Observational Study

Relationship between biological factors and catastrophizing and clinical outcomes for female patients with knee osteoarthritis

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Abstract

AIM

To investigate the correlations between clinical outcomes and biopsychological variables in female patients with knee osteoarthritis (OA).

METHODS

Seventy-seven patients with symptomatic knee OA were enrolled in this study. We investigated the age, body mass index (BMI), pain catastrophizing scale (PCS) and radiographic severity of bilateral knees using a Kellgren-Lawrence (K-L) grading system of the subjects. Subsequently, a multiple linear regression was conducted

to determine which variables best correlated with main outcomes of knee OA, which were pain severity, moving capacity by measuring timed-up-and-go test and Japanese Knee Osteoarthritis Measure (JKOM).

RESULTS
We found that the significant contributor to pain severity was PCS (β = 0.555) and BMI (β = 0.239), to moving capacity was K-L grade (β = 0.520) and to PCS (β = 0.313), and to a JKOM score was PCS (β = 0.485) and K-L grade (β = 0.421), respectively.

CONCLUSION
The results suggest that pain catastrophizing as well as biological factors were associated with clinical outcomes in female patients with knee OA, irrespective of radiographic severity.

Key words: Osteoarthritis; Pain catastrophizing; Knee pain; Physical function; Japanese Knee Osteoarthritis Measure

Core tip: Plenty of previous studies have focused on biological factors such as aging, gender, body mass index, ethnicity and history of knee injury for knee pain in cases where there was a discordant relationship between radiographic severity and symptoms in knee osteoarthritis (OA). However, in the present study, we found that pain catastrophizing thought was highly associated with knee-related clinical outcomes, irrespective of radiographic severity, for female patients with knee OA, especially pain severity and quality of life.

INTRODUCTION

Knee osteoarthritis (OA) is a common problem causing knee pain and functional decline and disabilities in the elderly[1-3]. Although there is a widespread belief of inconsistency between clinical symptoms and radiographic disease severity[4], recent studies have revealed that knee symptoms were associated with not only disease severity but also female gender, aging, overweight and psychological factors[5-11], in spite of the fact that these independent variables are sometimes associated with each other.

To establish comprehensive outcome measures relevant to the disabilities, the OMERACT conference first convened in 1992 (OMERACT was originally an acronym for Outcome Measures in RA Clinical Trials, now it represents the more inclusive scope of "Outcome Measures in Rheumatology"). Several years later, a key objective of the OMERACT III conference was to establish a core set of outcome measures for OA[12]. A consensus was reached by at least 90% of expert participants that the following 4 domains should be evaluated for knee, hip, and hand OA: Pain, physical function, patient global assessment, and joint imaging.

On the other hand, although a number of previous studies have revealed that radiographic disease severity, female gender, aging, being overweight and psychological factors such as catastrophizing thought were related to knee OA symptoms, it still remains unclear which variables best correlated with clinical disability.

It has been established that women are more sensitive to pain than men[13], and more likely to complain of chronic musculoskeletal burden compared to men[14]. Moreover, it has been suggested that women reported greater levels of catastrophizing with more painful symptoms than men[15]. Recently, pain catastrophizing has been studied in patients suffering from knee OA[11,16], and Somers *et al*[16] have reported that pain catastrophizing rather than radiographic severity appears to be an important variable in understanding pain, disability, and physical function in overweight/obese patients with knee OA. Therefore, it would be important to understand the lack of relationships between the outcomes of knee OA and related variables for female patients with knee OA. Hence, the aim of the present study was to address the correlations between each of the clinical outcomes or between each outcome and relevant variables in knee OA patients with chronic pain or stiffness, limited to female participants using bivariate correlation and multivariate regression analysis. We speculated that pain catastrophizing rather than radiographic severity was a more influential factor for predicting the severity of knee pain, functional capacity, and quality of life for female patients with knee OA.

