptoms in the participants [16]. This scale includes 14 items, which are rated on a 4-point Likert-type scale. Two subscales assessed depression and anxiety independently. The internal consistency is 0.90 for the full scale; 0.84 for the depression subscale; and 0.85 for the anxiety subscale [16].

Procedures

An information sheet with an explanation of the procedure and an informed consent form were given to all the participants. Once the subject had read the information from the study, they were allowed to ask any questions about its nature. The subjects that agreed to participate proceeded to fill in the sociodemographic questionnaire. Self-reported measures of disability, pain and disability self-reported variables were then assessed. This procedure was identical for both groups. The first follow-up was performed between July 2020 and September 2020 and the second between January 2021 and February 2021.

Statistical analysis

The statistical data analysis was performed using statistical SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). The normality of the variables was evaluated by the Shapiro–Wilk test. Descriptive statistics were used to summarize the data for continuous variables and are presented as mean ± standard deviation, 95% confidence interval. A 2-way repeated measures analysis of variance (ANOVA) was conducted to study the effect of the between-participant “group” factor in each of the two categories (EOA and HS) and the within-participant “time” factor, also in each of the three categories (i.e., pre-, post-1 and post-2).

A *post hoc* analysis with Bonferroni correction was performed in the case of significant ANOVA findings for multiple comparisons between variables. Effect sizes (*d*) were calculated according to Cohen’s method, in which the magnitude of the effect was classified as small (0.20–0.49), moderate (0.50–0.79) or large (0.8) [17]. The α level was set at 0.05 for all tests.

Results

A total of 105 participants were included (54 EOA and 51 HS). Some participants abandoned at the first and second follow-up (Fig. 1). All the variables presented a normal distribution. No statistically significant differences were found between groups for any of the primary variables, demographic data, or self-report variables at baseline (Table 1).

Table 1
Descriptive, demographic data and control variables.

	EOA (n = 54)	**HS (n = 51)**	***p* value**
Age (years)	51.85 ± 5.72	50.49 ± 6.21	0.46
BMI (kg/m^2)	27.40 ± 4.19	26.80 ± 3.68	0.43
Gender			0.17
Women	35 (64.8)	35 (68.6)	
Men	19 (35.2)	16 (31.4)	
Marital status			0.95
Single	5	7	
Married	31	30	
Widow	2	2	
Divorced	6	6	
Educational level			0.18
Primary	6	9	
Secondary	20	12	
College	18	24	
Smoking			0.27
No	18	23	
Yes	9	4	
Ex	21	19	
Alcohol			0.65
Never	8	4	
Seldom	13	18	
1–2 times/month	11	9	
1–2 times/week	15	15	
1 time day	2	2	
More than 1 a day	1	0	

Evolution classification

Following the Luyten et al., diagnostic criteria described above, participants were reclassified at each follow-up. In the EOA group, 4 participants at the first follow-up and other 4 participants at the second follow-up presented an improvement that caused their classification to change to HS. On the other hand, 18 healthy participants evolved to EOA at the first follow-up, but 6 of them were again classified as HS at the second follow-up. (Fig. 1). None of the participants progressed to advanced OA.

We reclassified then the patients in each follow-up following the suggestions of Mahmoudian et al. At baseline, the 105 subjects were classified as 44 EOA and 61 HS. In the EOA group, 5 subjects at the first follow-up and 2 at the second follow-up presented an improvement that changed their classification to HS. In addition, 14 HS evolved to EOA at the first follow-up (being 1 of them classified again as HS at the second follow-up), and 2 at the second follow-up (Fig. 2). None of the participants progressed to advanced OA.

Clinical progression

Pain intensity

The ANOVA did not reveal statistically significant changes in VAS rest measurement during time ($F = 1.89$, $p = 0.16$, $\eta^2 = 0.79$), showing no differences between baseline, follow-up 1 and follow-up 2 for EOA or HS groups. Similar results were found using Mahmoudian et al. classification (Table 2).

