Chapter 8

Body mass index and alignment and their interaction as risk factors for progression of knees with radiographic signs of osteoarthritis

Erlangga Yusuf[1], Jessica Bijsterbosch[1], P Eline Slagboom[2], Frits R Rosendaal[3], Tom WJ Huizinga[1], Margreet Kloppenburg[1]

From:
Leiden University Medical Center, Leiden, The Netherlands
[1] Department of Rheumatology
[2] Department of Molecular Epidemiology
[3] Department of Clinical Epidemiology

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ABSTRACT

Objective

To investigate in which way body mass index (BMI) and alignment affect the risk for knee osteoarthritis (OA) progression.

Methods

Radiographs of 181 knees from 155 patients (85% female, mean age 60 years) with radiographic signs of OA were analyzed at baseline and after 6 years. Progression was defined as 1-point increase in joint space narrowing score in the medial or lateral tibiofemoral (TF) compartment or having knee prosthesis during the follow-up for knees with a Kellgren and Lawrence score ≥1 at baseline. BMI at baseline was classified as normal (< 25 kg/m^2), overweight (25 to 30) and obese (> 30). Knee alignment on baseline radiographs was categorized as normal (TF angle between 182° and 184°) and malalignment (< 182° or > 184°). We estimated the risk ratio (RR) with 95% confidence interval for knee OA progression for overweight and obese patients and for malaligned knees relative to normal using generalized estimating equations (GEE). Additionally, we estimated the added effect when BMI and malalignment were present together on progression of knee OA. Adjustments were made for age and sex.

Results

Seventy-six knees (42%) showed progression: 27 in lateral and 66 in medial compartment. Knees from overweight and obese patients had an increased risk for progression (RR 2.4 (1.0 to 3.6) and 2.9 (1.7 to 4.1), respectively). RRs of progression for malaligned, varus and valgus knee were 2.0 (1.3 to 2.8), 2.3 (1.4 to 3.1), and 1.7 (0.97 to 2.6), respectively. When BMI and malalignment were included in one model, the effect of overweight, obesity and malalignment did not change. The added effect when overweight and malalignment were present was 17%.

Conclusion

Overweight is associated with progression of knee OA and shows a small interaction with alignment. Losing weight might be helpful in preventing the progression of knee OA.

8.1. INTRODUCTION

Osteoarthritis (OA) develops through different pathways in which overweight plays a prominent role.[1,2] Overweight is associated with higher mechanical load and exposure to systemic effects of fat, which could lead to cartilage damage. Cartilage damage is known to be the central pathological feature of OA.[1] The knee, as a weight-bearing joint, is affected most by obesity. Theoretically, overweight should not only be associated with the development of knee OA but also with its progression. However, according to a systematic review published in 2007 that included seven studies, the evidence on the association between body mass index (BMI) and progression of knee OA is conflicting.[2] Other observational studies [3,4] published after that review also showed conflicting results.

Besides overweight, another important mechanical factor that exerts its force on the knee is malalignment. It has been shown that malaligned knees are at higher risk to have knee OA progression.[5-7] Arguably, when the two forces: overweight and malalignment are present together in one knee, the chance of having knee OA progression would be increased. Interestingly, a recent study showed that knee alignment status could modify the association between BMI and knee OA progression. Niu et al. showed that knees from very obese subjects were associated with higher risk of knee OA progression only in neutral but not in varus and valgus aligned knees.[3] Overall, they did not observe an association between BMI and knee OA progression.

To understand the effect of overweight on knee OA progression, the influence of malalignment need to be taken into account. Therefore, we investigated how overweight and alignment affected the risk of knee OA progression. We also investigated the association between varus and valgus alignments with medial and lateral progression of knee OA. Our results will give more insight in the modifiable risk factor overweight.

