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Associations between obesity and the radiographic phenotype in knee osteoarthritis

Mehmet Derya DEMİRAĞ[1], Seçil ÖZKAN[2], Şeminur HAZNEDAROĞLU[3], Evin ARAS KILINÇ[4], Fatma Nur BARAN AKSAKAL[2], Sefer AYCAN[2], Berna GÖKER[3,*]

[1]Clinic of Internal Medicine, Section of Rheumatology, Samsun Education and Research Hospital, Samsun, Turkey
[2]Department of Public Health, Faculty of Medicine, Gazi University, Ankara, Turkey
[3]Department of Internal Medicine, Section of Rheumatology, Faculty of Medicine, Gazi University, Ankara, Turkey
[4]Institution of Public Health, Ministry of Health, Ankara, Turkey

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Background/aim: Investigation of the association between obesity and the distinction of radiographic patterns in knee osteoarthritis.

Materials and methods: Seven hundred and thirty-four women underwent weight-bearing antero-posterior knee radiography. Osteophytes and joint space narrowing (JSN) were graded according to the OARSI atlas. Each subject was assigned to one of the following groups with respect to the maximum score: osteophyte-dominant, indeterminate, JSN-dominant, and radiographically normal.

Results: Obese patients had a significantly more frequent osteophyte-dominant pattern compared to nonobese subjects (74.5% and 38%, respectively, $P < 0.001$). Logistic regression analysis demonstrated that obesity had a stronger association with an osteophyte-dominant pattern compared to a JSN-dominant pattern (OR and 95% CI = 7.16 (3.15–16.26) and 1.63 (0.96–2.78), respectively). Age had a very weak effect on the distinction to an osteophyte-dominant pattern and no effect on JSN dominance (OR and 95% CI = 1.1 (1.06–1.15) and 1.02 (0.99–1.05), respectively).

Conclusion: There might be an association between obesity and the radiographic phenotype in patients with knee osteoarthritis. The findings suggest that the association between obesity and the osteophyte formation is stronger than that of JSN.

Key words: Osteoarthritis, knee, radiography, phenotype, obesity, osteophyte, joint space narrowing

1. Introduction

Osteoarthritis (OA) of the knee is a significant cause of pain and disability and radiography is a major tool for its diagnosis. Osteophytes and joint space narrowing (JSN) are both typical radiographic findings of osteoarthritis, and they are among the radiographic parameters used in the grading systems (1). However, they are not always present to the same extent in the affected joints. In some subjects with knee OA, we observe marked JSN in the absence of a significant osteophyte, and vice versa. The factors associated with this discrepancy are unclear but this distinction probably reflects differences in the underlying pathogenetic mechanisms and signifies different phenotypes (2). Obesity is a risk factor for both the development (3-5) and progression (6) of knee OA. In addition, physical disability in obese subjects with knee OA can be significantly improved by moderate weight reduction regimes (7). Therapeutic approaches in the future are very likely to take phenotypes into consideration to reach significance (2). In the present study, we studied the association between obesity and the radiographic phenotype, i.e. osteophyte-dominant (O-dominant) versus JSN-dominant radiographic patterns in knee OA.

2. Materials and methods

Seven hundred and thirty-four women of 40 years of age or more (median 51 years) who had knee pain (subjects of an epidemiological study investigating the prevalences of OA in Turkey, who had knee radiography available) were included. The Local Ethical Committee of Gazi University Medical Faculty approved the study protocol. Written informed consent was obtained from all of the study subjects. In the original study, home visits were made to fill out a questionnaire for each subject and those who had pain in their knees, hips, or hand joints in most of the days for at least one month duration were invited for clinical evaluation. They underwent a musculoskeletal examination, as well as weight and height measurements.

* Correspondence: bgoker@yahoo.com

Those who had knee pain underwent a weight-bearing antero-posterior conventional radiography of the knees in extended position. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of body height in meters. Obesity was defined as BMI higher than 29.9 (8).

2.1. Radiographic evaluation

Detailed grading of the knee radiographies with respect to osteophytes (grade 0–3) and JSN (grade 0–3) according to the OARSI atlas (9) was done. In this grading system, osteophytes are evaluated at 4 sites (medial femoral condyle, medial tibial plateau, lateral femoral condyle, lateral tibial plateau) and JSN is evaluated at 2 sites (medial and lateral). All radiographs were evaluated by a single observer who was blinded to the age of the study subjects. The radiographs from 50 randomly selected subjects were re-graded by the same observer one month after the first evaluation for intra-observer variability. The highest grade at any site was used for classification of the radiographic phenotype and each subject was assigned to one of the following 4 groups: O-dominant (if the maximum osteophyte score is greater than the maximum JSN score), JSN-dominant (if the mean maximum JSN score is greater than the maximum osteophyte score), indeterminate (the maximum osteophyte score equal to the maximum JSN score), and radiographically normal.

