EXTENDED REPORT

Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis

S Amin, J Niu, A Guermazi, M Grigoryan, D J Hunter, M Clancy, M P LaValley, H K Genant, D T Felson

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See end of article for authors' affiliations

Correspondence to: Dr S Amin, Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA; amin.shreyasee@mayo.edu

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Objective: To examine the effects of smoking on cartilage loss and pain at the knee in individuals with knee osteoarthritis.

Methods: 159 men with symptomatic knee osteoarthritis who participated in a 30-month, prospective, natural history study of knee osteoarthritis were examined. The more symptomatic knee was imaged using magnetic resonance imaging (MRI) at baseline, and again at 15 and 30 months of follow-up. Cartilage was scored using the Whole-Organ MRI Score semiquantitative method at the medial and lateral tibiofemoral joints and at the patellofemoral joint. At baseline and follow-up visits, the severity of knee pain was assessed using a Visual Analogue Scale pain score (0–100 mm).

Results: Among the 159 men, 19 (12%) were current smokers at baseline. Current smokers were younger (mean (standard deviation (SD)) age 62 (9) *v* 69 (9) years) and leaner (mean (SD) body mass index (BMI): 28.9 (3.2) *v* 31.3 (4.8) kg/m^2) than men who were not current smokers. When adjusted for age, BMI and baseline cartilage scores, men who were current smokers were found to have an increased risk for cartilage loss at the medial tibiofemoral joint (odds ratio (OR) 2.3, 95% confidence interval (CI) 1.0 to 5.4) and the patellofemoral joint (OR 2.5, 95% CI 1.1 to 5.7). Current smokers also had higher adjusted pain scores at baseline (60.5 *v* 45.0, $p<0.05$) and at follow-up (59.4 *v* 44.3, $p<0.05$) than men who were not current smokers.

Conclusions: Men with knee osteoarthritis who smoke sustain greater cartilage loss and have more severe knee pain than men who do not smoke.

Cigarette smoking has been associated with chronic musculoskeletal conditions, such as low-back pain and degenerative disc disease.[1–4] However, the effect of smoking on the pathogenesis and progression of symptomatic knee osteoarthritis, one of the leading causes of disability in elderly people,[5] has been unclear.

Evidence suggests that cigarette smoke may have a negative effect on cartilage metabolism. Triggered by epidemiological evidence of a link between smoking and back pain,[1 2] animal and in vitro studies have shown that components of tobacco smoke have a deleterious effect on chondrocyte function in discs, inhibiting cell proliferation and extracellular matrix synthesis.[6–9] These findings raise concern about the potential negative effects of smoking on chondrocyte function in articular cartilage.

Further, the effect of smoking on severity of knee pain in people with knee osteoarthritis has not been well studied. Smokers not only have greater back pain[1 2] but may also have greater musculoskeletal pain in general.[10] If smoking were related to severity of knee pain in people with knee osteoarthritis, regardless of its effects on the cartilage, it would provide additional evidence for smoking having a negative effect on symptoms of another prevalent musculoskeletal condition.

Should cigarette smoking have a role in the progression of symptomatic knee osteoarthritis, it would be a potentially modifiable risk factor with important public health implications. To date, few studies have examined the association between smoking and symptomatic knee osteoarthritis, and findings have been conflicting.[11–18] To our knowledge, no one has examined the effect of current smoking on cartilage loss over time, or its relationship with the severity of knee pain, in people with prevalent knee osteoarthritis. We examined whether people with knee osteoarthritis who smoke have increased cartilage loss at the knee, as assessed by magnetic resonance imaging (MRI) and knee pain over a 30-month follow-up period.

