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Correlation of Amount of Cigarette Smoking with Thickness and Elasticity of Distal Femoral Cartilages using Sono-Elastography Techniques of Ultrasound, a Cross-Sectional Study

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ABSTRACT

Introduction:

Cigarette smoking is a well-known etiology for chronic musculoskeletal system disorders, like osteoarthritis, affecting the distal femoral cartilages. However, recent studies show protective effects of smoking against osteoarthritis. Ultrasound is an easily accessible and reliable imaging tool for the evaluation of the cartilages, measurement of their thickness, and tissue stiffness. This study seeks to objectively show the effects of smoking by affecting their knee joints' cartilage and clarify whether it has a chondroprotective effect, or support the usual evidence that smoking is harmful at any cost.

Methods:

This prospective cross-sectional study compares the thickness and elasticity of distal femoral cartilage in heavy, ordinary smokers and non-smokers using B-mode scanning and real-time strain elastographic technique of ultrasound respectively.

Results:

Among 377 individuals with a mean age of 27.66 years, male predominance (70 %) and mean Body Mass Index (BMI) of 24.55, a higher proportion (50 %) of volunteers were ordinary smokers (pack years <20). Elasticity strain ratios were found to be significantly lower in heavy smokers in both sides' distal femoral cartilages except in right lateral cartilage (p = <0.001) using Fisher's exact test. Significantly lower thickness was noted in both cartilages of the right side (p <0.001) and left lateral cartilage (p = 0.001) among heavy smokers. After adjusting for the effects of age, sex, BMI, and occupation using one-way ANOVA, similar results were obtained.

Conclusions:

Heavy cigarette smoking causes degradation of distal femoral cartilages by decreasing their thickness and elasticity.

Keywords: *Cartilage, Articular; Cigarette Smoking; Elasticity; Knee Joint*

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INTRODUCTION

Smoking cessation is highly advisable due to the direct toxic effects of nicotine on osteoblasts and osteoclasts and indirect actions on sex corticoids, Vitamin D, etc.[1] However, recent studies show protective effects of smoking against osteoarthritis. In a healthy population, smoking was associated with an increase in tibial cartilage volume and have a lower risk of radiographic osteoarthritis than non-smokers.[2,3]

Ultrasound is an easily accessible and reliable imaging tool for the evaluation of cartilage and measurement of its thickness. Elastography is a new ultrasound technique that objectively provides diagnostic information on tissue stiffness.

This study seeks to objectively determine the association between cigarette smoking and femoral articular cartilage thickness and elasticity. It doesn't suggest that smoking be used as a therapeutic intervention in osteoarthritis, as was the case with ulcerative colitis, but clarify whether it has a chondroprotective effect, or supports the usual evidence that smoking is harmful at any cost. [4,5]

METHODS

This is a prospective observational cross-sectional study conducted from January to September 2018 in a tertiary 1000 bedded government hospital. The research proposal was given approval from the institutional technical and ethics review committee (BMC/IRC/2016/00354). Informed consent was obtained from the study population before the study. Measures were taken to ensure confidentiality and anonymity.

Techniques for data collection:

- Data on the demography of subjects were recorded in the data form. For occupation of the participants, it was divided into two categories based on the level of physical strain they apply on their lower limbs with the score in the range of 1 to 10, as asked in the questionnaire provided. (Laborers: Rate >6, Non-laborers: Rate $\leq$ 6)
- Radiographically normal knee joints were regarded as normal knee joints and included.
- Smokers were categorized according to the pack-years (PY) of smoking. Heavy smokers: $\geq$20 PY, Ordinary smokers: <20 PY. Non-smokers: either never smoked once (0 PY) or less than 5 cigarettes up to now.
- The elasticity of the distal femoral cartilage was evaluated using strain elastography and strain ratios (Strain ratio: Reference tissue strain/ cartilage strain of each region of interest) using an ultrasound machine (Mindray DC-70, China). Ratio <1 = hard, Ratio =1= intermediate, Ratio >1= soft.
- For thickness, B-mode measurement in transverse and longitudinal planes at particular anatomical landmarks was taken. Each measurement was taken three times on each medial and lateral condylar cartilage area of both knees.
- With the patient lying supine and knee fully flexed (>125^{o}) measurements were taken from midpoints of the aforementioned areas by drawing a vertical line between cartilage bone and synovial space-cartilage surfaces.
- The researcher doing the procedure was blinded from the demographic data and/or smoking history.