MATERIALS AND METHODS

Subjects
A previous study found relationships (pr^2 = 0.10) between pain catastrophizing and pain severity of knee OA patients[16]. Based on this finding, the sample size for a power of 0.80 with two-tailed alpha at a 0.05 significance level to run a multivariate regression for seven predictors required a minimum of 74 subjects. After obtaining approval from the ethics committee, we announced research related to knee symptoms in female elderly patients 50 years of age or older from February to August 2015 and recruited participants who were interested in this study through physical-fitness center or orthopedic clinic located within Aichi Medical University. Before investigating their status, each subject was fully informed by the investigator 1: that content of this study and 2: that the personal information of the subject would be kept confidential.

Ninety-five people with chronic knee symptoms were interested in the study and they received a knee X-ray to confirm if they were eligible for the study. The eligibility criteria for this study were as follows: (1) female with knee symptoms persisting for at least three months or more; (2) 50 years old or older; (3) radiographic knee OA with a face of more than grade-2 according to the Kellgren-Lawrence (K-L) grading system on at least a unilateral knee, because most previous studies used grade-2 as a main defining feature for radiographic knee OA; and excluded (4) presence or history of major neurological disorders such as stroke and Parkinson's disease, and history of total knee arthroplasty (TKA).

In the end, we enrolled 77 female patients with knee pain in this study.

Data collection
Demographical background: First, we investigated the age, and body mass index (BMI) of the subjects. The BMI was calculated from weight and height measurements using the formula BMI = weight (in kg) divided by height (in m^{-2}).

The K-L grading system
After investigation of the subjects' demographic background (age, BMI), they underwent a radiographic examination of both knees by posterior-anterior view in the fixed standing position by a radiological technician. To avoid assessment error, all radiographs were assessed by two orthopedic physicians together (Tatsunori Ikemoto and Machiko Akao) according to the K-L grading system that uses the following grades: 0, normal; 1, possible osteophytes only; 2, definite osteophytes and possible joint space narrowing; 3, moderate osteophytes and/or definite joint space narrowing; and 4, large osteophytes, severe joint space narrowing, and/or bony sclerosis[17].

Previous studies related to knee OA have assessed either side, although OA often affects bilateral knees[18] and this bilaterality may amplify the magnitude of symptoms[19]. Firstly, we assigned the subjects into either a unilateral group or a bilateral group according to whether radiographic knee OA was observed in one side or both sides. Subsequently, we used the total score of both sides (*e.g.*, if the right side was grade-2 and the left side was grade-1 then the total was 3) as radiographic severity because of the possibility that they have a substantial influence on the outcome measures despite asymptomatic knees[20].

Japanese Knee Osteoarthritis Measure
The Japanese Knee Osteoarthritis Measure (JKOM) was developed to reflect the specifics of the Japanese cultural lifestyle, which is characterized by bending to the floor or standing up[21]. The validity and reliability of JKOM has been examined by comparing it with the widely accepted QOL measure, the Western Ontario and McMaster University osteoarthritis index (WOMAC) and the 36-item short-form health survey (SF-36). The JKOM consists

of a pain rating based on a visual analogue scale (VAS) which was a 100-mm line with "no pain" at one end and "worst pain possible" at the other end and scores for a subscale of four symptoms based on a disease-specific questionnaire addressing four dimensions: "Pain and stiffness in knee", "condition in daily life", "general activities" and "health conditions", with 8, 10, 5 and 2 items, respectively. Each item is rated on an ordinal scale from 0-4, with higher scores indicating a symptom or medical condition of higher severity. The four symptom subscales can be scored separately or combined to represent the aggregated total symptoms. Lower JKOM scores indicate better QOL. We assessed the pain severity of participants in accordance with the VAS score.

Pain catastrophizing
Catastrophizing was assessed using the Pain Catastrophizing Scale (PCS). The PCS consists of 13 items that describe an individual's specific beliefs about their pain and evaluates catastrophic thinking about pain[22].