Table 2
Clinical progression of OA patients

	Baseline	Follow-up 1	Follow-up 2
VAS Rest			
Luyten et al.,	2.04 ± 1.56	1.29 ± 2.05	2.21 ± 2.67
Mahmoudian et al.,	1.88 ± 2.31	1.50 ± 2.06	2.44 ± 2.78
VAS Walking			
Luyten et al.,	2.67 ± 2.73	2.42 ± 2.02	2.46 ± 2.40
Mahmoudian et al.,	2.69 ± 2.77	2.94 ± 2.11	2.63 ± 2.55
WOMAC			
Luyten et al.,	18.55 ± 10.15	16.56 ± 15.66	22.47 ± 17.23
Mahmoudian et al.,	17.62 ± 9.47	22.04 ± 16.75	25.26 ± 18.75
KOOS Pain			
Luyten et al.,	80.48 ± 13.44	78.62 ± 16.24	80.52 ± 19.97
Mahmoudian et al.,	86.17 ± 14.31	75.08 ± 19.40	74.25 ± 23.42
KOOS Symptoms			
Luyten et al.,	85.00 ± 12.71	79.62 ± 15.81	83.61 ± 12.45
Mahmoudian et al.,	85.92 ± 12.41	74.24 ± 16.58	77.67 ± 12.07
KOOS ADL			
Luyten et al.,	83.29 ± 16.94	79.62 ± 18.53	81.95 ± 18.67
Mahmoudian et al.,	86.83 ± 18.66	73.67 ± 21.62	73.92 ± 20.91
KOOS QQL			
Luyten et al.,	62.29 ± 26.56	51.86 ± 20.45	61.33 ± 24.59
Mahmoudian et al.,	65.17 ± 32.80	45.42 ± 18.64	50.08 ± 22.37
KOOS Sport			
Luyten et al.,	60.71 ± 30.83	55.71 ± 29.43	57.61 ± 26.77
Mahmoudian et al.,	58.75 ± 37.54	44.58 ± 30.63	46.25 ± 24.23
HAD Anxiety			
Luyten et al.,	5.42 ± 4.14	4.17 ± 3.81	5.29 ± 4.60

	Baseline	Follow-up 1	Follow-up 2
Mahmoudian et al.,	4.94 ± 3.35	4.75 ± 2.46	4.88 ± 3.20
HAD Depression			
Luyten et al.,	3.38 ± 3.07	3.13 ± 2.91	2.96 ± 3.32
Mahmoudian et al.,	2.81 ± 2.34	3.31 ± 2.85	2.50 ± 2.68

Table 3
Clinical progression of healthy subjects in risk to develop OA.

	Baseline	Follow-up 1	Follow-up 2
VAS Rest			
Luyten et al.,	0.1 ± 0.29	0.74 ± 1.36	0.91 ± 1.41
Mahmoudian et al.,	0.68 ± 1.85	0.77 ± 1.54	1.13 ± 1.77
VAS Walking			
Luyten et al.,	0.52 ± 1.76	1.3 ± 2.01	1.52 ± 1.86
Mahmoudian et al.,	1.06 ± 2.23	1.32 ± 1.85	1.68 ± 1.92
WOMAC			
Luyten et al.,	5.86 ± 4.3	9.57 ± 8.20	12.30 ± 10.30
Mahmoudian et al.,	9.32 ± 8.89	12.44 ± 8.45	12.77 ± 10.42
KOOS Pain			
Luyten et al.,	88.80 ± 13.05	87.60 ± 9.65	88.96 ± 12.28
Mahmoudian et al.,	84.10 ± 14.31	86.90 ± 9.31	87.47 ± 11.61
KOOS Symptoms			
Luyten et al.,	90.24 ± 10.83	91.80 ± 6.79	92.60 ± 8.80
Mahmoudian et al.,	88.20 ± 12.20	90.53 ± 7.84	91.30 ± 8.51
KOOS ADL			
Luyten et al.,	89.88 ± 14.37	90.32 ± 7.84	92.01 ± 9.78
Mahmoudian et al.,	86.13 ± 15.54	89.83 ± 7.66	91.20 ± 9.06
KOOS QQL			
Luyten et al.,	76.88 ± 22.29	75.12 ± 20.62	79.64 ± 21.88
Mahmoudian et al.,	71.57 ± 22.72	71.97 ± 20.53	75.93 ± 20.81
KOOS Sport			
Luyten et al.,	71.40 ± 26.71	71.60 ± 22.16	72.60 ± 23.29
Mahmoudian et al.,	67.67 ± 25.72	71.33 ± 21.01	69.83 ± 22.03
HAD Anxiety			