8.2. PATIENTS AND METHODS

8.2.1. Study design and patient population

This study is part of the Genetic ARthrosis and Progression (GARP) study, a cohort study aimed at identifying determinants of OA susceptibility and progression.[8] In this study, 192 Caucasian sibpairs (aged 40 to 70 years) were included with symptomatic OA at multiple joint sites in the hands or OA in two or more of the following joint sites: hand, spine (cervical or lumbar), knee, or hip. Patients with secondary OA, familial syndromes with a clear Mendelian inheritance, and a shortened life expectancy (<1 year) were excluded. Patients underwent baseline assessment between August 2000 and March 2003. The follow-up assessment was performed between April 2007 and June 2008 (mean follow-up 6 years).[9] This study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

To be eligible for the present study, a patient needed to have radiographic signs of OA, [10] indicated by Kellgren and Lawrence (K&L) (appendix C.1) score of 1 (possible osteophyte lipping) or higher, in at least one knee at baseline.

8.2.2. Radiographs

Standardized non-fluoroscopic weight-bearing/semiflexed posterior anterior (PA) radiographs of the knees were obtained by a single experienced radiographer at baseline and after 6 years using a standard protocol with a fixed film focus distance (1.30 m). To facilitate uniform anatomical alignment of the knee, a SynaFlex X-ray positioning frame (Synarc. Inc., San Francisco, CA) was used. Baseline radiographs were analog films and were digitized using a film digitizer at a resolution corresponding to a pixel size of 100 mu. Follow-up radiographs were obtained digitally.

8.2.3. Evaluation of risk factors

Demographic data were recorded using standardized questionnaires. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively (shoes, socks and bulky clothing removed). BMI was calculated as weight in kilograms divided by squared height (in meters). We categorized BMI into three categories: < 25 (normal, referent), 25 to 30 (overweight), and > 30 kg/m^2 (obese).

Anatomic knee angle was measured on baseline radiographs by two trained examiners (AT, EY) as the medial angle formed by the femur and tibia as described by Moreland and colleagues.[11] Two lines originating at least 10 cm from the knee joint margins were drawn: one passing through the middle shaft of the femur and the other one through the middle shaft of the tibia. The medial angle subtended at the meeting point of these two lines was defined as the anatomic tibiofemoral angle (TF angle). This measurement technique of alignment has been shown to be a valid alternative of alignment measurement using hip-knee-ankle (HKA) axis.[12] The inter-observer reproducibility expressed as intraclass correlation coefficient (ICC) based on measurement of 16 randomly selected knees was excellent. The ICC was 0.94.

The knees were categorized based on TF angle into three groups: normal (TF angle between 182° and 184°), varus (TF angle < 182°) and valgus alignment (TF angle > 184°). These cutoffs were based on values for normal, varus and valgus alignment at full-limb radiograph as described by Moreland et al.[11] with 4° adjustment for the offset in valgus direction when TF angle was measured on knee radiograph.[5]

8.2.4. Radiographic progression

Baseline and 6-year radiographs were scored paired in chronological order, by a team of two experienced readers (EY, JB) that was blinded for patient characteristics. Using the Osteoarthritis Research Society International (OARSI) atlas (appendix C.2), [13] joint space narrowing (JSN) was graded 0 to 3 in the medial and lateral compartment leading to a sum score of JSN ranging from 0 to 6. Joint space was assessed because it reflects articular cartilage damage.[6] The ICC for intra-reader reproducibility based on 25 randomly selected pairs of radiographs was excellent: 0.98.

Radiological progression was defined as difference between the sum of JSN scores at follow-up and at baseline above the smallest detectable change (SDC). The SDC reflects the change above the measurement error and was calculated in the present study by scoring 25 randomly selected pairs of radiographs twice.[14] In the present study, a 1-point increase in JSN score was considered as radiological progression. Also considered as progression were knees with prosthesis during the follow-up.

8.2.5. Statistical analysis

We first examine the association between the risk factors and knee OA progression. The odds ratios (ORs) for knee OA progression for knees from obese and overweight categories and for malaligned knees were calculated relative to knees with normal weight and normal alignment (reference categories). The calculation was performed using generalized estimating equations (GEE) analysis to account for the correlations between two knees within a subject (PASW Statistics 17 (SPSS Inc., Chicago, USA)). Then, we included BMI and malalignment in one model to investigate whether the effect of BMI was confounded by alignment status. Additionally, we investigated whether varus and valgus knees were associated with a specific compartmental knee progression, by calculating the ORs for medial and lateral knee OA progression for varus and valgus knees relative to normal aligned knees.