Participants responded to each item using a Likert-type scale from 0 ("not at all") to 4 ("all the time"). The scale provides a total score and scores on 3 subscales: Rumination (4 items), magnification (3 items), and helplessness (6 items)[23]. This scale is well known for its reliability and validity in the Japanese version[24]. Although catastrophizing is known to be a cognitive distortion closely linked to anxiety and depression[22], we confirmed that no subjects took anti-anxiety drugs or anti-depressants in the present study.

The timed up and go test
Timed up and go test (TUG) measures the time it takes a subject to stand up from a chair (46 cm seat height from the ground), walk a distance of 3 m, turn and walk back to the chair, and sit down[25]. All subjects performed two trials and the superior time was used. TUG was originally established as an objective measure of physical function in the elderly population. It is also used to assess the risk of falls in older adults[26].

Statistical analysis
Data were presented as mean and standard deviation and median because each variable resulted in not only parametric but also non-parametric distributions.

We assumed that there were three outcomes, which were pain rating, TUG, and the JKOM score as essential measures for knee OA based on the OMERACT Ⅲ description. Firstly, we compared the differences in the scores of each outcome between the unilateral group and bilateral group by using the Mann-Whitney *U* test.

Subsequently, we also determined the four independent variables: Age, BMI, K-L grade, and PCS score, which were assumed to influence each clinical outcome. The relationship between each of the variables was analyzed using Spearman's correlation for bivariate regression analysis. Further analysis using a stepwise multiple linear regression was conducted to determine
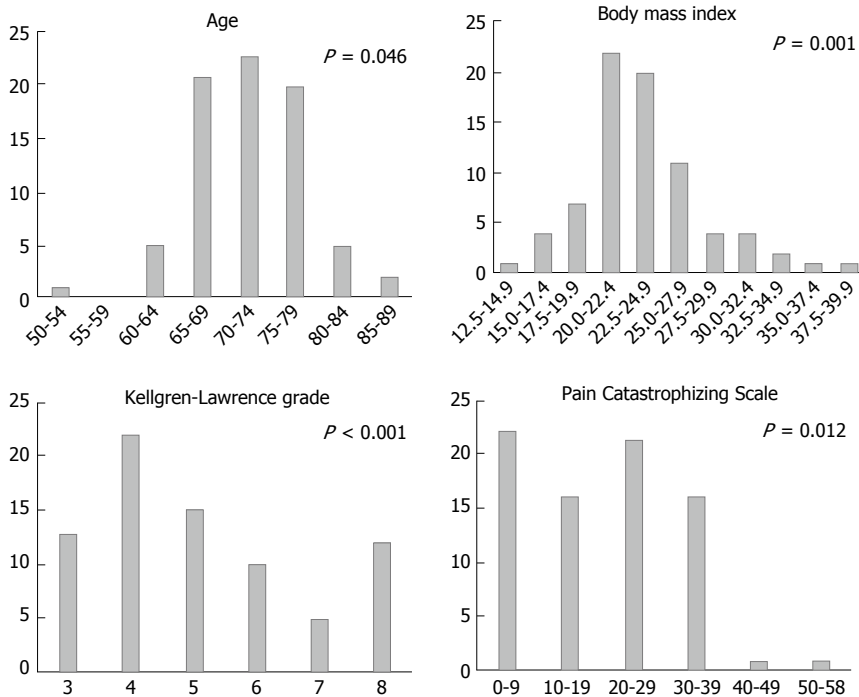
Figure 1 Distributions of the scores of each independent variable. Normality of each distribution was assessed by a Shapiro-Wilk test. The *P*-value within each variable indicates non-parametric distribution (*P* < 0.05).

Table 1 Characteristics of study subjects	
Variables	***n* = 77**
Age (yr)	72 (50-86)
BMI (kg/m^2)	23.7 (14.5-41.7)
K-L grade (Rt + Lt)	5 (3-8)
PCS	20 (0-50)
Pain rating (VAS)	26 (0-99)
TUG (s)	6.0 (4.1-16.5)
JKOM	18 (1-81)

Data are shown as the median (range). BMI: Body mass index; K-L grade: Kellgren-Lawrence grading system; VAS: Visual analogue scale; TUG: Timed up and go test; JKOM: Japanese Knee Osteoarthritis Measure; PCS: Pain Catastrophizing Scale.

