Author: Yusuf, Erlangga
Title: On how obesity links with osteoarthritis
Issue Date: 2013-01-16

Chapter 7

Difference in the association between obesity and pain in hip and knee osteoarthritis

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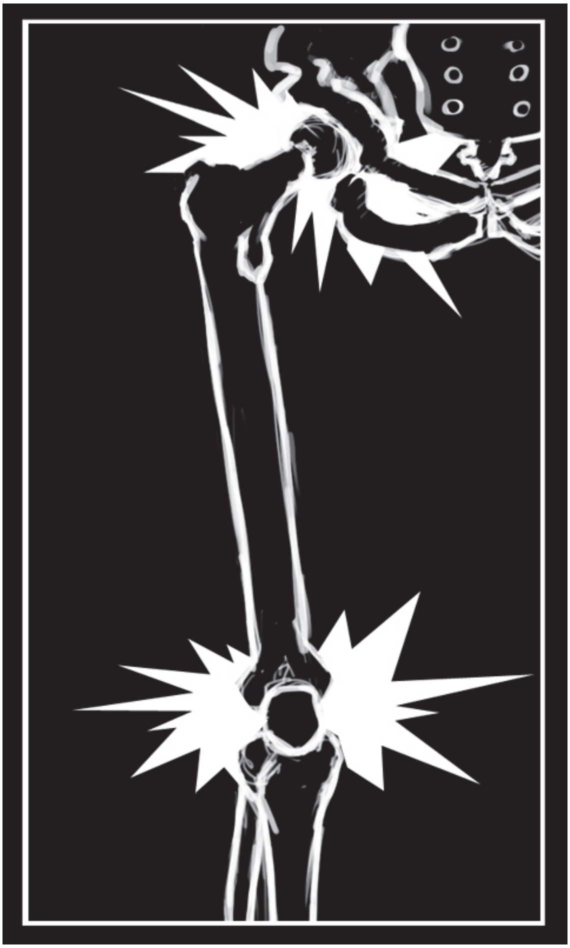

Submitted

ABSTRACT

Objective

To investigate: (i) the association between body mass index (BMI) and pain, (ii) the role of radiographic severity on this association, and (iii) the association between BMI and indication to perform total hip (THR) or knee replacement (TKR).

Methods

Cross-sectional study on 632 and 870 patients with hip and knee OA who visited orthopedic surgeons in 11 countries. Two types of self-reported pain were used: pain with activity (WOMAC pain subscale) and pain experience (ICOAP). Recommendation for THR/ TKR was defined by the surgeon. Association between BMI and pain index were investigated using linear regression. The role of radiographic severity was analyzed using method of Baron and Kenny. The odds ratios (ORs) with (95% confidence interval) for having indication for THR/ TKR were calculated for BMI categories: overweight, obese and very obese relative to normal BMI category using logistic regression analysis. All analyses were adjusted for age and sex in knee and hip OA population.

Results

The mean age, BMI (SD) and percentage of women in hip OA population were: 65 (12) years, 28 (5) kg/m^2, and 56%. These numbers were: 68 (10) years and 31 (7) kg/m^2 and 8% in knee OA. In hip OA participants, beta-regression coefficient with WOMAC and ICOAP respectively were the same: 0.5 (0.2 to 0.9). In knee OA, beta-regression coefficient with WOMAC was 0.5 (0.3 to 0.7) and with ICOAP pain (0.1 (-0.1 to 0.4)). Radiographic severity acts as mediator in the association between obesity and pain in knee but not in hip OA. ORs of having TJR indication for obese compared with normal weight patients for hip and knee OA were respectively 1.8 (1.03 to 3.2) and 2.3 (1.4 to 3.7).

Conclusion

BMI is associated with pain and TJR. The effect of BMI pain differs in hip and in knee OA. In knee OA, radiographic severity acts as mediator on the association between BMI and pain.