Inclusion criteria:

- The adults aged (25-50 years).
- The subjects should give informed consent for the study.
- All subjects should have the normal radiographic appearance of the knee joints

(e.g., normal condylar architecture, maintained joint space, no subchondral sclerosis or articular surface irregularity).

Exclusion criteria:

- Those subjects with known knee joint-related diseases based on a questionnaire, for eg: rheumatoid arthritis, crystal arthropathy, knee injury requiring non-weight-bearing treatment, reactive arthritis, restricted knee range of motion, history of arthroscopy procedures, lower limb mechanical axis deviation, hip arthritis diagnosed by a medical practitioner and history of knee infection, operation, fracture, ligamentous or meniscal injury, osteochondral lesion, and knee replacement.

Sample size and sampling method:

Sample Size: 384

Use the formula, n=N * X/(X+N-1) where,

X = Zα/22xpxq/E2

Zα/2 = tabulated critical value of standard variate. Usually we consider 1.96 for 95% confidence level

p= Sample Proportion (0.5), q= 1-p

E= Maximum permissible error (5%)

N = Population of the city (196,003 as per 2015 census)

Z and MOE are fixed in advance.

Statistical analysis:

Stata MP Version 14 was used for data analysis. Continuous variables were presented as mean/ standard deviation or median/interquartile range (IQR) while categorical variables were presented as frequency/ percentage. Continuous variables were compared by smoking status using independent t-test and One Way ANOVA. Significant ANOVA results were further analyzed using Tukey HSD. Categorical variables were compared by smoking status using Fisher's exact test.

To determine the association of smoking status with strain ratio, logistic regression analysis was performed. Meanwhile, linear regression analysis was utilized to determine the association between smoking status and cartilage thickness. The relationships were further adjusted for the effects of age, sex, BMI, and occupation. p values ≤0.05 were considered statistically significant. Charts and graphs were created using MS Excel.

RESULTS

A total of 384 records were gathered, seven were excluded in the analysis due to the following reasons: four (data loss due to machine malfunction) and three (joint-related diseases/injury). The final sample size included 377 individuals.

The mean age of the participants was 27.66 years (range: 21-40 years old) with the majority of males (70%). About two-thirds were laborers. The calculated mean BMI was 24.55 (range: 19.38-31.79). None of the participants were underweight. A higher proportion of participants were ordinary smokers with mean pack-years of 4.20±3.24 and median: 2.75 (IQR: 2.25-5).

Only 3% were heavy smokers, all males, non-laborers, with normal BMI and had significantly higher age compared to non-smokers and ordinary smokers. (Table 1)

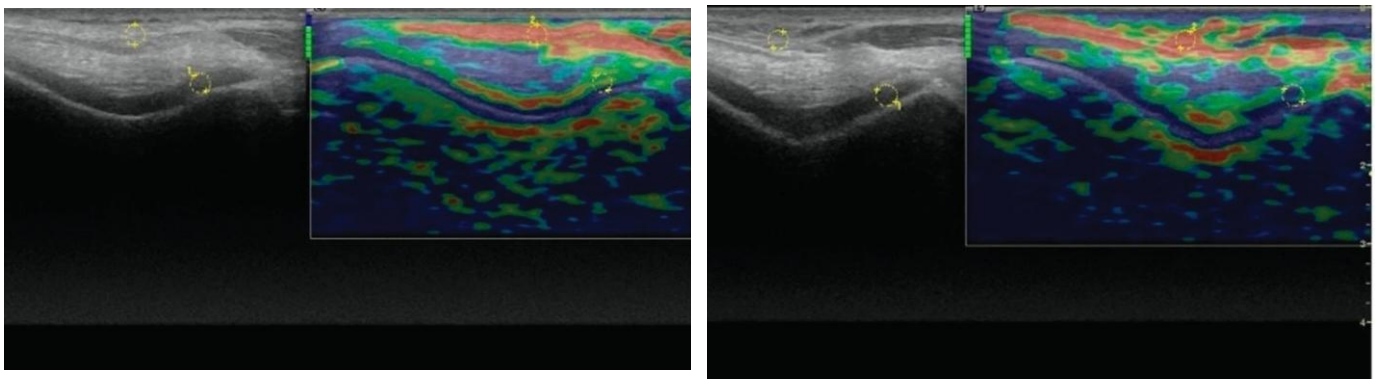

Figure 1: a, b. Strain elastography procedure on the lateral distal femoral cartilage at same anatomical landmarks in two different sessions (a) and (b)