Table 2 Comparison of each outcome between unilateral and bilateral knee osteoarthritis			
Variables	**Unilateral (*n* = 17)**	**Bilateral (*n* = 60)**	***P*-value**
Pain rating (VAS)	24 (0-95)	26 (0-99)	0.51
TUG (s)	5.5 (4.4-7.2)	6.3 (4.1-16.5)	0.02
JKOM	13 (2-35)	18 (1-81)	0.23

Data are shown as the median (range). The Mann-Whitney *U* test was used to compare differences between two groups. VAS: Visual analogue scale; TUG: Timed up and go test; JKOM: Japanese Knee Osteoarthritis Measure.

which independent variables best correlated with the severity of each outcome measure.

For a priori power analysis, we used G*power3 software[27] to determine sample size for study destination. Bivariate correlation analysis and multivariate regression analysis were performed with SPSS software (version 20.0J; SPSS Inc., Chicago, IL, United States). Differences were always considered significant at a level of *P* < 0.05.

RESULTS

The subject characteristics are presented in Table 1 and Figure 1 shows the distributions of the scores of each independent variable.

The subjects were assigned as follow: 17 subjects (22%) in the unilateral group; and 60 subjects (78%) in the bilateral group. Comparisons of the dichotomous groups revealed that there were no significant differences

in severity of knee pain and JKOM scores between the unilateral group and bilateral group, while TUG was significantly faster in the unilateral group than in the bilateral group (Table 2).

The correlation coefficients (ρ) between each of the clinical outcomes or between each outcome and relevant variables using a bivariate regression analysis are shown in Table 3. Each outcome measure was significantly associated with each other. The pain rating showed significant positive correlations with K-L grade and PCS. TUG showed significant positive correlations with BMI, K-L grade, and PCS. The JKOM score showed a significant positive correlation with K-L grade and PCS.

In addition, the results of a stepwise multiple linear regression analysis for each outcome measure are shown in Table 4. We found that the significant contributor to a pain rating was PCS (β = 0.555) and BMI (β = 0.239), to TUG was K-L grade (β = 0.520) and PCS (β = 0.313), and to a JKOM score was PCS (β = 0.485) and K-L grade (β = 0.421), respectively.

Table 3	Spearman's correlation coefficients between each variable						
	Age	BMI	K-L grade	PCS	Pain rating	TUG	JKOM
Age	1.000	-0.144	0.100	-0.023	-0.079	0.170	-0.017
BMI		1.000	0.322[b]	0.084	0.212	0.257[a]	0.046
K-L grade			1.000	0.182[d]	0.281[a]	0.587[d]	0.467[d]
PCS				1.000	0.574[d]	0.404[d]	0.594[d]
Pain rating					1.000	0.487[d]	0.721[d]
TUG						1.000	0.588[d]
JKOM							1.000

Value (ρ): Correlation coefficient. Small letters show the statistical significance: [a]$P < 0.05$, [b]$P < 0.01$, [d]$P < 0.001$. BMI: Body mass index; K-L grade: Kellgren-Lawrence grading system; PCS: Pain Catastrophizing Scale; TUG: Timed up and go test; JKOM: Japanese Knee Osteoarthritis Measure.

DISCUSSION

In the present study, although there is some disagreement regarding our speculation, pain catastrophizing has been highly associated with knee-related clinical outcomes for female patients with knee OA, especially pain severity and QOL score. To our knowledge, this is the first report that comprehensively investigates the relationships between knee OA related outcomes and related factors limited to female samples.