7.1. INTRODUCTION

Patients with OA seek medical attention mostly because of pain.[1,2] In OA, pain and structural damage are not always concordant.[2] Some patients with severe pain have only mild joint space narrowing (JSN) or osteophytes while many others with mild pain have extensive signs of OA on radiograph.[3] OA patients are often obese.[4,5] Obesity, measured as Body Mass Index (BMI) has been shown to be associated with structural incidence and progression of OA, mainly for knee OA.[4] Whether obesity is also associated with joint pain itself, is less known.

In several diseases such as: chronic pain, fibromyalgia, abdominal pain and migraine, obesity has been shown to be linked with pain.[6] It is reasonable to think that obesity could also cause joint pain in OA. This can happen through the increased weight-bearing effect on already damage OA joint such as knee. Alternatively, this happens independent of structural damage associated with OA. To investigate the effect of obesity on pain in OA, hip and knee OA can be compared since hip is considered as less weight-bearing than the knee joint.[7] If the difference in the effect of BMI on pain in knee and hip OA patients indeed exists, it will lead to more insight in the etiology of pain in OA and could also have consequence in treatment aimed at reducing pain in knee and hip OA.

The joint damage in OA could eventually progress into total joint failure needing joint prosthesis. Several studies have investigated the association between obesity and total joint replacement (TJR).[8-11] In these studies, joint replacements were defined as the actual performed surgery. However, performance of total joint replacement (TJR) is influenced by numerous non-health related factors such as patient race, ethnicity, income and non-musculoskeletal health factors such as co-morbidity.[12] Another remark is that in these studies, severe obesity (i.e. BMI larger than 35 kg/ m^2) is not studied separately from obesity patients (i.e. BMI larger than 30 kg/ m^2). Yet, in clinical practice, it is still the matter of debate whether severe obesity is a contraindication to TJR. A better alternative in defining joint failure in OA would be indication for TJR, independent whether the TJR is performed or not.[12] Moreover the association of severe obesity with TJR should be investigated too. To our knowledge, no studies have investigated the association between obesity and indication for TJR.

This study had several aims. Firstly, to investigate the association between obesity and pain level in knee and hip OA. We used two types of self-reported pain scores: pain on activity (as measured with WOMAC pain subscale (appendix B.1)) and pain experience (as measured with ICOAP score (appendix B.2 and B.3)). Secondly to investigate in which way structural damage influences this association. Thirdly, to investigate the association between BMI and the indication for TJR.

7.2. PATIENTS AND METHODS

7.2.1. Study design and subjects

The present study was a part of an observational cross-sectional study conducted by OARSI-OMERACT Task Force on total joint replacement in the orthopaedics departments of tertiary-care and secondary-care centers in 11 countries (12 centers, one per country in the Czech Republic, Italy, Spain, Sweden, and the United Kingdom; two per country in France and The Netherlands; three in Germany), Canada (two centers), the United States of America (two centers), and Australia (two centers). The main aim of the task force was to elaborate a set of criteria in defining a non-acceptable symptom and structural state in knee/hip OA that could be used as an endpoint in clinical trials evaluating potential disease modifying drugs in OA.[12,13] Ethical approval was obtained from all participating centers.

Participant inclusion and exclusion criteria have been described in detail elsewhere.[12] In short, consecutive patients with knee or hip OA, who consulted an orthopedic surgeon to discuss the possibility of a joint replacement, were included. The diagnosis of OA was made by the consulted surgeon based on clinical judgment and the presence of radiographic signs of OA. Only patients for whom the surgeon answered ‘There are definite radiographic signs of OA of the target joint’ were included. Excluded were patients with prior joint replacement or prior osteotomy in the target joint, patients with concomitant inflammatory joint disease and patients who were unable to understand and to fill in the questionnaires.

7.2.2. Demographic data

Demographic data (i.e. age, sex, height and weight) were collected using standardized questionnaires. BMI was calculated as weight (in kilograms) divided by the square of height (in meters). Complete demographic data were available from 632 and 870 patients with hip and knee OA, respectively.