	Baseline	Follow-up 1	Follow-up 2
Luyten et al.,	2.83 ± 3.34	3.04 ± 3.34	2.87 ± 2.79
Mahmoudian et al.,	3.74 ± 4.21	3.45 ± 4.09	3.71 ± 4.31
HAD Depression			
Luyten et al.,	1.17 ± 2.05	1.52 ± 2.27	1.26 ± 1.18
Mahmoudian et al.,	2.03 ± 3.04	1.84 ± 2.54	1.94 ± 2.62

The ANOVA did not reveal statistically significant changes in VAS walking measurement during time (F = 0.051, p = 0.61, η^2 = 0.02), showing no differences between baseline, follow-up 1 and follow-up 2 for EOA or HS groups. Similar results were found using Mahmoudian et al. classification (Table 2).

Disability

The ANOVA revealed statistically significant changes in WOMAC measurement during time (F = 3.10, p = 0.048, η^2 = 0.181) showing differences between baseline and follow-up 2 for EOA and HS groups. Similar results were found using Mahmoudian et al. classification (Table 2).

Psychological variables

The ANOVA did not reveal statistically significant changes in HAD Anxiety measurement during time (F = 0.14, p = 0.86, η^2 = 0.01) and HAD Depression (F = 0.66, p = 0.52, η^2 = 0.02) showing no differences between baseline, follow-up 1 and follow-up 2 for OA or HS groups.

Finally, the ANOVA did not reveal statistically significant changes in any KOOS subscales (pain, symptoms, QQL, ADL and sport subscales) measurements during time for EOA or HS groups. Similar results were found using Mahmoudian et al. classification (Table 2).

Discussion

Diagnosis criteria of EOA

With the objective to evaluate the clinical progression of our patients, we used Luyten's criteria to classify them in HS or EOA. These classification criteria are intended only for research, as the authors declare, and have shown a specificity of 76.5% for detection of clinical progression [9,18].

At present, very few studies have evaluated the progression of patients with knee EOA. In this regard, we found some HS meeting criteria for EOA diagnosis in a moment of time that, afterwards, scored as HS again; also, we found subjects classified as EOA at the beginning that scored as HS in one or both follow-

ups. It should be noted that these criteria are mainly based on clinical condition, so this finding made us wonder if it would be possible that they were not actually detecting changes related to the onset of OA, but knee pain due to other reasons, leading to a misdiagnosis.

Recently, Mahmoudian et al., 2020, evaluated the classification criteria for EOA, trying to find some aspects that could refine the diagnosis [18]. Their results showed how these criteria can contribute to the prediction of structural and clinical progression (sensitivity of 29% and 43.5%, specificity of 73.1% and 76.5%, respectively). In addition, these authors noted that for detecting structural evolution, a K&L grade I could be a better predictor. In relation to clinical evolution, it seems that adding more clinical aspects such as effusion or Heberden´s nodes could increase the predictive value of the criteria, emphasizing the importance of physical examination, and they found the best predictive performance for KOOS4 ≤ 80% [18]. We analyzed our sample again considering these suggestions, mainly the KOOS4 ≤ 80%, as we had a very small sample of subjects with K&L I, and none of our subjects had Heberden's nodes. After applying these modifications, we still found some changes from EOA to HS groups at the follow-ups, but they were fewer than initially.

Clinical progression of OA

Our data are in agreement with previous results in the field of musculoskeletal pain and specifically in OA [19,20]. In this regard, it has been found that patients with OA showed fluctuations and exacerbations that are directly related to a linear progression of the disease or to the radiographic development of OA [21,22].

It is possible that EOA may not be progressive for some time, and it is possible that the clinical course depends on individual epigenetic, neurophysiological or metabolic factors, which need to be studied further [23,24]. In addition, there is also no impairment of functional capacity due to pain or anticipation of pain, something that has been previously suggested [25,26]. In fact, our results also show fluctuations in the functional status of OA patients, in agreement with some previous studies [27]. In this sense, our study shows new data about the clinical evolution of these patients diagnosed with EOA and HS, which could contribute to refine the models and create a gold standard in the diagnosis of EOA. Future studies with a longer period of follow-up should address this question and determine if there are indeed clinical variables that could determine EOA.

