Traumatic meniscal tears are associated with meniscal degeneration

SM Eijgenraam, MA Wesdorp, DE Meuffels, SMA Bierma-Zeinstra,
GJ Kleinrensink,
YM Bastiaansen-Jenniskens, M Reijman

Submitted for publication

ABSTRACT

Objective: Meniscal tears are traditionally classified into traumatic versus degenerative tears. Although this classification plays a major role in clinical decision making, no consensus exists on the exact definition of a 'traumatic' or 'degenerative' tear and the histopathological basis for this classification is unclear. Our aim was to assess the histological degree of meniscal degeneration in patients with a traumatic meniscal tear, compared to intact meniscal tissue and to osteoarthritic meniscal tissue.

Methods: Traumatically torn meniscal tissue was collected during arthroscopic partial meniscectomy. As control group, intact meniscal tissue, obtained during trans-femoral amputations or post-mortem dissections, was used. Meniscal tissue from osteoarthritic knees was obtained during total knee replacement surgery. Meniscal tissue was processed, stained, and histologically analyzed using the Pauli scoring system (comprising the subdomains surface integrity, cellularity, collagen organization, and matrix staining). Statistical analysis was performed using ANOVA, univariate and multivariate logistic regression models.

Results: The traumatic meniscal tear group contained 43 patients (34 men, median age 29 year), the intact group eight patients (three men, median age 58 year), and the osteoarthritic group 14 patients (four men, median age 66 year). After adjustment for sex, age, and BMI, patients with a traumatic meniscal tear showed a statistically significantly higher histological score than patients with intact vital meniscal tissue ($P = 0.035$). Histological score between the traumatic and osteoarthritic group was not significantly different. In the traumatic group, the degree of degeneration was not associated with time interval between trauma and surgery.

Conclusion: Traumatically torn menisci showed a higher degree of degeneration than intact menisci. These results may suggest that in patients suffering from a traumatic meniscal tear, a certain degree of meniscal degeneration might already have been present. These findings could potentially challenge the classic view of traumatic versus degenerative meniscal tears.

INTRODUCTION

A symptomatic meniscal tear is the most common knee injury affecting 2 in 1000 patients per year in The Netherlands [1-5]. A torn meniscus can lead to pain, disability and lower quality of life [6]. In the longer term, a meniscal tear is an important risk factor for the development and progression of knee osteoarthritis (OA) [6-8].

Meniscal tears are traditionally classified into traumatic versus degenerative tears, referring to their onset. Currently, this classification is based on medical history, the patient's age, and magnetic resonance imaging (MRI) indicating a specific tear pattern. This classification of meniscal pathology is essential in clinical decision making; traumatic meniscal tears are mostly treated by arthroscopic partial meniscectomy (APM) or repair [9,10], whereas non-operative management is generally the first choice for degenerative tears [10,11]. Classifying meniscal tears into "traumatic" versus "degenerative" tears can, however, be challenging as there is no consensus on how exactly to define degenerative and traumatic tears. In some cases, traumatic tears are caused by a very minor trauma (e.g., walking stairs), and, on the other hand, degenerative tears are incidentally found in asymptomatic ''healthy" knees [12,13]. Moreover, studies have shown that traumatic meniscal tears may result from early degenerative disease processes [14,15]. Thus, differentiation between these two types is not as straight forward as it may seem.

In soft tissues other than the meniscus, the role of tissue condition in pathophysiological processes has been studied before. For instance, degenerative changes were already present in ruptured Achilles tendons [16-20]. These findings have led to the view that degeneration of a tendon can cause it to rupture in absence of an abnormal movement or force; representing the so-called "continuum theory" [21,22]. The continuum theory explains the pathological basis of the heterogeneity between healthy and degenerative tissue eventually leading to tendinopathy or rupture [22]. This rationale might be extended to meniscal tissue. Hence, it is highly relevant to increase knowledge on tissue condition of a torn meniscus. This knowledge could begin to establish a pathophysiologic basis for the classification of meniscal tears. To date, there are no studies published evaluating the degree of histological degeneration in traumatically torn meniscal tissue. Moreover, no research compared traumatically torn to intact meniscal tissue regarding histological degeneration. Histological research so far mainly focused on osteoarthritic and degenerative menisci [23].