In all analysis, adjustment was made for age and sex. All ORs were transformed to risk ratios (RRs) with 95% confidence interval (95% CI) using the approximation formula of Zhang because ORs of common outcomes in a cohort study are not a good approximation of RRs.[15]

The amount of interaction between BMI and malalignment on progression of knee OA, was calculated using a method described by Rothman for departures of additive effects.[16] BMI and alignment were first re-categorized into two categories. BMI into: normal (≤ 25 kg/m^2) and overweight (> 25), and alignment into: normal (TF angle between 182° and 184°) and malalignment (TF angle < 182° or > 184°). Then, the increase in RR for malalignment knees among knees with normal BMI was calculated. Similarly, the increase in RR was calculated for knees with overweight among knees with normal alignment. The sum of these increases together with the background effect was then compared with the RR of the combined joint effect, i.e., the RR for knee with malalignment and overweight relative to knee with normal alignment and normal BMI. The difference represents the amount of additive effect on knee OA progression when BMI and malalignment were present together.

8.2.6. Sensitivity analysis

A sensitivity analysis was performed to evaluate whether the association between BMI and knee OA progression would change when the sub-sample of knees with definite OA (K&L scores of ≥2 at baseline) was used. In this sub-sample, the RR of knee OA progression across the BMI categories was calculated relative to normal BMI. A sensitivity analysis was also performed to examine the effect of obesity on knee OA progression across alignment status: varus, valgus and normal in patients with K&L scores of ≥2 at baseline.

8.3. RESULTS

8.3.1. Population

The flow of participants is shown in figure 8.1. Of 237 patients with radiographic signs in at least one knee at baseline, 160 patients were available for follow-up. Eleven patients died during follow-up, eight were lost to follow-up, two emigrated and 56 did not give consent to perform follow-up radiographs. Most frequent reasons for non-consent were unavailability of transport and large distance (n = 23), loss of interest to participate (n = 20) and health problems not related to OA (n = 13). At baseline, mean age of patients with follow-up (SD) was 59.6 (7.5) years, 85.2% was female and mean BMI (SD) was 27.7 (5.3) kg/m^2 (table 8.1). Mean age (SD) of patients without follow-up was 63.6 (7.8) years, 77% was female, and mean BMI (SD) was 28.0 (5.5) kg/m^2.

Of the 320 knees from 160 patients with follow-up, 139 knees were excluded from the analysis: 107 had no signs of knee OA, 10 due to missing alignment data (corresponding to five patients in which analog radiographs could not be digitized), 12 due to knee prosthesis at baseline and 10 due to maximum K&L score of 4 at baseline (table 8.1).

Of the eligible 181 knees from 155 patients, 51 knees had normal, 74 varus and 56 valgus alignments. Seventy six of 181 knees (42%) had progression, 27 had lateral, 66 had medial progression and 25 knees had prosthesis during the follow-up.

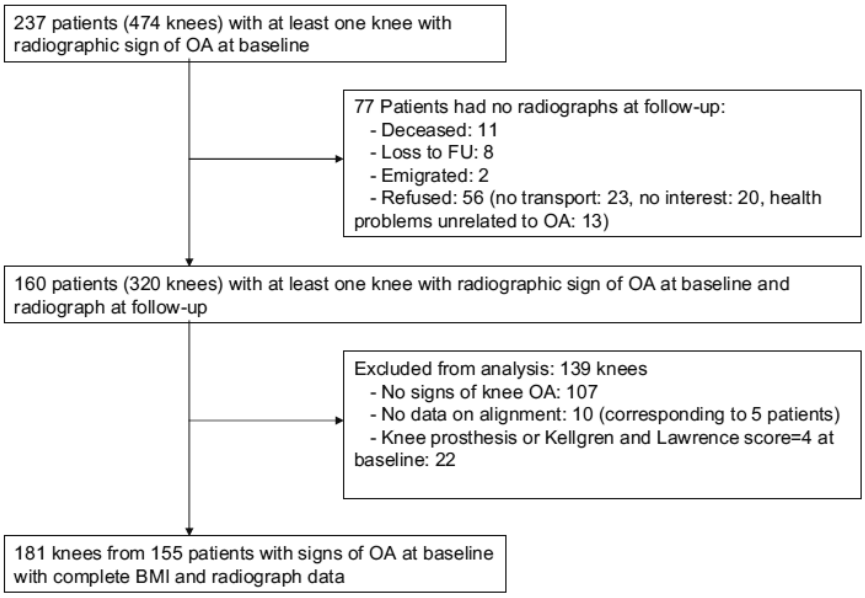

Figure 8.1 Study flowchart.