Limitations

This study has some limitations that must be considered. The cross-sectional nature of this study makes it impossible to establish causality. In addition, there is some variability in follow-up and a longer time is needed to evaluate the progression of these patients and confirm our findings. Also, as we describe in discussion, we are using the existing classification criteria to divide our patients in HS and EOA, so we can evaluate the clinical progression, but due to the variability in this classification through time, we can not be sure this classification is correct.

Conclusions

The results of the present study suggest that the current classification criteria for EOA based on self-reported measures could, make it difficult to clearly diagnose OAE, leading to changes in the classification of patients according to their condition at each particular moment. Further work on the classification criteria is still needed.

Secondarily, our results suggest that HS at risk for OA and patients diagnosed as EOA with the current classification criteria did not significantly worsen their pain data, disability, and psychological variables.

Declarations

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Figures

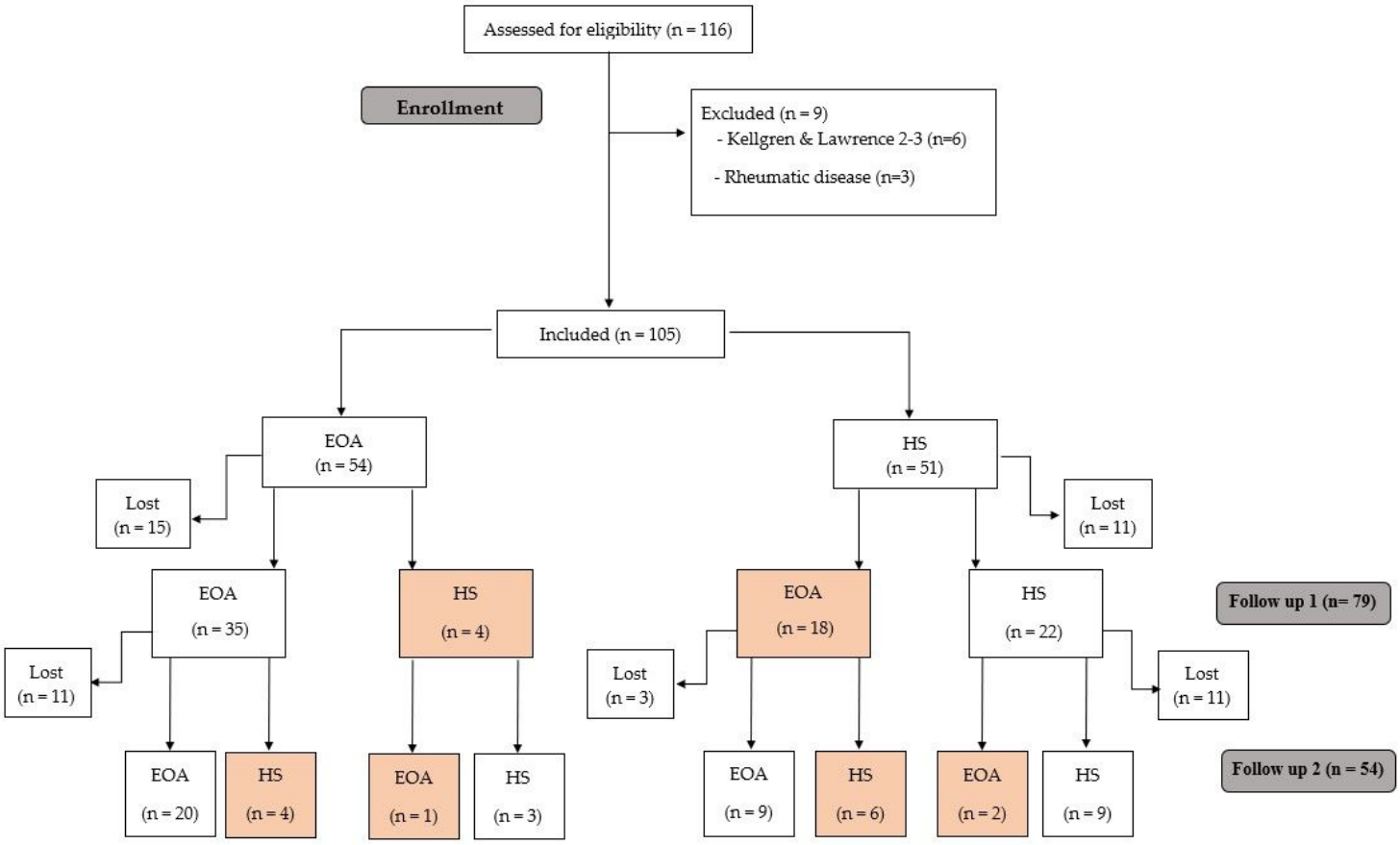

Figure 1

Study flow chart following Luyten et al., criteria.

