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Clinical phenotypes in patients with knee osteoarthritis: a study in the Amsterdam osteoarthritis cohort

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SUMMARY

Objective: To identify and validate previously established phenotypes of knee osteoarthritis (OA) based on similarities in clinical patient characteristics.
Methods: Knee OA patients ($N = 551$) from the Amsterdam OA (AMS-OA) cohort provided data. Four clinical patient characteristics were assessed: upper leg muscle strength, body mass index (BMI), radiographic severity (Kellgren/Lawrence [KL] grade), and depressive mood (the Hospital Anxiety and Depression Scale [HADS] questionnaire). Cluster analysis was performed to identify the optimal number of phenotypes. Differences in clinical characteristics between the phenotypes were analyzed with ANOVA.
Results: Cluster analysis identified five phenotypes of knee OA patients: “minimal joint disease phenotype”, “strong muscle strength phenotype”, “severe radiographic OA phenotype”, “obese phenotype”, and “depressive mood phenotype”.
Conclusions: Among patients with knee OA, five phenotypes were identified based on four clinical characteristics. To a high degree, the results are a replication of earlier findings in the OA Initiative, indicating that these five phenotypes seem a stable, valid, and clinically relevant finding.

Introduction

Knee osteoarthritis (OA) is a heterogeneous disease with distinct characteristics during the various stages of disease progression[1,2]. It has been hypothesized that knee OA consists of different subgroups or phenotypes[3]. To identify subgroups or phenotypes, several approaches are available, focusing on etiological and risk factors (metabolic, traumatic, inflammatory, and subchondral bone turnover)[4], focusing on genetic factors[5], or focusing on clinical characteristics[6]. The latter approach seems particularly relevant, as the ultimate goal of identifying clinical phenotypes is that clinicians can identify and manage subgroups of knee OA patients in their practices[6]. There is, however, a paucity of studies identifying clinical, homogenous knee OA subgroups. Most studies focused on a single clinical characteristics such as pain[7], knee malalignment[8], and race and gender[9]. Only one recent study from our own group based on data of the OA Initiative (OAI) included several clinical characteristics at the same time[10].

In the last-mentioned study, five clinically relevant phenotypes were identified with data from the open-population-based “progression subcohort” of the OAI cohort[10]. These five phenotypes were “minimal joint disease phenotype”, “strong muscle phenotype”, “non-obese and weak muscle phenotype”, “obese and weak muscle phenotype”, and “depressive phenotype”. These phenotypes were based on four patient characteristics i.e., upper leg muscle strength, body mass index (BMI), radiographic OA, and depressive mood. The four clinical characteristics are regularly

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assessed and relevant to clinical practice[6], and have a major impact on disease progression and clinical outcome[6]. In clinical practice, patients differ highly on these characteristics, necessary for cluster analysis[11].

For reasons of robustness, there is a need to determine whether the five phenotypes can be replicated in another sample. The present study aimed to identify and validate previously established phenotypes of knee OA based on similarities in clinical patient characteristics, i.e., upper leg muscle strength, BMI, radiographic OA, and depressive mood in patients with knee OA from a clinical population.

Methods

Patients and methods

The Amsterdam OA (AMS-OA) cohort contains patients with OA of the knee and/or hip who have been referred to a secondary care outpatient rehabilitation center (Reade, Center for Rehabilitation and Rheumatology, Amsterdam, the Netherlands)[12]. The examination protocol involves assessments by rheumatologists, radiologists, and rehabilitation physicians. Demographic, clinical, radiographic, biomechanical, and psychosocial factors related to OA were assessed. Total knee replacement, rheumatoid arthritis, or any other form of inflammatory arthritis (i.e., crystal arthropathy or septic arthritis) were exclusion criteria. In the present study, 551 patients from the AMS-OA cohort with a unilateral or bilateral diagnosis of knee OA according to the American College of Rheumatology (ACR) were included[13]. The group of patients was defined as established knee OA due to the combination of confirmed diagnosis of knee OA according to the ACR criteria and the presence of knee OA related symptoms making a visit for secondary care necessary. All patients provided written, informed consent according to the Declaration of Helsinki. The study was approved by the Slotervaart Hospital/Reade Institutional Review Board.