Table 8.1 Characteristics of the study population (n=155 patients) at baseline.

Characteristics	
Mean age (SD), years	59.6 (7.4)
Number of female, %	132 (85.2)
Mean BMI (SD), kg/m^2	27.7 (5.3)
Normal (< 25), %	94 (34.2)
Overweight (25-30), %	112 (40.7)
Obese (>30), %	69 (25.1)
Knee level data	n=310
Kellgren&Lawrence score	
0	107
1	51
2-3	130
4	10
Knee prosthesis	12

8.3.2. Association between BMI, malalignment, BMI and malalignment with progression of knee OA

Compared to knees of patients with normal weight, the RR (95% CI) for progression in knees from patients with overweight was 2.4 (1.3 to 3.6) (table 8.2) and for knees from patients with obesity was 2.9 (1.7 to 4.1).

Knees with malalignment had a RR of 2.0 (1.3 to 2.8) for progression compared to knees with normal alignment. For varus knees the RR was 2.3 (1.4 to 3.1) and for valgus knees the RR was 1.7 (0.97 to 2.6) for progression in comparison to normal aligned knees.

When BMI and alignment were included in one model, the effect of overweight and obesity did not change much: the RR for knees of overweight patients was 2.3 (1.2 to 3.5) and for knees of obese patients was 2.7 (1.5 to 3.9) compared to knees in normal weight patients. The effect of malalignment was also not affected by controlling for BMI, the RR for knee OA progression for knees with malalignment relative to knee with normal alignment was 1.8 (1.1 to 2.7). Finally, the effects of the two types of malalignment were also virtually unaffected by adjustment for BMI: compared to knees with normal alignment, the RR for knee OA progression for knees with varus alignment (TF angle < 182°) was 2.1 (1.2 to 2.9) and knees with valgus alignment (TF angle: > 184°) was 1.5 (0.8 to 2.5).

Table 8.2 Association between alignment, body mass index (BMI) with knee osteoarthritis progression (n=181 knees).

	Knee OA progression		Risk Ratio (95% CI)[1]	Risk Ratio (95% CI)[2]
	Yes	No		
BMI (kg/m²)				
Normal (< 25)	10	42	1 (reference)	1 (reference)
Overweight (25 to 30)	41	44	2.4 (1.3 to 3.6)‡	2.3 (1.2 to 3.5)‡
Obese (> 30)	25	19	2.9 (1.7 to 4.1)‡	2.7 (1.5 to 3.9)‡
Tibiofemoral alignment, (°)				
Normal (182 to 184)	12	39	1 (reference)	1 (reference)
Malalignment	64	66	2.0 (1.3 to 2.8)‡	1.8 (1.1 to 2.7)‡
Varus (<182)	41	33	2.3 (1.4 to 3.1)‡	2.1 (1.2 to 2.9)‡
Valgus (>184)	23	33	1.7 (0.97 to 2.6)	1.5 (0.8 to 2.5)

[1] adjusted for age and sex, [2] in the model: BMI, alignment, age and sex
‡ significant at level p< 0.05

8.3.3. Association between malalignment and medial and lateral progression of knee OA

Varus alignment (TF angle < 182°) was associated with medial knee OA progression. The RR (95% CI) for medial progression for varus knees compared to normal aligned knees was 2.4 (1.5 to 3.3); no significant association was seen with lateral progression (RR 4.1(1.0 to 12.1)) (table 8.3). Valgus alignment (TF angle > 184°) was associated with lateral knee OA progression (RR 6.0, 95% CI 1.6 to 15.1) but not with medial progression (RR 1.2, 95% CI 0.6 to 2.2) compared to subjects with normal alignment.

Table 8.3 Association between knee alignment with medial and lateral knee osteoarthritis progression (n=181 knees).