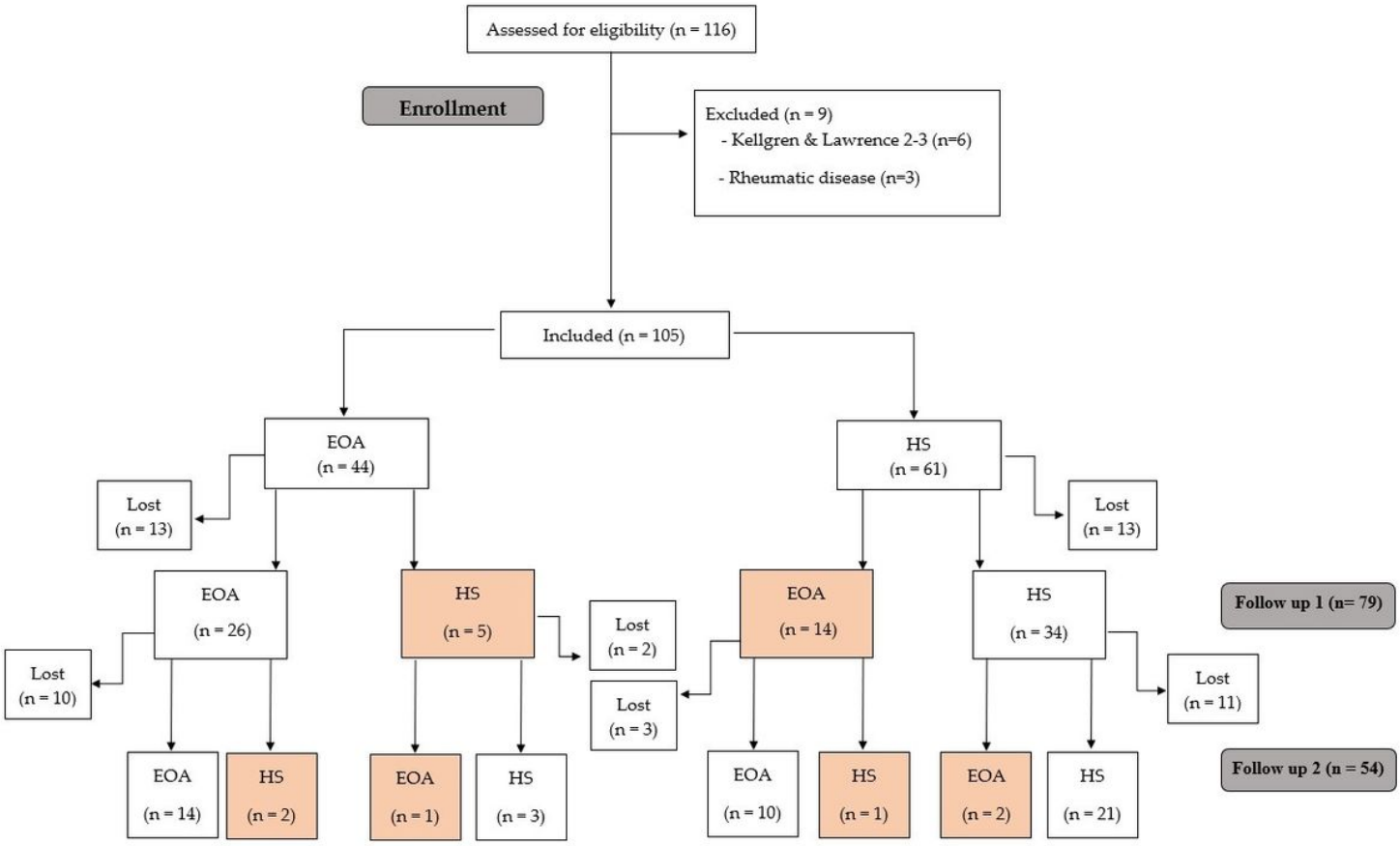

Figure 2

Study flow chart following Mahmoudian et al., criteria.