Knee pain with OA is known as a cause of disabilities among older adults as well as low back pain[28,29]. Knee pain is also an important outcome for patients with knee OA. However, previous studies have focused on biological factors such as aging, gender, BMI, ethnicity and history of knee injury for knee pain in cases where there was a discordant relationship between radiographic severity and symptoms[4,30]. On the other hand, recent studies have suggested that there were apparent relationships between pain catastrophizing and physical disabilities as well as pain severity in both pediatric and adult patients with musculoskeletal disorders[11,31,32]. Moreover, Forsythe *et al*[33] have reported that preoperative PCS scores predicted the presence of postoperative pain in patients who received TKA for primary knee OA.

In the present study, we found no interrelationships between pain catastrophizing and age, BMI and radiographic severity, while pain catastrophizing was a significant predictor which correlated with pain severity, and disease-specific QOL scores in female patients with knee OA, irrespective of disease severity. This finding is not only consistent with a previous report[16], but also suggests that pain catastrophizing is an important factor rather than aging, and body weight associated with physical disabilities in female patients with knee OA, if radiographic severity is progressive.

The term catastrophizing was originally introduced by Ellis[34] and subsequently adapted by Beck *et al*[35] to describe a mal-adaptive cognitive style employed by patients with anxiety and depressive disorders. Keefe *et al*[36] found a high test-retest correlation between catastrophizing thought during a 6-mo period in patients

with rheumatoid arthritis, and suggested it was invariable. Three prospective studies of TKA have included measures of catastrophizing in their test batteries[31,37,38]. In these studies, catastrophizing scores did not significantly decline over time despite reduced pain in study participants and therefore it could be a personality trait such as neuroticism. By contrast, Wada *et al*[39] recently reported that a change in pain intensity was associated with a change in catastrophizing for patients with TKA during a 6-mo follow-up. Furthermore, a number of studies have examined whether pain catastrophizing is an active cognitive process variable in multidisciplinary pain treatment settings, and have shown that pre- to post-treatment reductions in pain catastrophizing are associated with reductions in pain severity[40-42]. Indeed, Marra *et al*[43] have reported that multidisciplinary intervention for knee OA was superior to usual care with an educational pamphlet in terms of overall improvements, pain and function scores according to the Western Ontario and McMaster Universities' Osteoarthritis Index.

Besides, in the present study, TUG as an index of moving capacity was associated with not only disease severity but also pain catastrophizing after adjusting for BMI. We found that a correlation coefficient between TUG and K-L grade was higher than that between TUG and pain rating. This indicates that an assessment of bilateral knees may predict the moving capacity in female patients with knee OA, irrespective of pain severity. While a significant relationship between moving capacity and catastrophizing was consistent with a report by Somers *et al*[16], the underlying mechanism, which can explain the correlation between them, is still unknown. Perhaps, pain-related fear may be related to physical performance with effort (*i.e.,* walking fast) in chronic pain[16,44].

Taken together, this study suggests that clinicians should make sure to include an assessment of radiographic severity bilaterally and pain catastrophizing to explain the outcome measures in female patients with knee OA. This is because they may be able to improve both functional capacity and symptoms even at a progressive stage without knee arthroplasty by psychological intervention, which ameliorates mal-adaptive cognition in patients with high catastrophizing thought.

Several limitations should be taken into account when interpreting our data. Firstly, this was a cross-sectional study, therefore causal relationships between each outcome score and related variables could not be identified. Further longitudinal investigation is necessary to identify the interactions between the chronology of outcome measures and changes in variables. Secondly, the severity of radiographic OA was only assessed by posterior-anterior view in this study, although knee joints consisted of three components. Lanyon *et al*[45] have reported that 24% of patients with radiographic knee OA was missed by not visualizing the patella-femoral joint. Thirdly, although we assess biological and psychological factors as influential variables on the outcome in knee OA, we didn't evaluate the strength of the quadriceps, which has been consistently associated with knee pain

Table 4 Multiple linear regression analysis of factors associated with each outcome