2.2. Statistical analysis

Data were given as mean ± standard deviation (SD), except for age. Age was given as median. One way analysis of variance (ANOVA) was performed to analyze the differences between groups with respect to weight and BMI. The Tukey HSD test was used for post hoc analysis. A P value of less than 0.05 was considered statistically significant. Age was not normally distributed; therefore, the comparison was tested with the Kruskal–Wallis test. If a P value from the Kruskal–Wallis test was less than 0.05, paired comparisons were also subsequently tested with the Mann–Whitney U test, where a P value of less than 0.05/number of the comparisons (Bonferroni correction) was considered statistically significant. The chi-square test was used for comparisons of the frequencies in the dominant radiographic patterns between obese and nonobese subjects, and ORs (95% CI) and P values were adjusted for age by using Mantel– Haenzel analyses. Multivariate logistic regression analysis was used to analyze the age adjusted relationships between obesity and radiographically dominant patterns. Reproducibility of the radiographic evaluations was assessed using the weighted kappa (κ) statistics.

3. Results

The reproducibility of both osteophyte and JSN assessments were excellent. Intra-observer reproducibility was better for osteophyte assessments compared to JSN assessments (κ = 0.92 for osteophyte scores and κ = 0.82 for JSN scores). Subjects with O-dominant radiographic patterns were older and heavier and had higher BMI when compared to the others. Subjects with no radiographic findings of OA according to the OARSI atlas were the youngest and had the lowest weight and BMI values compared to the other groups. In paired comparisons, the differences between those with O-dominant and JSN-dominant radiographic patterns, as well as between O-dominant and normal radiography groups, were statistically significant for all variables tested, including age, body weight, and BMI. In addition, the differences between those with indeterminate and JSN-dominant radiographic patterns, as well as between indeterminate and normal radiographic patterns, were also statistically significant for all variables. The characteristics of the study subjects are provided in Table 1.

Table 1. Characteristics of the study subjects.

N	Normal	O-dominant	Indeterminate	JSN-dominant	P (overall)
	68	127	221	318	-
Age, median, (years)	45	57	55	49	<0.001
Body weight, mean ± SD, (kg)	76.5 ± 11	84 ± 14	82 ± 16	78.5 ± 13	<0.001
BMI, mean ± SD, (kg/m^2)	31 ± 4	35 ± 5	34 ± 6	32 ± 5	<0.001

O-dominant vs. normal and O-dominant vs. JSN-dominant, P values < 0.001 for age and BMI, 0.001 for body weight. Normal vs. indeterminate, P < 0.001 for age and BMI, 0.02 for body weight, JSN-dominant vs. indeterminate, 0.001 for age, <0.001 for BMI and 0.02 for body weight.
Other paired comparisons were not statistically significant.

The relationship between obesity and radiographic pattern was analyzed using those with normal radiography as the control group, and the differences in the frequencies of the dominant radiologic pattern between obese and nonobese subjects were adjusted for age. Obese subjects had significantly a more frequent O-dominant pattern compared to nonobese subjects. However, the frequency of a JSN-dominant pattern did not differ between obese and nonobese subjects (Table 2).

Multivariate logistic regression analysis showed that obesity was significantly associated with an O-dominant pattern; however, when the subjects with normal radiography comprised the reference group, this had no effect on JSN-dominancy (Table 3). Similar results were obtained in all tertiles of BMI (Table 4). In addition, age was also associated only with an O-dominant pattern (Table 3).

Analysis using mean osteophyte and JSN scores, instead of the maximum scores, revealed similar results. Osteophyte scores at 4 sites were summed and divided by 4 to get a mean osteophyte score for each subject. Similarly, mean JSN scores were found by dividing medial plus lateral JSN scores by 2. Each subject was similarly assigned to one of the following 4 groups: O-dominant (if the mean osteophyte score is greater than mean JSN score), JSN-dominant (if the mean JSN score is greater than mean osteophyte score), indeterminate (if the mean osteophyte score is equal to the mean JSN score), and radiographically normal. Similarly, subjects with O-dominant radiographic patterns were older and heavier and had higher mean BMI compared to the others ($P < 0.001$ for all). Obese subjects had a significantly more frequent O-dominant pattern as well as a JSN-dominant pattern compared to nonobese subjects (Table 5). Multivariate logistic regression analysis

Table 2. Frequencies of the radiographic patterns in obese and nonobese subjects.