Our aim was to investigate the histological degree of degeneration in traumatically torn meniscal tissue, compared to intact vital meniscal tissue as a control group. Osteoarthritic menisci were used as a reference for a degenerative state of the meniscus. Our hypothesis was that traumatically torn meniscal tissue shows a higher degree of histological degeneration compared to intact vital meniscal tissue. A secondary aim was to identify patient related factors that are associated with a higher amount of degeneration.

METHODS

Subjects and data collection

In this study, meniscal tissue in three different conditions was collected, from different subject groups: traumatically torn meniscal tissue (from now on referred to as TM), intact meniscal tissue (from now on referred to as IM), and osteoarthritic meniscal tissue (from now on referred to as DM). Traumatically torn meniscal tissue was collected during APM. Inclusion criteria were as follows: age under 45 year, history of a traumatic event in the last 6 months followed by clinical knee complaints, an MRI-proven meniscal tear without signs of knee OA, and an indication for APM. As a control group, intact meniscal tissue was collected during acute trans-femoral amputation or post-mortem dissection. Inclusion criteria were: age between 18 and 70 year, no history of knee injury, no radiological or clinical signs of knee OA, and no signs of knee OA at macroscopic inspection of the meniscus. Menisci from patients with vascular- or inflammatory diseases involving the knee or with systemic diseases were excluded. Inclusion criteria for degenerative osteoarthritic meniscal tissue were: age above 18 years, radiographically confirmed knee OA, and indication for total knee replacement surgery. Osteoarthritic meniscal tissue was used as reference standard, representing degenerative meniscal tissue.

Data was collected on the patient characteristics age, sex and body mass index (BMI). In the TM group, additional information was collected on time interval between trauma and surgery, and on associated anterior cruciate ligament (ACL) ruptures. This study was approved by the Medical Ethics Committee of the Erasmus MC University Medical Center (MEC-2004-322 and MEC-2015-180).

Meniscal tissue processing

Directly after harvesting, meniscal tissue was stored in formalin fixative (formaldehyde 4%). Tissue was processed within 1-3 days after surgery in a standardized way, according to the method of Pauli et al. [23] (Figure 1). Meniscal tissue was cut into two different planes in 5 mm-samples. The sagittal (i.e., vertical) cut, oriented perpendicular to the circumferential collagen bundles, provided an overview of the meniscal surface and matrix composition. The horizontal cut, at a 30° angle relative to the tibial plateau, revealed the longitudinal organization of collagen bundles and matrix morphology (Figure 1). Samples were further processed by dehydration and infiltration with paraffin, followed by cutting them into 6 µm-sections using a microtome (Leica Microsystems). Subsequently, the sections were stained with hematoxylin and eosin (H&E, Sigma) to assess surface integrity and cellularity. Additionally, Safranin O-Fast Green and Picrosirius Red (Sigma) staining was applied to analyze proteoglycan content of the meniscus and collagen fiber organization, respectively.

Figure 1. Harvesting meniscal tissue. A) Meniscal tissue after resection of a medial bucket handle tear in 24-year-old male. B) vertical cut from the posterior horn. C) horizontal cut from the posterior horn.

Histological analysis

All meniscal sections were scored using the validated histological scoring system for meniscal degeneration by Pauli et al. [23] (Figure 2). The Pauli score contains the following subdomains: surface integrity (tibial surface, femoral surface, and inner rim), cellularity, collagen organization, and matrix staining intensity. A score ranging from 0 to 3 (depending on the degree of degeneration) was assigned in each subdomain, resulting in a total histologic score ranging from 0 to 18. Scoring of the samples was performed independently by two researchers (MW & SE), blinded to condition, region of the meniscal tissue, and patient data. Three weeks after initial evaluation, one researcher (MW) scored the sections again. The latter scores were exclusively used to calculate intra-observer reliability.