Table 1: Demographic and clinical profile of participants by smoking status

Characteristics	Non-Smokers (n=150) n(%)	Ordinary Smokers (n=213) n(%)	Heavy Smokers (n=13) n(%)	p-value
Age (in years), Mean: 27.66±5.11 <30 years old ≥30 years old	25.58±2.23 128 (85) 22 (15)	28.39±5.45 165 (77) 48 (23)	40±0 0 13 (100)	< 0.001
Sex Male Female	 67 (45) 83 (55)	 181 (85) 32 (15)	 13(100) 0	< 0.001
Occupation Laborers Non-laborers	 127 (85) 127 (85)	 131 (62) 82 (38)	 0 13 (100)	< 0.001
Weight (in kilograms), Mean: 66.59±12.17	61.75±12.31	69.92±11.31	67±0	< 0.001
Height (in meters), Mean: 1.64±0.09	1.65±0.09	1.64±0.10	1.67±0	0.5285
BMI† (in kg/m^2), Mean: 24.55±31.79 Normal Overweight Obese	22.68 ± 3.19 106 (71) 44 (29) 0	25.89 ± 3.11 76 (36) 106 (50) 31 (14)	24.02 ± 0 13 (100) 0 0	< 0.001

†BMI, Body mass index

Figure 2: Mean strain ratio by smoking status and cartilage

Table 2: Elasticity strain ratio categories by smoking status and cartilage

	Non-Smokers (n=150) n (%)	Ordinary Smokers (n=213) n (%)	Heavy Smokers (n=13) n (%)	p-value
MEDIAL CARTILAGE				
Left				< 0.001
Hard	31 (21)	108 (51)	13 (100)	
Soft	119 (79)	105 (49)	0	
Right				0.001
Hard	99 (66)	120 (56)	13 (100)	
Soft	51 (34)	93 (44)	0	
LATERAL CARTILAGE				
Left				< 0.001
Hard	35 (23)	72 (34)	13 (100)	
Intermediate	23 (15)	2 (1)	0	
Soft	92 (61)	139 (65)	0	
Right				< 0.001
Hard	76 (51)	75 (35)	2 (15)	
Intermediate	0	30 (14)	1 (8)	
Soft	74 (49)	108 (51)	10 (77)	