7.2.3. Pain assessment

Self-reported pain was assessed using the intermittent and constant osteoarthritis pain (ICOAP) score (appendix B.2 and B.3).[14] It assessed continuous pain (five items) and pain that comes and goes (six items). The ICOAP questionnaire had previously undergone translation and cross-cultural adaptation into each of the participating countries languages.[15] In addition, self-reported pain (five items) was evaluated by using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (appendix B.1)[16] The ICOAP and WOMAC pain subscale were assessed with Likert response options and transformed to 0 to 100 score, where higher scores indicated greater pain.

7.2.4. Indication for TJR

Indication for TJR was defined by the orthopedic surgeon's opinion, stating that: (i) TJR was recommended for the patient; or (ii) the patient's pain and functional disability were severe enough to indicate TJR but surgery was not indicated because of comorbidity or patient declining surgery. This was irrespective of whether the TJR was performed or not.

7.2.5. Radiographic severity

The local investigator assessed the joint space narrowing (JSN) of the knees or the hips. The JSN was categorized as: none, < 25%, 25 to 50%, > 75%. Only JSN data for 418 knees and 322 hips were available since not all centers participated in the evaluation of radiographic severity,

7.2.6. Statistical analysis

Data were analyzed using PASW Statistics 17 (SPSS Inc., Chicago, Ill, USA). Means with standard deviation (SD) were used to describe the hip and knee study population. Distributions of patient characteristics were evaluated for the presence of marked deviation from normal distribution. All analyses described below were performed separately in hip and knee OA population and adjusted for age and sex. An association was considered significant when $p<0.05$.

To investigate the association between BMI and pain scores, linear regression analysis was used to calculate the beta-regression coefficients with its 95% confidence interval (CI).

To investigate whether structural damage (JSN) acts as mediator in the association between BMI and pain, the method described by Baron and Kenny to asses mediation was used.[17] This method described that to be determined as a mediator, a variable (in this case radiographic severity measured as JSN) needs to meet all the following conditions: (i) independent variable (in this case BMI) was associated with presumed mediator (JSN), (ii) presumed mediator (JSN) is associated with dependent variable (in this case pain), and (iii) when the association between BMI and pain was controlled for JSN, the previous significant association between BMI and pain became not significant.

To investigate the association between BMI and indication for joint replacement, BMI was first categorized into four categories: < 25 (normal, referent), 25 to 30 (overweight), 30 to 35 (obese) and > 35 kg/m^2 (very obese). Patients with BMI > 30 kg/m^2 were divided into obese and very obese to examine dose-response relationship and to examine whether very obese patients were less likely to have TJR. The odds ratios (ORs) of total hip replacement (THR) or total knee replacement (TKR) with (95% CI) were calculated using logistic regression analysis.

7.3. RESULTS

7.3.1. Characteristic of the study population

The mean age (SD) and BMI (SD) of the study population with hip OA (n=632) were 65 (12) years and 28 (5) kg/m^2, respectively; 56% were women. The mean age (SD) and BMI (SD) of the study population with knee OA (n=870) were 68 (10) years and 31 (7) kg/m^2, respectively; 58% were women (table 7.1). Study population with hip OA had slightly higher scores of WOMAC pain and ICOAP than study population with knee OA. In both populations, both scores were normally distributed.

Table 7.1 Characteristics of study population.

	Hip OA (n=632)	Knee OA (n=870)
Mean age, years	65 (12)	68 (10)
Women sex (%)	344 (56)	496 (58)
Mean BMI, kg/m^2	28.3 (5)	31.0 (7)
Pain scores		
WOMAC pain subscale	56 (21)	52 (21)
ICOAP	53 (23)	49 (22)
Radiographic scores, n (%)*		
None	0	5 (1.2)
< 25%	23 (7.2)	48 (11.5)
25 to 50%	28 (8.7)	70 (16.8)
50 to 75%	91 (28.2)	143 (34.3)
> 75%	180 (55.9)	151 (36.2)

Abbreviations: TKR: total knee replacement, THR: total hip replacement, n=number of study population.
Results are presented as mean (standard deviation) unless otherwise mentioned.
* of available data (417 for the knee and 322 for the hip).