PARTICIPANTS AND METHODS

Study participants

Study participants were enrolled in a 30-month natural history study on symptomatic knee osteoarthritis (Boston Osteoarthritis of the Knee Study) whose recruitment has been described in detail previously.[19 20] Potential participants answered yes to the following two questions: ''Do you have pain, aching or stiffness in one or both knees on most days?'' and ''Has a doctor ever told you that you have knee arthritis?'' A subsequent interview was conducted to exclude other forms of arthritis. Eligible participants all had to have an osteophyte present on radiographs of their symptomatic knee, be able to walk, with or without the aid of a cane, and be willing to participate in the longitudinal study. In all, 324 people (201 men and 123 women) met the eligibility criteria. All participants met the American College of Rheumatology criteria for symptomatic knee osteoarthritis.[21] We focused our study on the men recruited, as too few women (4%) reported smoking at baseline. The minimum age of entry for men was 45 years. Among the 201 eligible men, 5 had contraindications to MRI, so 196 men were enrolled in the study.

Study overview

Examinations were conducted at baseline, and at 15 and 30 months, and included imaging studies of knees and questionnaire data. The institutional review boards of the Boston University Medical Center and the Veteran Affairs Boston Healthcare System, Boston, Massachusetts, USA, approved the baseline and follow-up evaluations.

Abbreviations: BMI, body mass index; MRI, magnetic resonance imaging; VAS, Visual Analogue Scale; WORMS, Whole-Organ MRI Score

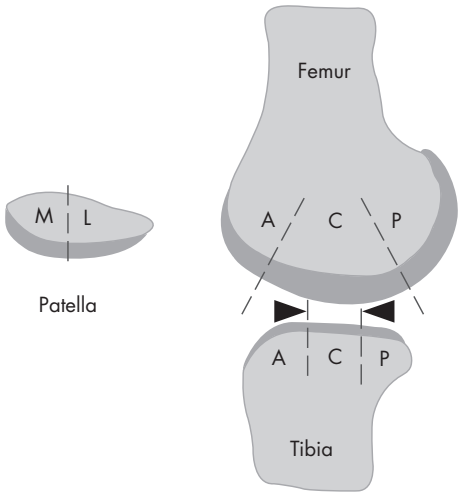

Figure 1 A sketch of the knee (sagittal view) and patella illustrating the five cartilage plates of the tibiofemoral joint (central and posterior femur; and anterior, central and posterior tibia) and four plates of the patellofemoral joint (medial and lateral patella and anterior femur). A, anterior; C, central; L, lateral; M, medial; P, posterior.

Cigarette smoking status

At baseline and 15 months, participants were queried on cigarette smoking using a standard questionnaire. As we were interested in the potential toxic effects of current smoking on cartilage over follow-up, participants were characterised into two groups based on whether or not they were currently smoking at their baseline evaluation.

MRI evaluation of knee articular cartilage and definition of cartilage loss

At baseline, participants without contraindications underwent MRI of the more symptomatic knee, and this knee was imaged again at 15 and 30 months. MRI scans were acquired on a General Electric Signa 1.5-T MRI system (GE Medical Systems, Milwaukee, Wisconsin, USA) using a phased-array knee coil. An anchoring device for the ankle and knee was used to ensure uniformity of positioning between patients and for follow-up. The imaging protocol included sagittal spin-echo proton density and T2-weighted images, as well as coronal and axial spin-echo, fat-saturated, proton-density and T2-weighted images (repetition time, 2200 ms; time to echo, 20/80 ms) with a slice thickness of 3 mm, a 1-mm interslice gap, 1 excitation, a field of view of 11–12 cm and a matrix of 256×192 pixels.

Cartilage morphology at the tibiofemoral and patellofemoral joint was assessed using the Whole-Organ MRI Score (WORMS) semiquantitative method for knee osteoarthritis.[22] As previously described, a total of three trained readers scored all MRI scans[23] and were blinded to smoking status of participants. A musculoskeletal radiologist and a musculoskeletal researcher, from the Osteoporosis and Arthritis Research Group of the University of California, San Francisco, California, USA, read most subjects (86%) with longitudinal MRI scans, reading as a pair, together.[23] Cartilage morphology was scored on all five regions of the tibiofemoral joint (central and posterior femur; and anterior, central and posterior tibia), each for the medial and lateral compartment (fig 1). The patellofemoral joint was scored at all four regions: the medial and lateral surfaces of the patella and anterior femur (fig 1). Cartilage morphology was scored using a 0–6 scale: 0, normal thickness and signal; 1, normal thickness but increased signal on T2-weighted images; 2, solitary focal defect of <1 cm at the greatest width; 3, areas of partial-thickness defects (<75% of the region) with areas of preserved thickness; 4, diffuse partial-thickness loss of cartilage (⩾75% of the region); 5, areas of full-thickness loss (<75% of the region) with areas of partial thickness loss; and 6, diffuse full-thickness loss (⩾75% of the region).[22] Intraclass correlation coefficient on agreement for cartilage readings ranged from 0.72 to 0.97 for the examiners.[23]