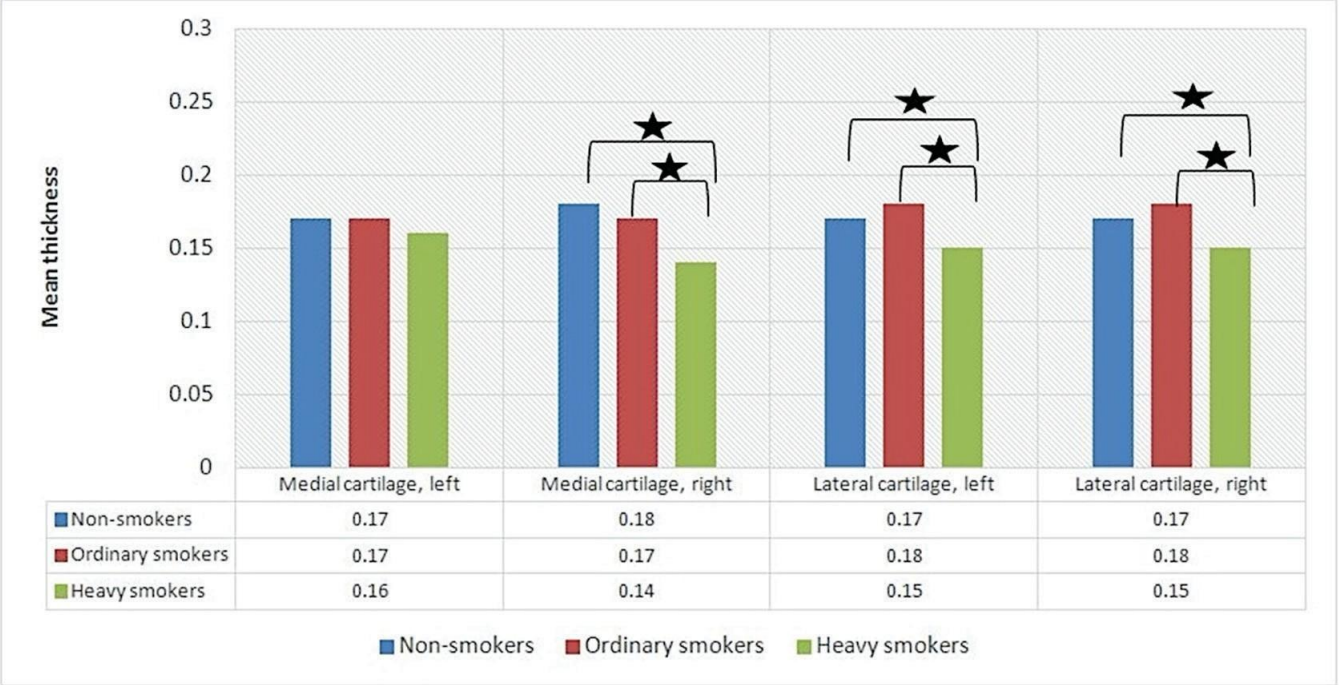

Figure 3: Mean thickness by smoking status and cartilage

Table 3: Association between smoking status and elasticity strain ratio

	†Model 1 (OR)	p-value	‡Model 2 (OR)	p-value	§Model 3 (OR)	p-value	‖Model 4 (OR)	p-value
Medial cartilage, left	4.42 (2.75-7.11)	<0.001	5.44 (3.29-8.98)	<0.001	9.49 (5.07-17.78)	<0.001	8.38 (4.38-16.02)	<0.001
Medial cartilage, right	0.74 (0.48-1.13)	0.163	0.48 (0.30-0.76)	0.002	0.44 (0.26-0.72)	0.001	0.33 (0.19-0.57)	<0.001
Lateral cartilage, left	1.98 (1.25-3.15)	0.004	2.13 (1.31-3.46)	0.002	2.23 (1.31-3.80)	0.003	1.87 (1.05-3.33)	0.034
Lateral cartilage, right	0.50 (0.33-0.77)	0.001	0.57 (0.36-0.88)	0.012	0.89 (0.54-1.47)	0.645	0.88 (0.45-1.73)	0.711

†Model 1: unadjusted model; ‡Model 2: adjusted for age; §Model 3: adjusted for age and sex; ‖Model 4: adjusted for age, sex, BMI and occupation; OR: Odds Ratio (95% CI)

Table 4: Association between smoking status and cartilage thickness

	†Model 1 (OR)	p-value	‡Model 2 (OR)	p-value	§Model 3 (OR)	p- value	||Model 4 (OR)	p-value
Medial cartilage, left	-0.0003 (-0.01 - 0.01)	0.939	-0.005 (-0.01- 0.002)	0.183	-0.02 (-0.03- -0.02)	<0.001	-0.02 (-0.03- -0.02	<0.001
Medial cartilage, right	-0.01 (-0.02- -0.01)	<0.001	-0.02 (-0.02- -0.01)	<0.001	-0.03 (-0.03- -0.02)	<0.001	-0.03 (-0.03- -0.02)	<0.001
Lateral cartilage, left	0.01 (0.001- 0.02)	0.024	0.01 (0.004- 0.02)	0.003	-0.001 (-0.001- 0.01)	0.883	-0.01 (-0.01- 0.002)	0.152
Lateral cartilage, right	0.01 (0.005- 0.02)	0.001	0.01 (0.01- 0.02)	<0.001	0.001 (-0.01 –0.01)	0.721	-0.01 (-0.01- 0.002)	0.158

Cartilage elasticity analysis

Mean medial cartilage strain ratios on both sides and in the left lateral femoral cartilage were significantly lower in heavy smokers compared to non-smokers and ordinary smokers (p<0.001). (Fig.2) However, the mean right lateral cartilage strain ratio in non-smokers was significantly lower compared to ordinary smokers and heavy smokers (p<0.001). (Table 2)

For both left and right sides, all heavy smokers had hard medial cartilage which was significantly higher compared to non-smokers and ordinary smokers. For the left side, all heavy smokers had hard lateral cartilage, which was significantly higher compared to non-smokers and ordinary smokers, but for the right side, a significantly higher proportion of non-smokers had hard lateral cartilage compared to ordinary smokers and heavy smokers. (Table 2)

Smoking was found to be associated with four-fold higher odds of having hard left medial cartilage compared to non-smokers in the unadjusted model. After adjusting for the effects of age, sex, BMI, and occupation, the ratio increased (OR=8.38). In the unadjusted model, no significant association between smoking and the presence of hard-right medial cartilage was observed. After adjusting the parameters, smokers had lower odds compared to non-smokers. Smoking was also found to be associated with higher odds of having hard left lateral cartilage. This association remained significant after adjusting; 87% higher in smokers. In the unadjusted model, smokers had lower odds of having hard right lateral cartilage compared to non-smokers. However, after adjusting the association was no longer significant. (Table 3)

Cartilage thickness analysis

Mean right medial cartilage thickness significantly differed by smoking status (p<0.001). Further analysis showed that cartilage thickness in heavy smokers was significantly lower compared to non-smokers and ordinary smokers. (Fig.3) Mean lateral cartilage thickness, on both sides, significantly differed by smoking status. Further analysis showed that cartilage thickness in heavy smokers was significantly lower compared to non-smokers and ordinary smokers.