Outcome	Independent variables	R²	Unstandardized coefficients: B	95%CI for B	β	*P*-value
Pain rating		0.397				
	BMI		0.162	0.039-0.284	0.239	0.010
	PCS		0.139	0.093-0.184	0.555	< 0.001
TUG		0.431				
	K-L grade		0.638	0.419-0.856	0.52	< 0.001
	PCS		0.053	0.023-0.082	0.313	0.001
JKOM		0.492				
	K-L grade		4.556	2.737-6.374	0.421	< 0.001
	PCS		0.719	0.470-0.968	0.485	< 0.001

TUG: Timed up and go test; JKOM: Japanese Knee Osteoarthritis Measure; BMI: Body mass index; K-L grade: Kellgren-Lawrence grading system; PCS: Pain Catastrophizing Scale.

and disabilities[46]. Furthermore, we didn't evaluate the patient's background such as underlying disease, educational level and previous treatment which might be associated with clinical outcome. Finally, we have emphasized catastrophizing for the outcome and mentioned the possibility of improving catastrophizing thought in patients with chronic pain by a multifaceted intervention. However, there is little consensus on the effectiveness of a cognitive-behavioral intervention for knee OA pain[47]. Hence, we must attempt to ameliorate these limitations and conduct a further investigation into whether an intervention to catastrophizing in relation to knee pain can improve the clinical outcomes for the female patient with knee OA.

This study showed that pain catastrophizing was a significant predictor which correlated with pain severity, physical function, and disease-specific QOL scores in female patients with knee OA, irrespective of disease severity. This finding suggests that pain catastrophizing is an important factor to explain knee symptoms and disabilities in female patients with knee OA.

ACKNOWLEDGMENTS

COMMENTS

Background
There is a widespread belief of inconsistency between clinical symptoms and radiographic disease severity in knee osteoarthritis (OA). Recent studies revealed that knee symptoms were associated with not only disease severity but also female gender, aging, overweight and psychological factors. However, there is little evidence reporting comprehensive relationships between biological and psychological factors and severity of symptoms in female patients with knee OA.

Research frontiers
Although a recent study has suggested that pain catastrophizing thought, as a psychological factor for pain symptoms, was associated with functional capacity as well as severity of knee pain in patients with knee OA, to what extent this psychological factor contributes to the severity of symptoms in female patients with knee OA, is still poorly understood. The research hotspot is to introduce the contributing degrees of both biological and psychological factors to the severity of symptoms in female patients with knee OA.

Innovations and breakthroughs
Knee pain is an important outcome for patients with knee OA. However, previous studies have focused on biological factors such as aging, gender, body mass index (BMI), ethnicity and history of knee injury for knee pain in cases where there was a discordant relationship between radiographic severity and symptoms. On the other hand, the study revealed that pain catastrophizing has been highly associated with knee-related clinical outcomes for female patients with knee OA, irrespective of disease severity, especially pain severity and QOL score. To our knowledge, this is the first report that comprehensively investigates the relationships between knee OA related outcomes and related factors limited to female samples.

Applications
This study suggests that clinicians should make sure to include an assessment of pain catastrophizing as well as radiographic severity to explain the outcome measures in female patients with knee OA, because they may be able to improve both functional capacity and symptoms even in a progressive stage without knee arthroplasty by psychological interventions which ameliorate mal-adaptive cognition in patients with high catastrophizing thought.

Terminology
The term "catastrophizing" was originally introduced by Albert Ellis and subsequently adapted by Aaron Beck to describe a mal-adaptive cognitive style employed by patients with anxiety and depressive disorders. In the present study, catastrophizing was assessed using the Pain Catastrophizing Scale (PCS) invented by Sullivan *et al* (1995). The PCS consists of 13 items that describe an individual's specific beliefs about their pain and evaluates catastrophic thinking about pain.

Peer-review
The authors investigated the factors associated with clinical outcomes in female patients with knee OA. They concluded that pain catastrophizing scores well correlated with ADL scores and gait ability. The manuscript was concise and well written.

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