Scores of 1 and 2 were infrequent in our population.[23] Also, grade 1 represents a change in the signal of an otherwise normal cartilage morphology, whereas grades 2 and 3 represent similar abnormalities, focal defects without overall thinning. Therefore, to create a consistent scale for evaluating change in cartilage morphology over follow-up, we collapsed the original WORMS cartilage scores to a 0–4 scale for analyses, where the original WORMS scores of 0 and 1 were collapsed to 0, the original scores of 2 and 3 were collapsed to 1, and the original scores of 4, 5 and 6 were considered 2, 3 and 4, respectively.[23] Using this new scale, cartilage loss at each region of the knee (eg, the central tibia region) was defined by the increase in score over follow-up (range of scores for cartilage loss 0–4).

Table 1 Baseline characteristics of 159 men included in the study

Baseline characteristics	
Mean (SD) age, years	68 (9)
Mean (SD) body mass index, kg/m^2	31.0 (4.7)
Current smokers, n	19
Knees with Kellgren and Lawrence grade ⩾2, %	70
Knees with cartilage morphology scores ⩾1 in any region within a compartment or joint*†, %	
Tibiofemoral joint	
Medial compartment	85
Lateral compartment	59
Patellofemoral joint	90

* Baseline cartilage morphology score of ⩾1 at ⩾1 of the 5 regions within a compartment of the tibiofemoral joint or at ⩾1 of the 4 regions of the patellofemoral joint.
†Equivalent to original Whole-Organ MRI cartilage morphology score (0–6 scale) of ⩾2.

Knee pain

At baseline and all follow-up visits, participants were asked to rate the severity of pain in each knee over the past week, which they scored by using a 100-mm Visual Analogue Scale (VAS), generating a score from 0 (no pain) to 100 (most severe pain possible).

Covariates

At all visits, participants were weighed, with shoes off, on a balance beam scale, and height was measured. They also completed the Physical Activity Scale for the Elderly,[24] a validated questionnaire for assessing physical activity among older people. Alignment at the knee was assessed at the first follow-up examination, at which time long-limb films were obtained with a 14×51 cassette, using methods described previously.[25]

Statistical analyses

Statistical analyses were performed using SAS V.8.2.

Cigarette smoking and articular cartilage loss

We examined cartilage loss at the tibiofemoral joint (medial and lateral compartments were analysed separately) and the patellofemoral joint using 30-month follow-up data, unless unavailable, in which case 15-month data were used. The cartilage loss at each region of the knee within a compartment or joint took on whole number values from 0 (no loss) to 4 (maximum loss) and was

Table 2 Baseline characteristics by smoking status of the 159 men followed up longitudinally

Baseline characteristics	Current smokers	
	Yes (n = 19)	No (n = 140)
Age, years	62 (9)*	69 (9) (p = 0.0026)
BMI, kg/m^2	28.9 (3.2)*	31.3 (4.8) (p = 0.0089)
Knees with Kellgren and Lawrence Grade ⩾2, %	68	70
Knees with cartilage morphology scores ⩾1 in any region within a compartment or joint†, %		
Tibiofemoral joint		
Medial compartment	77	86
Lateral compartment	29*	63 (p = 0.0083)
Patellofemoral joint	94	89
VAS pain score (mean, SD), 0–100 mm	61.1 (26.3)*	43.4 (25.5) (p = 0.0065)
Physical Activity Scale for the Elderly Score (mean, SD)	106.6 (82.2)	138.2 (92.8)
Knee alignment, degrees (mean, SD)‡	5.2 (7.6)	4.9 (5.5)