Statistical analysis

Baseline characteristics for each subject group (i.e., TM, IM, and DM) were collected and tested for normality using Shapiro-Wilk tests. Depending on data distribution, differences in continuous data between groups were assessed using one-way ANOVA or Kruskal-Wallis tests, followed by post hoc Wilcoxon Rank Sum analysis with Bonferroni correction. Categorical data were analyzed using a Fisher's exact test with Bonferroni correction for pairwise comparisons. Inter- and intra-observer reliability of histological scoring was evaluated using intraclass correlation coefficients (ICC). A two-way mixed model based on absolute agreement for single measures was used. Reliability was regarded as excellent if ICC > 0.75. [24]

To investigate and correct for potential confounding variables within the subject groups, a multiple linear regression model was designed. Based on existing literature on potential factors associated with meniscal degeneration or osteoarthritis, the variables age, sex, and BMI [23,25,26] were included in a forced-entry analysis. Univariate linear regression analysis was performed within the TM group on the variables "time interval between trauma and surgery", and "associated anterior cruciate ligament rupture" to assess their association with histological scores. In case an association was found for those variables, they were included to the multivariate model.

All statistical analysis included two tailed tests. A P value of < 0.05 was considered to indicate statistical significance. SPSS statistics package version 21.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all analysis.

1. Surface integrity		
	Femoral surface	**Score**
	• Smooth	0
	• Slight fibrillation	1
	• Moderate fibrillation	2
	• Severe fibrillation	3
	Tibial surface	
	• Smooth	0
	• Slight fibrillation	1
	• Moderate fibrillation	2
	• Severe fibrillation	3
	Inner rim	
	• Smooth	0
	• Slight fibrillation	1
	• Moderate fibrillation	2
	• Severe fibrillation	3
2. Cellularity		
	• Normal	0
	• Hypercellularity	1
	• Diffuse hypocellularity	2
	• Acellular	3
3. Collagen organization/alignment and fiber organization		
	• Collagen fibers organized	0
	• Collagen fibers organized and foci of mucinous degeneration	1
	• Collagen fibers unorganized and foci of mucinous degeneration	2
	• Collagen fibers unorganized and fibrocartilaginous separation	3
4. Matrix staining (Safranin O-Fast Green)		
	• None	0
	• Slight	1
	• Moderate	2
	• Strong	3

Note: the range of possible total scores is 0 – 18. The total score can be converted to a grade as follows: grade 1 = 0-4 (normal), grade 2 = 5-9 (mild degeneration), grade 3 = 10-14 (moderate degeneration), grade 4 = 15-18 (severe degeneration). In the present study, the Pauli score was used as continuous measure; no conversion to grades was performed.

Figure 2. Histopathological scoring system for meniscal degeneration by Pauli et al.

RESULTS

Patient characteristics

In total, 65 meniscal tissue samples were analysed: 43 traumatically torn samples, eight intact menisci, and 14 degenerative menisci. Due to limited sample sizes in each subject group, most data were non-parametric and was reported as median with interquartile range. Baseline characteristics, stratified per subject group, are summarized in Table 1. The median age was 29 years in the TM group, 58 years in the IM group, and 66 years in the DM group. Statistically significant differences in age were encountered between the TM and IM group ($P = 0.001$), and the TM and DM group ($P < 0.001$). Age was not different between the IM and DM group. The median BMI in the TM group (23.6 kg/m^2) was statistically significantly lower than the DM group (28.4 kg/m^2, $P = 0.043$. BMI in the IM group (29.7 kg/m^2) was not

different from the TM or DM group. A statistically significant higher percentage of males was present in the TM group compared to the DM group (79% versus 29%, P = 0.003). No difference in sex distribution was observed in both subject groups compared to the IM group (38%). The median time interval between trauma and surgery in the TM group was 13 weeks. 40% of the latter patients had a history of ACL rupture in their index knee.

Table 1. Characteristics of patients in traumatic, intact and degenerative group.