In the unadjusted model, no significant association between smoking and left medial cartilage thickness was observed. After controlling for the effects of age, sex, BMI, and occupation, the thickness was found to be 0.02 cm lower among smokers. A significant association was observed on right medial cartilage both in the unadjusted and adjusted models showing cartilage thickness 0.03 cm lower in smokers. Left and right lateral cartilage are 0.01 cm higher in smokers compared to non-smokers. These relationships were no longer significant after controlling the parameters. (Table 4)

DISCUSSION

This cross-sectional study aims to explore whether objectively we can show the effects of cigarette smoking on the radiologically normal knee joints, particularly the distal femoral cartilages of young, otherwise healthy volunteers. We have observed that among 377 individuals with a mean age of 27.66 years, male predominance (70 %), and mean BMI of 24.55, a higher proportion (50 %) of volunteers were ordinary smokers (pack years <20). Elasticity strain ratios were found to be significantly lower in heavy smokers in both left and right sides' distal femoral cartilages except in right lateral femoral cartilage. Hence, for both sides, all heavy smokers have hard medial cartilages and left lateral cartilages which are significantly higher compared to non-smokers and ordinary smokers. Regarding cartilage thickness, a significantly lower thickness was noted in both cartilages of the right side and left lateral cartilage among heavy smokers. After adjusting for the effects of age, sex, BMI and occupation also, similar results were obtained.

The study of Amin et al. included 159 symptomatic osteoarthritic men with 30 months follow-up period and the use of MRI for their measurements. Results showed that current smokers (10 % of subjects) were younger and leaner. When age and BMI were adjusted, smokers had an increased risk for cartilage loss, particularly in medial distal femoral cartilage, and had more severe pain.[6] Wilder et al. study had 2505 men and women volunteers where osteoarthritis was noted in 32% of subjects but when other parameters were adjusted, no significant association was noted with cartilage thickness.[7]

There were 297 volunteers in the study of Racunica et al. and smoking was associated with increased tibial cartilage volume without the presence of tibiofemoral cartilage defects.[2] Ginger et al. had 88 individuals in their study with mean smoking pack-years of 10.3±8.9 and male predominance showing thicker cartilage among smokers in the medial, intercondylar and lateral distal femoral cartilages of the dominant extremity's knee joint; contrary to the results from our study. It showed a negative correlation of smoking with medial cartilage's strain ratio representing harder elasticity.[8]

In patients with Bechet's disease and mean age of 32.87+8.5 years, cartilage thickness was 1.6 to 2.3 mm and in the control population, 1.8 to 2.7 mm.[9] Those with hypothyroidism the femoral cartilage thickness ranged from 1.7 to 1.89 mm.[10] Shepherd et al in their study of 11 sets of cadaveric study with a mean age of 65.1 years, normal thickness of distal femoral cartilage was 1.76 to 2.65 mm.[11] In our study with normal individuals, the average cartilage thickness was 1.4 to 1.6 mm among heavy smokers and 1.7 to 1.8 mm among non-smokers and ordinary smokers.

There are certain limitations to this study. We used a questionnaire instead of proper laboratory tests to rule out other diseases affecting the knee joints. We used the strain elastography technique to determine the elasticity of the distal femoral cartilages instead of shear wave elastography using ultrasound or MR elastography with higher sensitivity and specificity. A cross-sectional study was done to determine the parameters in this study, however, a prospective study following up the cases until their 7th or 8th decades will be a much better study to determine the positive or negative effects of cigarette smoking on the cartilages. We couldn't correlate the serum TNF-α levels, serum, and synovial cytokines levels in this study which was being used in some of the studies. Bigger sample size would have better results in such studies. We also had a lesser number of heavy smokers in this study; a larger population smoking heavily would have probably given a more significant result.

CONCLUSION

All heavy smokers have hard medial cartilages on both sides and left lateral cartilage of the distal femur. Also, all heavy smokers have lower cartilage thickness in lateral cartilages of both sides and the right medial cartilage of the distal femur with statistical significance and association with the amount of smoking. Hence, heavy cigarette smoking causes degradation of distal femoral cartilages by decreasing their thickness and elasticity.

CONFLICT OF INTEREST

None

SOURCES OF FUNDING

None

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