Alignment	Knees with medial OA progression		Risk Ratio for medial progression[1] (95% CI)	Knees with lateral OA progression		Risk Ratio for lateral progression[1] (95% CI)
	Yes (n=66)	No (n=115)		Yes (n=27)	No (n=154)	
Normal	11	40	1 (reference)	2	49	1 (reference)
Varus	40	34	2.4 (1.5 to 3.3)‡	12	62	4.1 (1.0 to 12.1)
Valgus	15	41	1.2 (0.6 to 2.2)	13	43	6.0 (1.6 to 15.1)‡

[1] in the model: varus or valgus alignment, age and sex.
‡ significant at level p< 0.05.

8.3.4. Detection of interaction between BMI and alignment on progression of knee OA

The observed RR for knees with malalignment and overweight was 4.1 (table 8.4). Among knees from patients with normal BMI, malalignment had an increase in RR of 0.9 for progression relative to normal alignment. The increase in RR of being overweight in knees with normal alignment was 1.5. The sum of these components together with the background effect (RR = 1) was 3.4. The difference between the sum of these components with the observed joint RR was 0.7 (=4.1 to 3.4). The part of RR that was attributable to interaction between malalignment and overweight was thus 0.7/4.1=17%.

Table 8.4 Risk ratio (with 95% confidence interval) of progression by alignment status and the presence or absence of overweight (n=181 knees).

Tibiofemoral alignment	Normal BMI (≤25 kg/m²), n=52	Overweight (> 25 kg/m²), n=129
Normal (182 to 184), n=51	1 (background effect) (n=24)	2.5 (0.7 to 5.1) (n=27)
Malalignment (<182 or >184), n=130	1.9 (0.5 to 4.8) (n=28)	4.1 (1.8 to 6.1) (n=102)

8.3.5. Sensitivity analysis

In the subgroup of knees with K&L scores of ≥2 at baseline (n = 128), the RR (95% CI) for OA progression in knees from obese and overweight patients relative to knees from normal weight patients, was 1.8 (1.1 to 2.3) and 1.4 (0.8 to 2.0) respectively after adjustment for age and sex. Among varus knees with K&L scores of ≥2 at baseline (n= 64), higher BMI was associated with knee OA progression. Varus knees from obese and overweight patients had a RR of 3.0 (1.2 to 2.6) and 1.7 (0.5 to 3.0), respectively to have progression relative to varus knee from normal weight patients. No significant association was shown with BMI in valgus knees (n = 35) and normal aligned knees (n = 29). In normal aligned knees, the RRs for progression were 1.1 (0.2 to 2.6) and 1.7 (0.4 to 3.0) for knees from obese and overweight patients, relative to knees from patients with normal weight, respectively. In normal aligned knees, there were only seven knees in the stratum obese (BMI > 30 kg/m²).

8.4. DISCUSSION

In the present study, obesity and malalignment were associated with the progression of knee OA. It seemed that malalignment modified the association between obesity and knee OA progression in some amount. We also found that varus alignment was associated with medial progression and valgus alignment with lateral progression.

Our findings do not support the results from a study by Niu et al. where no overall relationship between obesity and the progression of knee OA was shown.[3] Probably, the difference in the BMI between the study populations explains the difference in

the results. More than 80% of Niu's study population had a BMI above 25 kg/m^2 (mean BMI ± SD was 30.4 ± 5.7), leading to less contrast between overweight or obese patients with normal weight patients. One might argue that the difference in the results could be caused by the difference in the definition of the study population. In the present paper, we investigated the OA progression among knees with signs of OA at baseline (K&L scores ≥1) because K&L grade 1 definitely does not represent normal knees. This definition has also been used by others to define OA, for example in a clinical trial on glucosamine.[17] While going from K&L grade 1 to 2 is characterized as progression in our study, it was characterized as incidence in the study from Niu et al. Yet, in our study, when we performed a sensitivity analysis by selecting only cases with K&L scores ≥2, obesity was still shown to be associated with knee OA progression with smaller RR. Overweight was also still positively associated with progression, however, the association is no longer significant.