BMI, Body Mass Index; VAS, Visual Analogue Scale; WORMS, Whole-Organ Magnetic Resonance Imaging Score.
Values are mean (SD) unless specified.
*Statistically different, at $p<0.05$, between men who were and were not current smokers.
†Equivalent to original WORMS cartilage morphology score (0–6 scale) of ⩾2.
‡Results limited to 81% of 159 men (current smokers, n = 17; and not current smokers, n = 112) who had measures of knee alignment. Values >0 correspond to varus alignment and <0 correspond to valgus alignment.

analysed as ordered categories using the proportional odds logistic regression model. A generalised estimating equation correction was applied to regression models to account for the association in cartilage loss outcome between regions within a knee compartment or joint. Analyses were adjusted for age, body mass index (BMI) and baseline cartilage scores. In secondary analyses, we considered the effect of other potential confounders, including knee pain and physical activity at baseline, and alignment.

Cigarette smoking and knee pain

We used the knee-specific VAS pain scores for the knee that was imaged over follow-up in analyses. We used 30-month data unless unavailable, in which case 15-month data were used. We examined whether there were differences in mean VAS knee pain scores between men who were and were not current smokers, at baseline as well as follow-up, adjusted for age, BMI and cartilage scores. We also performed a linear regression analysis to examine the difference between change in pain scores over follow-up, defined as the change in score from baseline to longest available follow-up, between those who were and were not current smokers, adjusted for baseline age, BMI and cartilage score.

RESULTS

Among 196 men with baseline knee MRI, 163 (83%) underwent follow-up MRI at either 15 months, 30 months or both. We found no statistical differences between men who were and were not followed up with respect to age (mean (standard deviation (SD)) 68 (9) *v* 69 (9) years, respectively, mean (SD) BMI (31.0 (4.7) *v* 30.5 (4.9) kg/m^2)), baseline Kellgren and Lawrence grade (70% *v* 76% knees with grade ⩾2), or current smoking status (12% *v* 15%).

Among the 163 men who were followed up, we excluded four participants from analyses because they had MRIs unreadable for cartilage loss. The baseline characteristics for the 159 men in the analyses (table 1) were similar to those of the 163 men. In all, 133 (84%) men had 30-month data for analyses, with no differences in availability of 30-month data by smoking status (89% *v* 83% for men who were *v* were not current smokers); the remaining 26 (16%) had 15-month data. At baseline, 19 (12%) were current smokers, reporting smoking on average (SD) 21 (10) cigarettes/day for a mean 45 (10) years. Over follow-up, four men who were current smokers at baseline quit smoking, whereas one man who was not smoking at baseline reported starting to smoke.

Table 2 lists the baseline characteristics for men who were and were not current smokers. Current smokers tended to be younger and leaner than those who were not smoking. The proportion of current smokers with abnormal cartilage morphology scores at the lateral compartment of the tibiofemoral joint was significantly lower. Current smokers were physically less active and had significantly greater knee pain at baseline. We found no differences between the two groups of men with respect to alignment at the knee (p = 0.9).

Cigarette smoking and articular cartilage loss

In adjusted analyses, current smokers were at increased risk for cartilage loss at the medial compartment of the tibiofemoral joint and the patellofemoral joint compared with men who were not current smokers (table 3). There was no increased risk for cartilage loss at the lateral compartment (table 3).

Table 3 Loss of cartilage at the knee over follow-up by smoking status in 159 men

Proportion of regions within a compartment or joint of the knee with cartilage loss (%)				
	Current smokers		OR (95% CI)	
Compartment or joint	Yes	No	Unadjusted*	Adjusted†
Tibiofemoral joint				
Medial compartment	35	19	2.2 (1.1 to 4.6)	2.3 (1.0 to 5.4)
Lateral compartment	6	6	1.1 (0.3 to 4.1)	1.2 (0.3 to 4.2)
Patellofemoral joint	16	10	1.6 (0.8 to 3.4)	2.5 (1.1 to 5.7)

*Adjusted for baseline cartilage scores only.
†Adjusted for baseline age, body mass index and cartilage score.