Clustering variables

Muscle strength was used in analyses as the mean score of left and right lower limb isokinetic muscle strength (quadriceps and hamstring strength in Newton meters), because the correlation between left and right muscle strength for extension and flexion muscle strength was $r = .64$ and $r = .72$ ($P < .001$), respectively[14]. BMI was calculated by dividing mass (in kilograms) by squared height (in meters). *Radiographic severity* of knee OA (ROA) was scored by an overall severity grade (Kellgren and Lawrence grade (KL))[15] ranging from 0 to 4, based on weight-bearing fixed-flexion knee radiograph[16]. The inter-rater agreement of scoring the radiographic features was good[17]. In analysis the most severely damaged knee was used. *Depressive mood* was based on the Hospital Anxiety and Depression Scale (HADS) questionnaire, which is one of the most frequently used questionnaires for depressive mood experiences with very strong psychometric properties[18]. The 7-item subscale measures depressive mood on a 4-point response scale (from 0, no symptoms, to 3, maximum symptoms), with possible scores for the subscale ranging from 0 to 21. The HADS is a valid and reliable questionnaire for detecting mood disorder in people with OA[19].

Statistical analysis

Identification of subgroups

K-means (or its equivalent “non-hierarchical”) cluster analysis was used to identify homogeneous subgroups of knee OA patients (i.e., phenotypes). Cluster analysis is a data analysis technique aimed at grouping entities on the basis of their similarity with respect to selected variables. Members of the resulting groups are as similar as possible to others within their group (high within-group homogeneity) and as different as possible to those in other groups (low between-group homogeneity). This analysis implicates that members are permitted to be member of a single group (i.e., phenotype)[20]. The following clinical characteristics were included in cluster analysis: mean of left and right lower limb muscle strength (quadriceps and hamstring strength), BMI, KL grade of the most severely damaged knee, and score on the HADS questionnaire (depressive mood) (see Table I for more information). Since cluster analysis techniques are sensitive to outliers, outlier cases should be identified and removed from the dataset before cluster analysis[21]. The FASTCLUS procedure of the SAS package[22] was used. An estimation of the optimal number of clusters (between three and eight clusters) was based on the Calinski and Harabasz pseudo F-statistic[23], which is the best performing clustering criterion according to Milligan and Cooper[24]. Additionally, a second clustering criterion was used, as recommended by Milligan and Cooper[24]. This second criterion was the Beale's F-ratio, which tests the hypothesis of the existence of an additional cluster vs the already detected clusters[25]. The addition of one cluster in the cluster solution should continue until the hypothesis – tested by Beale's F ratio – was rejected[25]. This analysis was continued till the highest pseudo F value was found, considering that this was the most adequate number of clusters.

Spearman's correlation coefficients were computed to examine the bivariate associations between the four clinical characteristics: muscle strength, KL grade, BMI and HADS scores. Differences of muscle strength, KL grade, BMI, and HADS scores between the clusters (phenotypes) were evaluated with analysis of variance (ANOVA) and a Bonferroni post-hoc analysis.

Results

No outliers were found and therefore a total of 551 patients were included in the study. The characteristics of the study group are displayed in Table I. The mean age was 61.7 ($SD = 8.8$) years and 68 % of the patients were women. Knee symptoms were present for more than 5 years in 72% of the patients. Radiographic evidence of knee OA (i.e., KL grade ≥ 2) was found in 63% of the patients. Mean muscle strength (Nm) and HADS-depressive mood were 70.26 ($SD = 35.81$) and 4.81 ($SD = 3.47$), respectively. The mean values of

Table I
Characteristics of study group (mean and standard deviation, unless otherwise stated)

Characteristic	Mean (SD)
N	551
Age, years	61.7 (8.8)
Gender (% female)	68
Duration of knee symptoms:	
Less than 5 years (%)	28
More than 5 years (%)	72
Bilateral knee pain (% yes)	67
Co-occurrence of hip pain (% yes)	15
Number of comorbidities (median and IQR)	2 (1–3)
Muscle strength, Nm	70.3 (35.8)
Body mass index, kg/m^2	30.4 (6.2)
Obesity (BMI $\geq$ 30.0) (%)	46
Radiographic knee OA:	
K/L score 0 (%)	5
K/L score 1 (%)	32
K/L score 2 (%)	27
K/L score 3 (%)	22
K/L score 4 (%)	14
HADS depressive mood score	4.8 (3.5)

IQR = interquartile range.

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