In the subgroup of patients with K&L scores ≥2, we also found that higher BMI was associated with knee OA progression among varus knees but not among normal and valgus knees. The failure in showing the association in normal and valgus aligned knees might be caused by small numbers of knees in the obese stratum. There were only seven knees with normal and five knees with valgus alignment in the obese stratum. Our results are in contrast with the results of Niu et al. where they did not find the association between obesity and knee OA progression among varus knees.[3] Niu et al. did find the association between obesity and incidence of knee OA (K&L scores ≥2 at 30-months follow-up) among varus knees in knees with K&L scores ≤1 at baseline. They hypothesized that the effect of varus alignment differed across different stages of OA: varus might has smaller role in incidence of OA than obesity, but it might drive the progression of OA more than obesity. They based their explanation on the observation that varus malalignment was more common in knees with definite OA (K&L scores ≥2) than in knees with K&L scores ≤1 at baseline (60.8% vs 40.6%, respectively). In our study population, we also found that varus alignment was more common in knees with K&L scores ≥2 (50.4%) than in knees with K&L scores ≤1 (29%). Yet, we still found the association between obesity and knee OA progression in varus aligned knees with K&L scores ≥2 at baseline. Therefore, we do not support the hypothesis from Niu et al.

Re-evaluating the studies included in a systematic review by Belo and colleagues [2] on BMI as risk factor of knee OA progression.[18-24] We notice that the studies that failed to observe an association between overweight or obesity and progression were small (study population less than 110 patients).[19,21,23] However, those studies showed positive effect sizes with wide confidence intervals. Therefore, lack of statistical significance was erroneously interpreted as an absence of an association (type II error). In larger studies, Cooper et al., in a study in 354 subjects with K&L score ≥1 at baseline, found an OR of 2.6 (95% CI 1.0 to 6.8) for ≥1 increase in K&L score in at least one of the knees, when patients within the highest BMI tertile (BMI > 25.4 kg/m^2) were compared with the lowest tertile (BMI < 22.7 kg/m^2).18 Yet, the RR became smaller and not significant (1.3, 95% CI 0.3 to 5.0) when only subjects with K&L score ≥2 at baseline were selected. Ledingham et al. investigated 350 OA knees and found an OR for an increase in JSN of 1.07 (95% CI 1.02 to 1.14).[20] A population based study in 1507 patients showed a Hazard Ratio of 1.04 (95% CI 1.01 to 1.07). Schouten and colleagues investigated 422 subjects showing ORs of 3.82 (95% CI 1.2 to 12.2) and 8.8 (2.8 to 27.8), respectively for a comparison between patients with a BMI of 26 to 27.7 kg/m^2 and a BMI > 27.8 kg/m^2 to subjects with a BMI < 24.3 kg/m^2.[22] None of these studies investigated alignment.

Concerning alignment, our study support the notion that varus alignment is associated with medial progression of knee OA and valgus alignment is associated with lateral progression of knee OA as shown for the first time by Sharma and colleagues.[6] Our results support the biomechanical studies that varus and valgus alignment increase medial and lateral load, respectively, and do so with similar risk increases.[6]

Our study has several limitations. An important limitation is that we do not have full-limb radiographs, therefore preventing accurate measurement of mechanical alignment. Yet, we put efforts in approximating the mechanical alignment by using flexed knee protocol and by using a mean offset of 4° in the valgus direction in categorizing knees as normal, varus or valgus. This offset has been reported by Kraus et al. as the offset for anatomic compared to mechanic alignment.[25] Although not optimal, the anatomical axis was shown to be correlated very well with mechanical axis measured using HKA axis (r= 0.88).[12] There is a possibility that the effect of

obesity on knee OA progression is not eliminated after adjustment for malalignment due to a possible misclassification of knee alignment status. Another limitation of the present study is the small sample size. The sample size is enough to detect the overall effect of BMI, malalignment and varus alignment on the risk for knee OA progression. However, to prevent type II error, we could not draw any conclusion on the effect of obesity on knee OA progression among normal and valgus knees.

Our findings have implications for clinical studies and studies in the pathophysiology of adipose tissue in OA. Clinical trials on the effect of weight loss in preventing knee OA progression and studies that investigate the effects of physical therapy intervention which reduce the stresses on a given alignment [6] could be done in separate trials or simultaneously to look at synergistic effects.

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