Table 4 Knee pain at baseline and follow-up by smoking status among 159 men

	Adjusted least squares mean (95% CI) for knee-specific VAS pain score Current smokers	
	Yes (n = 19)	No (n = 140)
Baseline	60.5 (46.9 to 74.2)†	45.0 (40.3 to 49.6)
Follow-up	59.4 (45.6 to 73.1)†	44.3 (39.5 to 49.1)

VAS, Visual Analogue Scale (0–100 mm).
*Baseline VAS score adjusted for age, body mass index and cartilage score at baseline; follow-up VAS score adjusted for age, body mass index and cartilage score at follow-up.
†Statistically different at $p<0.05$ between men who were and were not current smokers.

Although we recognised that the number of men who were smokers was not large, we did explore the effect of additionally adjusting for baseline knee pain and physical activity, given the differences seen in these parameters between the two groups. Results remained similar. For the medial and lateral tibiofemoral joints and the patellofemoral joint, the adjusted ORs were 3.5 (95% CI 1.4 to 8.6), 1.0 (95% CI 0.3 to 3.7) and 2.4 (95% CI 1.0 to 5.7), respectively. Although not all men had measures of knee alignment, we found no differences in this measure between the two groups, and additional adjustment for alignment yielded similar results, with a significant increased risk for cartilage loss at the medial tibiofemoral and patellofemoral joints, and no effect on the lateral tibiofemoral joint.

Cigarette smoking and knee pain

Although the adjusted change in knee-specific VAS pain scores over follow-up was not significantly different between men who were and were not current smokers (−0.3, 95% CI −14.9 to 14.3, *v* −1.0, 95% CI −6.0 to 4.0, respectively, with a negative score signifying an improvement in the pain score at follow-up), current smokers had significantly higher adjusted knee-specific VAS pain scores at both baseline and follow-up than men who were not smoking (table 4). Adjustment for physical activity or alignment did not influence the findings.

DISCUSSION

In this longitudinal study on men with symptomatic knee osteoarthritis followed for up to 30 months, current smokers were more likely to have articular cartilage loss at the knee than men who were not current smokers. We also found that current smokers had overall greater knee pain, both at baseline and follow-up. Our findings suggest that current smoking may have a deleterious effect on progression of symptomatic knee osteoarthritis among men.

Although relatively few studies have examined the association between smoking and knee osteoarthritis, our findings differ from previous findings. Some have found no association,[13 15 17 18] whereas others have reported a possible protective effect of smoking on knee osteoarthritis.[11 12 14 16] These studies have used radiographs to assess disease, an insensitive measure of articular cartilage damage, and most have been either cross-sectional in nature or have examined incident knee osteoarthritis. The Framingham Study examined the effect of previous smoking status on the presence of knee osteoarthritis, and found smoking to be protective, even after adjustment for weight or BMI.[12] As smokers were leaner, residual confounding from long-term obesity among non-smokers could have produced the protective association observed in that study. Although Sandmark *et al*[17] reported that smokers were less likely to undergo total knee arthroplasty, they acknowledged that it was unknown whether these finding were due to differences in severity of actual disease or other risk factors that precluded surgical intervention. Lastly, the effects of smoking may differ for incident and prevalent knee osteoarthritis. The deleterious effect of smoking on articular cartilage may be greatest when cartilage is already damaged by other mechanisms. Although Schouten *et al*[13] did not find smokers to be at increased risk for progression of knee osteoarthritis over 12 years of follow-up, radiographs were used to assess progression and smoking status was determined only at baseline. To our knowledge, our study is the first to examine the effects of current smoking on loss of articular cartilage, assessed using MRI, among those with established knee osteoarthritis who have been followed up longitudinally.