7.3.2. Association between BMI and pain scores

In hip OA participants, BMI was positively associated with both pain measures before and after additional adjustment for radiographic severity. Adjusting for age and sex, the beta-regression coefficients for the association between BMI and WOMAC pain and ICOAP were the same: 0.5 (0.2 to 0.9). Adjusting for age, sex, and radiographic severity the beta-regression coefficients for the association between BMI and WOMAC pain and ICOAP were respectively 0.7 (0.2 to 1.2) and 0.5 (0.1 to 1.0).

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In the study population with knee OA, BMI was associated with WOMAC pain subscale (beta-regression coefficient: 0.5 (0.3 to 0.7) but not with ICOAP pain (beta-regression coefficient 0.1 (-0.1 to 0.4)). After further adjustment for radiographic severity, this association between BMI with WOMAC pain was no longer significant (beta-regression coefficient was 0.3 (-0.1 to 0.7).

7.3.3. Investigating radiographic scores as a possible mediator in the association between BMI and pain score

In hip OA population, radiographic severity, measured as JSN did not act as mediator. It fulfilled these two criteria: (i) BMI was associated with JSN (beta-regression coefficient was -0.02 (-0.04 to -0.001) and (ii) JSN was associated with WOMAC pain subscale and ICOAP pain. Beta-regression coefficients were respectively 5.8 (3.7 to 8.4) and 4.3 (1.4 to 7.2). Yet, it did not fulfill the last criteria. When JSN was used in the analysis to control the previous significant association between BMI and WOMAC pain scores and ICOAP, these associations remained significant. The beta-regression coefficients were 0.5 (0.05 to 1.0) and 0.2 (0.1 to 1.0), respectively.

In knee OA population, JSN acted as mediator. It fulfilled all criteria to be considered as a mediator. Firstly, BMI was associated with JSN (beta- regression coefficient was 0.03 (0.01 to 0.05). Secondly, JSN was associated with WOMAC pain subscale (beta-regression coefficient: 5.3 (3.3 to 7.3)) and ICOAP (beta-regression coefficient: 4.0 (1.8 to 6.3)). Lastly, when JSN was used to control the previous significant association between BMI and WOMAC pain and ICOAP, these associations were no longer significant. Beta-regression coefficients were 0.3 (-0.01 to 0.7) and -0.1 (-0.5 to 0.4).

7.3.4. Association between BMI and indication for joint replacement

Greater BMI were associated with surgeon's indication for THR. ORs of receiving a THR indication for obese and overweight patients compared with normal weight patients were respectively 1.8 (1.03 to 3.2) and 1.7 (1.04 to 2.6) (table 7.2). Yet, being very obese was not associated with indication for THR (OR: 1.3 (0.7 to 2.6)), compared to normal weight patients. The association between BMI and surgeon's indication for THR was no longer significant after adjustment with pain or radiographic severity.

Table 7.2 Association between BMI and indication to perform hip and knee replacement.