	Obese % (n)	Nonobese % (n)	OR* (95% CI)	P
O-dominant	74.5 (108)	38 (19)	4.57 (2.04–10.1)	<0.00001
Normal	24.5 (37)	62 (31)		
JSN-dominant	85.1 (211)	77.7 (108)	1.56 (0.89–2.77)	0.13
Normal	14.9 (37)	22.3 (31)		

P values and ORs are adjusted for age.
*ORs reflected comparisons between obese and nonobese groups.

Table 3. Associations of obesity and age with radiographic patterns.

OR (95% CI)	O-dominant	JSN-dominant
Obesity	7.16 (3.15–16.26)	1.63 (0.96–2.78)
Age	1.1 (1.06–1.15)	1.02 (0.99–1.05)

ORs (95% CI) are with respect to those with normal radiography; all values are adjusted for age (for obesity), obesity (for age). Nonobese subject was defined as BMI <29.9 kg/m^2.

Table 4. Radiographic patterns with respect to BMI tertiles.

BMI	O-dominant (OR (95% CI))	JSN-dominant (OR (95% CI))
>29.9	7.16 (3.15–16.26)	1.63 (0.96–2.78)
>34.9	10.41 (4.14–26.17)	1.87 (0.90–3.86)
>39.9	52.42 (5.99–458.69)	7.46 (0.97–57.19)

ORs (95% CI) are with respect to those with normal radiography. All values are adjusted for age.

Table 5. Frequencies of the radiographic patterns in obese and nonobese subjects when mean scores are taken.

	Obese % (n)	Nonobese % (n)	OR* (95% CI)	P
O-dominant	80.9 (157)	38 (19)	6.97 (2.93–15.42)	<0.001
Normal	19.1 (37)	62 (31)		
JSN-dominant	89 (298)	81.9 (140)	1.76 (1.01–3.05)	0.04
Normal	11 (37)	18.1 (31)		

P values and ORs are adjusted for age.
*ORs reflect comparisons between obese and nonobese groups.

showed that obesity was independently associated with both O- dominant and JSN-dominant patterns. However, the association between obesity and JSN dominance was weak (Table 6). Moreover when tertiles of BMI are evaluated separately, this association was seen in only the highest tertile of BMI (Table 7).

4. Discussion

In this study, we classified knee OA according to the dominant radiographic feature using the OARSI atlas. This classification has not been previously used to analyze the relationship between obesity and radiographic features. Development of radiographic features does not occur to the same degree in all subjects, and the reasons for this remain unclear. We could hypothesize that the pathogenesis of osteophyte formation is different to that of JSN. Hence, the classification we described here might be helpful in studies analyzing pathogenetic mechanisms in OA subjects and phenotyping. We reported both maximum and mean scores and they are close to each other; however, maximum scores resulted in a stronger statistical significance and seem to work better for the distinction between the two groups. Therefore, we would recommend using maximum scores for radiographic phenotyping.

Obesity is a risk factor for OA, and JSN may be more subjective and it might be considered that there is a chance that we are identifying more true OA in the obese group vs. nonobese group. However, only those who had knee pain most of the days for at least one month were invited for physical examination. Other causes of knee pain were excluded by questions in the questionnaire, as well as by physical examination. Therefore, we think that all the

Table 6. Associations of obesity and age with radiographic patterns when mean scores are taken.

OR (95% CI)	O-dominant	JSN-dominant
Obesity	11.69 (4.83–28.28)	1.87 (1.1–3.15)
Age	1.13 (1.09–1.18)	1.03 (1–1.06)

ORs (95% CI) are with respect to those with normal radiography; all values are adjusted for age (for obesity), obesity (for age). Nonobese subject was defined as BMI <29.9 kg/m^2.

Table 7. Radiographic patterns with respect to BMI tertiles when mean scores are taken.

BMI	O-dominant OR (95% CI)	JSN-dominant OR (95% CI)
>29.9	11.69 (4.83–28.80)	1.87 (1.1–3.16)
>34.9	16.70 (6.40–43.58)	2.03 (0.99–4.13)
>39.9	108.80 (12.18–971.41)	8.19 (1.08–62.01)

ORs (95% CI) are with respect to those with normal radiography. All values are adjusted for age.

patients had symptomatic clinical OA and hence true OA.