Our study also examined the effect of current smoking on pain in individuals with symptomatic knee osteoarthritis. Current smokers had overall greater knee pain throughout the study than men who were not current smokers. The mechanism for this effect is unclear. As cartilage does not have pain fibres, the relationship of smoking with greater knee pain is unlikely to be due to the relationship between smoking and cartilage loss. Smoking may have direct effects on other articular structures mediating knee pain or may modify the threshold for musculoskeletal pain among smokers, as suggested by others.[10] On the other hand, socioeconomic status could have influenced pain perception. Current smokers were less likely to have more than a grade 12 education (67% *v* 81%) or be currently employed (17% *v* 34%). In additional analyses, we explored whether current employment or educational level influenced results, and found that it did not (data not shown).

Our study has limitations. We were unable to determine the risk of smoking on cartilage loss in women, as too few women in our study were current smokers. The number of men who were current smokers was also small. Our ability to deal with all possible confounders in analyses was therefore limited; however, we did consider the effects of severity of pain, level of physical activity and alignment at the knee. Bone marrow lesions in the knee have been shown to be related to cartilage loss and knee pain in this study population, but were driven by knee alignment.[20] Further, bone marrow lesions were similar between groups (mean score 4.0 *v* 3.2 in men who were *v* were not current smokers). We also found no differences between groups in interim knee injury (21% *v* 19% for men who were *v* were not current smokers). Although we did not find an increased risk of cartilage loss in the lateral tibiofemoral joint among smokers, there was very little overall loss of cartilage there to have shown an effect, if it was present. Interestingly, current smokers had much less cartilage damage in the lateral tibiofemoral compartment at baseline compared with men who were not current smokers. We could not identify a clear explanation for this apparent difference at the lateral tibiofemoral compartment, as there were no differences in medial or lateral meniscal pathology between groups, or history of knee injury. Current smokers were leaner as well as younger. We adjusted for baseline cartilage scores in our analyses, in addition to age and BMI.

Despite the study limitations, our findings are provocative and suggest the need for further study on the effects of smoking in knee osteoarthritis, especially given the number of potential mechanisms by which cigarette smoke may have an adverse effect on articular cartilage. In studies on animals, the intervertebral discs of smoke-exposed rats showed disordered chondrocytes on histopathology compared with controls,[9] and nicotine markedly inhibited cell proliferation and extracellular matrix synthesis in bovine intervertebral disc chondrocytes cultured in vitro.[6–8] However, others have suggested that nicotine may be beneficial for articular cartilage.[26] Smoking increases oxidant stresses,[27] and oxidant stress may contribute to cartilage loss.[28] Cigarette smoking also increases carbon monoxide levels in arterial blood, contributing to tissue hypoxia,[29] which may, in turn, impair cartilage repair in smokers. Articular cartilage is avascular, receiving its nutrition and oxygen supply by diffusion from the synovial fluid and subchondral bone.[30 31] The partial pressure of oxygen in synovial fluid from healthy joints ranges from 50 to 60 mm Hg,[32] which is lower than in arterial blood, whereas in osteoarthritic joints, the oxygen tension is further decreased.[33] In animal models, long-term hypoxia down-regulated gene expression levels of collagen and growth factors in knee articular cartilage.[30] Although knee articular cartilage expresses the hypoxia-inducible factor 1α, which helps tissue function at low-oxygen tension,[33 34] smoking has been shown to reduce its expression, at least in other tissue.[35] Further research is needed to understand the net effects of smoking on articular cartilage, especially as smoking is a potentially modifiable risk factor.

In summary, men with symptomatic knee osteoarthritis who smoke have an increased risk for articular cartilage loss and have more severe knee pain than men who do not smoke.

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Authors' affiliations

S Amin, Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA
J Niu, D J Hunter, M Clancy, M P LaValley, D T Felson, Clinical Epidemiology Research and Training Unit and Arthritis Center, Boston University School of Medicine, Boston, Massachusetts, USA
A Guermazi, M Grigoryan, H K Genant, Osteoporosis and Arthritis Research Group, University of California at San Francisco, San Francisco, California, USA

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