Characteristics	Traumatic meniscal tear (n = 43)	Intact meniscus (n = 8)	Osteoarthritic meniscus (n = 14)
Age at time of surgery in years†	29 (22 - 40)[1,2]	58 (54 - 64)[1]	66 (63 - 70)[2]
Body mass index (kg/m²)†	24 (22 - 26)[2]	30 (22 - 36)	28 (24 - 32)[2]
Sex‡			
Male	34 (79%)[2]	3 (38%)	4 (29%)[2]
Meniscal region examined‡			
Medial posterior horn	28 (65%)	8 (100%)	12 (86%)
Medial midbody	6 (14%)		
Lateral posterior horn	7 (16%)		1 (7%)
Lateral midbody	1 (2%)		
Lateral anterior horn	1 (2%)		
Unknown			1 (7%)
Time between injury and surgery (weeks)†	13 (6 - 30)		
History of ACL-rupture‡*:*	17 (40%)		
Bucket handle tear‡*:*	23 (54%)		

† Continuous data are presented as median (interquartile range)
‡ Categorical data are described as frequency (percentage)
1 Statistically significant difference between traumatic and intact group p <0.05
2. Statistically significant difference between traumatic and osteoarthritic group p<0.05
Abbreviations: ACL = anterior cruciate ligament

Histological analysis

Representative histological images, illustrating the range of histological scores, are presented in Figure 3. The overall scores in each subdomain are reported in Figure 4. The mean histological score in the TM group was 4.4 ± 2.2 (range 0-9), in the IM group 3.2 ± 1.6 (range 1-6), and in the DM group 7.1 ± 2.9 (range 2-12) (Figure 4).

Inter-observer reliability for histological scoring based on absolute agreement was excellent (ICC 0.95, 95% Confidence Interval (CI) 0.86-0.99). Similar findings were observed regarding intra-observer reliability (ICC 0.96, 95% CI 0.90-0.98).

Multivariate analysis on histological scores

To identify and adjust for potential confounders between subject groups, a multivariate linear regression analysis was performed (Table 2). After adjustment for age, sex, and BMI, menisci in the TM group showed a statistically significant higher histological score compared to the IM group (2.7 point higher ± 1.3, P = 0.035). Furthermore, the adjusted histological score