BMI (kg/m^2)	TJR+	TJR-	Adjusted for age and sex	Adjusted for age, WOMAC subscale pain scores	Adjusted for age and ICOAP pain scores	Adjusted for age and radiographic severity scores
Association with hip replacement (THR)						
	(n=474)	**(n=158)**				
< 25 (normal)	113	54	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25 to 30 (overweight)	206	58	1.7 (1.04 to 2.6)‡	1.4 (0.9 to 2.3)	1.6 (0.9 to 2.5)	1.4 (0.7 to 3.0)
30 to 35 (obese)	108	27	1.8 (1.03 to 3.2)‡	1.4 (0.8 to 2.6)	1.6 (0.9 to 2.9)	1.6 (0.7 to 4.1)
> 35 (very obese)	47	19	1.3 (0.7 to 2.6)	1.1 (0.5 to 2.3)	1.1 (0.6 to 2.4)	1.1 (0.4 to 3.3)
Association with knee replacement (TKR)						
	(n=494)	**(n=376)**				
< 25 (normal)	69	72	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25 to 30 (overweight)	172	145	1.2 (1.02 to 2.4)‡	1.6 (1.03 to 2.5)‡	1.6 (1.003 to 2.5)‡	0.9 (0.4 to 2.0)
30 to 35 (obese)	133	79	2.3 (1.4 to 3.7)‡	2.3 (1.5 to 3.7)‡	2.4 (1.5 to 3.7)‡	1.3 (0.6 to 2.8)
> 35 (very obese)	120	80	2.5 (1.5 to 4.1)‡	2.6 (1.6 to 4.2)‡	2.5 (1.5 to 4.0)‡	0.5 (0.2 to 1.1)

Abbreviation: TKR +, indication to perform total knee replacement; TKR -, no indication to perform total knee replacement.
‡ Statistically significant at $p<0.05$.

Greater BMI was associated with greater likelihood of receiving an indication for TKR. Patients with BMI > 35 kg/m^2 (very obese) were 2.5 (1.5 to 4.1) times more likely to be recommended TKR compared with normal weight patients (table 7.2). Patients with BMI 30 to 35 kg/m^2 (obese) and in 25 to 30 kg/m^2 (overweight) were 2.3 (1.4 to 3.7) and 1.2 (1.02 to 2.4) times more likely to be recommended for TKR compared with normal weight patients, respectively. These associations remained significant after adjustment for pain (either WOMAC pain subscale or ICOAP pain). However, the association was no longer significant when adjustment was made for radiographic severity. ORs (95% CI) for very obese, obese and overweight, were 0.5 (0.2 to 1.1), 1.3 (0.6 to 2.8) and 0.9 (0.4 to 32.0) compared with normal weight patients, respectively.

7.4. DISCUSSION

The present study shows that obesity is associated with pain in hip and knee OA. Yet, this association differs in hip and knee OA. Radiographic severity, measured as JSN, acts as mediator in the association between obesity and pain in knee, but not in hip OA. Furthermore, obesity is associated with the indication for THR and TKR. However, the association is no longer significant after adjustment with pain score in knee OA. In hip OA, the association remains significant.

Obesity and pain has been link with several diseases characterized by pain such as chronic pain, fibromyalgia, abdominal pain and migraine.[6] Studies on the link obesity and pain in OA are limited. In general, these studies in OA showed that obesity is associated with pain but they did not explore the aspects such as the role of radiographic severity in the association, and the types of pain (pain on activity or pain experience). Anandacoomarasamy et al. showed that the bodily pain scores measured by SF-36 were more severe in patients with knee OA.[18] In another study, Desmueles et.al. showed that one-point increase in BMI was associated with 0.46 increase in WOMAC pain score after adjusting for contralateral knee pain and psychological distress.[19]

In our study, we add more dimension on the association between BMI and pain. We compare hip and knee OA, investigate the role of radiographic severity and use two types of pain scores: pain with activity (WOMAC pain score) and pain experience (ICOAP). While in hip OA, BMI is associated with both type of pain, in knee OA BMI is only associated with pain with activity. To explain this, we need to take into account the observation that the association between BMI and hip OA is weaker than that with knee OA [20] that might suggest that hip is less weight-bearing than knee. In hip, obesity alone could lead to pain experience, as observed by its association with pain experience (ICOAP). On the other hand, in knee OA, obesity alone does not give pain, but it is the additional factor to the damaged knee that consequently leads to pain on activity (WOMAC). This explanation is supported by two other results in the present study. Firstly, the association between obesity and WOMAC is no longer significant after adjustment with radiographic severity in knee OA while in hip OA the association remains significant. Secondly, using a widely-used statistical method to define a mediator, it is shown that radiographic severity acts as mediator in the association between obesity and pain in knee but not in hip OA.