The major limitation of the present study is that the control group comprised subjects with knee pain rather than healthy subjects. Therefore, some of these subjects might have clinical OA according to the American College of Rheumatology's classification criteria for the knee OA (10). However, we aimed to investigate the association between radiographic features and obesity. Hence, we did not use ACR classification criteria because these criteria do not include any radiographic features of OA except for osteophytes (10). A second limitation of the study is that test–retest variability was unable to be confirmed. Knee radiographs were not repeated at short intervals to assess the variability related to repeat radiography; this step was not included in the protocol of the primary study in order to reduce radiation exposure.

Age is an important risk factor for OA (11) and aging is strongly associated with development of knee OA in women (3). We have demonstrated that among women ≥40 years of age who had knee pain, radiographic patterns differed with respect to age. Those with normal radiography were the youngest, followed by those with JSN-dominant patterns, indeterminate, and lastly O-dominant patterns. Similarly, in the Chingford study, those with incident knee osteophytes during the follow up were older (3).

Subjects with O-dominant radiographic patterns had significantly higher body weight and BMI compared to those with JSN-dominant patterns and to those with normal radiography. Analysis of both mean and maximum scores gave similar results. The relationship between obesity and OA has been extensively studied in the cohort of the Framingham study. In the Framingham study (12), which is a population-based longitudinal study, a strong association between obesity and knee OA was demonstrated. Furthermore, it was shown that weight loss is associated with a significantly reduced risk regarding the development of knee OA (13). We found that the frequency of O-dominant patterns is significantly higher in obese subjects than in nonobese subjects. However, JSN dominancy did not differ between obese and nonobese subjects. The relationship between obesity and osteophyte formation has been investigated by several studies. In the Chingford study (3), the authors demonstrated a significant association between BMI higher than 26.4 kg/m^2 and incident osteophytes. In the extended report of the Chingford study, the same authors demonstrated that obesity was also an important risk factor for the progression of the osteophyte score (4). Similarly, Cooper et al. (5) also found that obesity was the only statistically significant predictor of progression of knee OA based on osteophyte formation. The age-adjusted analyses of obesity and OA radiographic patterns in our study are consistent with the results of these studies. We found that the association between obesity and the distinction to O-dominant pattern was stronger than that of JSN-dominant pattern. In agreement with our findings, the Chingford study (3) also demonstrated that obesity was not associated with incident JSN and, in its extended report (4), the majority of the incident disease was due to osteophyte formation in obese subjects and progression of JSN grades in the obese groups was not uniform. However, in these previous studies radiographic findings were not categorized with respect to dominant radiographic pattern.

Obesity might be associated with certain radiographic patterns in subjects with OA of the knee. Our findings suggest that the effect of obesity on osteophyte formation might be stronger than its effect on JSN. These results might shed light on the pathogenesis of osteoarthritis and the evolution of its individual radiographic phenotypes.

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References

1. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 1957; 16: 494-502.
2. Tonge DP, Pearson MJ, Jones SW. The hallmarks of osteoarthritis and the potential to develop personalised disease-modifying pharmacological therapeutics. Osteoarthr Cartilage 2014; 22: 609-621.
3. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. Arthritis Rheum 1999; 42: 17-24.
4. Spector TD, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. Ann Rheum Dis 1994; 53: 565-568.
5. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, Dieppe PA. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000; 43: 995-1000.
6. Schouten JS, van den Ouweland FA, Valkenburg HA. A 12 year follow-up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. Ann Rheum Dis 1992; 51: 932-937.
7. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese subjects diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 2007; 66: 433-439.

8. Akram DS, Astrup AV, Atinmo T, Boissin JL, Bray GA, Carrol KK, Chitson P, Chunming C, Dietz WH, Hill JO et al. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva, Switzerland: World Health Organization; 2000.

9. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007; 15 Suppl A: 1-56.

10. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheum 1986; 29: 1039-1049.

11. Felson DT. Epidemiology of osteoarthritis. In: Brandt KD, Doherty M, Lohmander LS, editors. Osteoarthritis. 2nd ed. Oxford, UK: Oxford University Press; 2003. pp. 9-16.

12. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med 1988; 109: 18-24.

13. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med 1992; 116: 535-539.