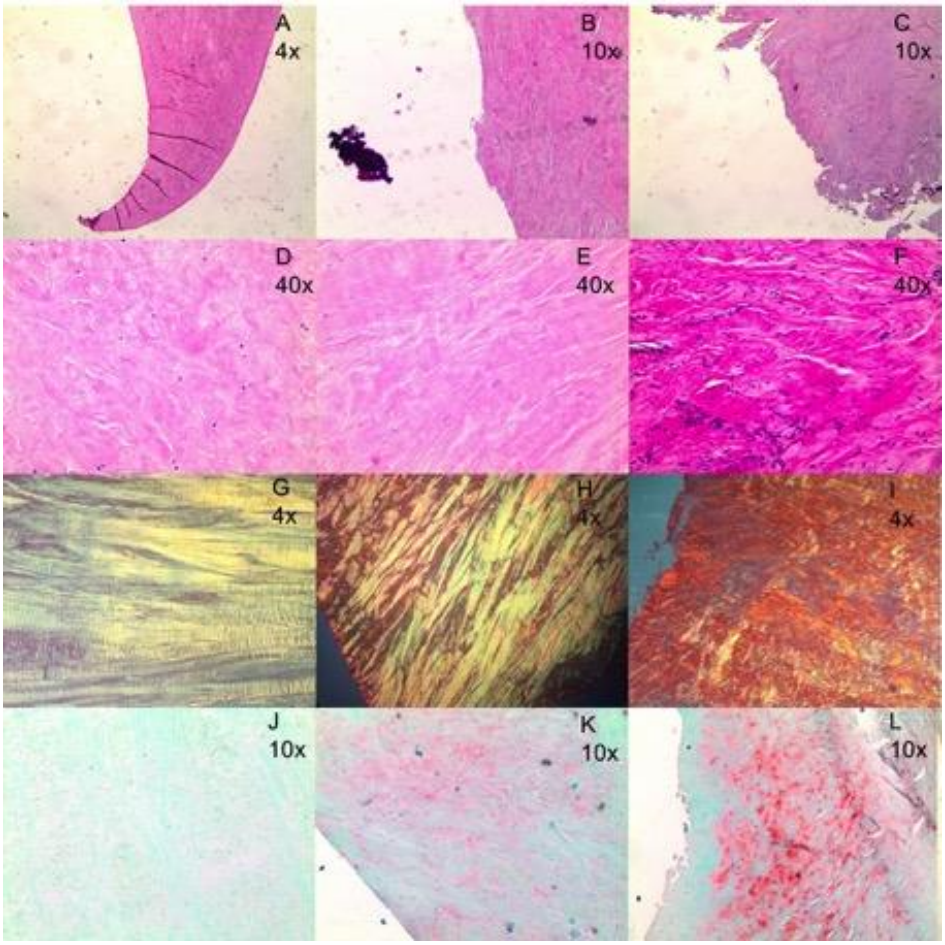

Figure 3. Representative examples of histological evaluation. A-C) Histological score 0, 1 and 2 (left to right) on subdomain *surface integrity*, Hematoxylin and Eosin staining. D-F) Histological score 0, 1 and 2 (left to right) on subdomain *cellularity*, Hematoxylin and Eosin staining. G-I) Histological score 0, 1 and 2 (left to right) on subdomain *collagen organization*, Safranin-O-Green staining. J-M) Histological score 0, 1 and 2 (left to right) on subdomain *matrix staining intensity,* Safranin-O-Green staining.

for the DM group was statistically significantly higher than those of the IM group (4.0 point higher ± 1.2, P = 0.001). The histological score of the TM group did not differ from the DM group, after adjustment. BMI appeared to be independently associated with histological score. An increase in BMI by one unit resulted in an increase of 0.16 ± 0.07 in histological score (P = 0.04) (Figure 5). The histological score and the variables age and sex were not associated.

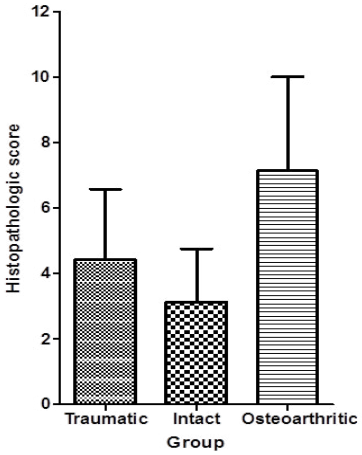

Figure 4. Histologic scores in traumatic meniscal tissue group, intact meniscal tissue group, and osteoarthritic meniscal tissue group. Data is presented as mean, vertical bar represents standard deviation.

Effect of "time interval between trauma and surgery" and "ACL rupture" on degree of degeneration in TM group

Univariate regression analysis revealed an increase of 0.21 ± 0.09 point in histological score for each unit in BMI increase (P = 0.03). No association was found between the histological score and the independent variables age at time of surgery, sex, meniscal region, time interval between trauma and surgery, and ACL rupture (Table 3).

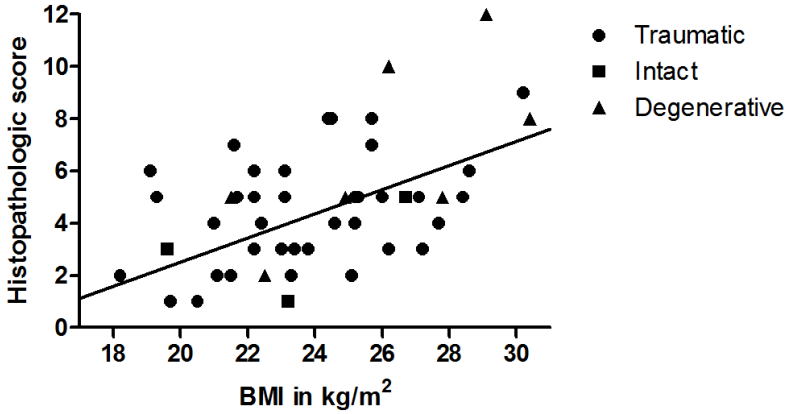

Figure 5. Correlation between BMI and histological degree of degeneration. Scatter plot showing correlation between BMI and histological score. Each symbol represents a unique sample. Abbreviations: BMI = body mass index.