The joint damage in OA could eventually progress into total joint failure needing total joint replacement (TJR).Many studies have been shown the positive association between BMI and TJR.[8,10-11] In those studies, joint replacements were defined as the actual performed surgery. However, performance of total joint replacement (TJR) is influenced by numerous non-health related factors such as patient race, ethnicity, income and non-musculoskeletal health factors such as co-morbidities. It is a well known clinical practice that obesity is considered as one of the co-morbidities. Many surgeons hesitate to perform surgery on an obese patient with OA who actually need TJR because a very obese patient is expected to have more surgical complications.[12]

An indication for TJR would be a better alternative in defining joint failure in OA.[12]
Using this outcome definition, our study supports the evidence that higher BMI is associated with higher risk to have TJR. Interestingly, using this outcome definition, the pattern of the association between BMI and TJR differs in hip and knee OA population. In knee OA, the association between BMI and TKR showed a dose-

response relationship, while in hip OA the highest BMI category (BMI > 35 kg/m^2) did not shown an association with THR. This suggests that in the highest BMI category, another factor than OA play a role in consulting a surgeon. This could be pain or disability related to obesity.

Another interesting observation is that the association BMI and TJR in knee OA remains after adjusting for pain score but not after adjusting for radiographic severity. In hip OA, the association disappeared after adjusting with pain score or for radiographic severity. It is possible that in hip OA the decision in performing TJR is influenced by pain score or by radiographic severity. In knee OA, the decision in performing TJR in knee OA is merely influenced by radiographic severity as has been shown in an earlier study.[21]

The results of the present study show that the relation between BMI and TJR is complex. It is not merely the sequence: obesity leads to structural damage, consequently structural damage leads to pain, and consequently pain leads to TJR. Yet, our findings add to the body of evidence that the effect of obesity in hip and knee OA is different. In hip OA, the effect of BMI seems to be directly associated with pain experience, while in knee OA the effect of BMI on pain is mediated by structural damage. This could have a consequence in treatment. In hip OA, losing weight might not reverse the damage already done to joints, but it might be enough to lessen the pain. In contrast, in knee OA, influencing structural damage might be as important as losing weight.

Several limitations of our study need to be considered. Firstly, data on radiographic severity are not available from every patient. Yet, since the data omission happen at random (not all centers were participating with evaluation of radiographic severity), the results could be considered as valid. Secondly, height and weight were self-reported. People tend to overestimate their height and underestimate their length, this lead to underestimation of BMI and consequently lead to underestimation of the effect sizes in the present study.[22]

In conclusion, the effect of obesity in pain differs in patients with hip and knee OA. This difference could be explain by the difference in pathophysiology and should be considered in the studies on the effect of obesity in OA and OA's treatment.

Acknowledgments

The authors thank Simon Paternotte (France) for his assistance on managing the database. We also like to thank the other principal investigators of OARSI-OMERACT "total articular replacement as outcome measure in OA": Gaston Hill (United Kingdom), Jean Francis Maillefert (France), Leonardo Punzi (Italy), Emilio Martin-Mola (Spain), Klaus-Peter Gunther (Germany), Karel Pavelka (Czech Republic) and Maria Suarez-Almazor (USA). We also indebted to the following persons for their help in recruiting patients for the study: Adeline Ruyssen-Witrand (France), Emily Jonxis (Netherlands), Roberta Ramonda (Italy), Kelly McMaken, Patrick Fitzgerald and Amy Anderson (USA), David Parker, Myles Coolican, Andrew Ellis, Jowveria Mufti, Veronique Boukris-Sayag, Janis Lim, Eashwary Mageswaren and Professor Peter Choong (Australia), Stefan Kessler (Sindelfingen), Georg von Salis-Soglio (Leipzig) and Stephan Kirschner (Dresden), Germany.

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