Table 2. Multivariate analysis of risk factors on histologic score.

Characteristics	Regression coefficient	SE of regression coefficient	p-value
Age at time of surgery	0.02	0.03	0.497
Sex (female)	-0.88	0.66	0.190
Body mass index	0.16	0.07	0.040
Trauma group	2.73	1.26	0.035
Osteoarthritic group	3.97	1.16	0.001

Note: The intact meniscal tissue group is the reference group in the analysis.
Abbreviations: SE = standard error

Table 3. Univariate analysis of risk factors on histologic score in traumatically torn meniscal tissue group.

Characteristics	Regression coefficient	SE of regression coefficient	p-value
Age at time of surgery	-0.01	0.03	0.84
Sex (female)	-0.53	0.82	0.52
Body mass index	0.21	0.09	0.03
Timespan trauma to surgery	0.00	0.01	0.98
History of ACL rupture	1.06	0.64	0.10

Abbreviations: SE = standard error, ACL = anterior cruciate ligament

DISCUSSION

In this study, we assessed the degree of degeneration in traumatically torn-, intact- and osteoarthritic meniscal tissue, using a validated histological scoring system. Traumatically torn meniscal tissue showed a higher degree of degeneration than intact menisci. We identified BMI as an independent risk factor for meniscal degeneration. No clear association was observed between histological degree of degeneration and age, sex, or time interval between trauma and surgery.

To our knowledge, this is the first study assessing histological degeneration in different meniscal conditions. Most previous studies focused on one feature of degeneration. Mesiha and colleagues[26] reported that TM showed equal histological scores to DM. Their main outcome measure to assess degeneration was cellularity; low cellularity was observed in both TM and DM tissue. In a study by Meister et al. [14], Safranin-O matrix staining intensity (as a measure of the amount of glycosaminoglycans) was assessed and was found to be increased in patients with a traumatic meniscal tear [14]. In osteoarthritic menisci, the number of glycosaminoglycans is increased [27,28]. Therefore, the observed Safranin-O staining intensity in our study is regarded as a sign of degeneration of the meniscus. Collagen organization was disturbed in our traumatic meniscal tear samples. Park et al. [29] earlier concluded that torn meniscal tissue showed less organization of the collagen bundles and a lower amount of

collagen type I. Despite the fact that their research was done in a cohort of knee OA patients, torn meniscal tissue showed more disturbance of collagen alignment compared to patients without a tear. These findings may suggest that tissue quality plays an important role in the risk of a meniscal tear in the context of a traumatic event.

Much is unclear regarding the role of meniscal degeneration in traumatic meniscal tears. Currently, the most common view is that the majority of traumatic meniscal tears are the result of a tibiofemoral rotational force as the knee moves from flexion to extension or vice versa, while bearing weight [3]. Snoeker et al. showed that swimming was a risk factor for a meniscal tear too [25], thus suggesting that a large force transmission is not necessary in the occurrence of a "traumatic" meniscal tear. This highlights that classifying tears is not as straight forward as it seems. A more plausible view may be the earlier mentioned continuum theory: from a healthy to a degenerative meniscus. In this view, the chance to get a "traumatic meniscal tear" (partly) depends on the pre-existing degree of meniscal degeneration. That is, the more degeneration, the higher the risk of a torn meniscus in case of a traumatic event. The first clue for this theory was provided by the finding that older US Military servants showed a higher rate of meniscal injuries despite being exposed to the same activities and movements as their younger colleagues. Jones et al. concluded that the higher rate of injuries was related to degeneration of the meniscus as age increased [30]. Our findings challenge the classic view of "traumatic" versus "degenerative" meniscal tears and support the continuum theory in which degeneration of the meniscal tissue plays a major role in the risk of a meniscal tear organization [31].

In the present study, BMI was found to be independently correlate with the degree of meniscal degeneration. Previous clinical studies concluded that higher BMI is associated with a greater risk of a meniscal tear [7,25,32,33]. The effect of BMI on degeneration of the meniscus can be explained by its biomechanical role. An increase in BMI results in a greater force transmission by the meniscus [4]. Moreover, a higher BMI results in chronic inflammation of the knee joint. A chronic inflammatory state leads to an increase in metallo matrix protease production and degradation of collagen fibers [34,35]. This could be a partial explanation of the degenerative changes that occur in meniscal tissue. BMI might be used as a predictive factor of the degree of degeneration of the meniscus. Interestingly, we found no association between age and degree of degeneration of the meniscus, contradictory to previous evidence [23,26]. A possible explanation could be that in most previous studies the potential confounding effect of BMI regarding other factors and condition of the meniscus was not taken into account. It is well known that, when age increases, BMI increases as well [36-38]. In our study, after univariate testing of potential patient specific determinants, an association between age and histologic degeneration was observed. However, adjusted for BMI, this association lost significance (data not shown). Therefore, BMI might be a better explanation for a higher degree of degeneration instead of age.

Time interval between trauma and surgery showed no association with the degree of degeneration in the TM group. These findings are consistent with a previous study [26], which reported no differences in cell density and histological score with respect to time interval between trauma and surgery. Our findings suggest that degenerative changes did not change after the injury and might have been present before the injury occurred. However, critical interpretation of this finding is important given the cross-sectional study design without intra-subject longitudinal evaluation of the meniscal tissue composition. Moreover, literature shows that a meniscal tear has effects on other structures of the joint. This corresponds with the idea that a meniscal tear results in cartilage loss and thus accelerated development knee OA [39-42]. The loss of cartilage is greater in patients with a resected part of the meniscus, compared to patients without resection [43]. Englund et al. showed that knees with meniscal tears on MR imaging but without cartilage lesions were at higher risk of radiographic development of knee OA in later life than intact menisci. This implicates that visible meniscal damage occurs before visible cartilage changes [40,44]. These findings warrant careful decision making in the choice of treatment, and in case of APM timing of surgery.

The present study has some limitations that should be considered. First, we included only eight intact menisci (IM), due to the low incidence of acute trans-femoral amputations, especially in a younger population. Second, results on the subdomain "surface integrity" may be influenced by meniscal tears, affecting the meniscal surface. Nevertheless, a macroscopically intact portion of the meniscus was sectioned without the edge of the tear if possible.

In conclusion, we found a higher degree of meniscal degeneration in patients with a traumatic meniscal tear compared to intact menisci, and no association between time interval between trauma and surgery and histological score. A better understanding of the degeneration process is likely to help orthopedic surgeons decide on choice of treatment. This knowledge may also lead to new perspectives to prevent OA of the knee in patients with a torn meniscus after a traumatic event. Future studies should explore the possibilities of longitudinal *in vivo* evaluation of degeneration using for instance quantiitaivie MRI techniques.

Acknowledgements

This study was supported by the department of neuroscience. The department provided cadaver knees and the facility for resecting meniscal tissue. We thank all orthopedic surgeons and trauma surgeons of Erasmus MC University Medical Center for the collection of meniscal tissue. The authors are grateful for the technical assistance of Nicole Kops (Department of Orthopaedics, Erasmus MC) with the procedure of making the histologic sections.

REFERENCES

1. Clayton RA, Court-Brown CM. The epidemiology of musculoskeletal tendinous and ligamentous injuries. Injury 2008;39:1338-44.
2. Draijer LW, Belo JN, Berg HF, Geijer RM, Goudswaard AN. [Summary of the practice guideline 'Traumatic knee problems' (first revision) from the Dutch College of General Practitioners] De NHG-Standaard 'Traumatische knieproblemen' (eerste herziening): samenvatting. Ned Tijdschr Geneeskd 2010;154:A2225.
3. Brindle T, Nyland J, Johnson DL. The Meniscus: Review of Basic Principles With Application to Surgery and Rehabilitation. Journal of Athletic Training 2001;36:160-9.
4. Fox AJ, Wanivenhaus F, Burge AJ, Warren RF, Rodeo SA. The human meniscus: a review of anatomy, function, injury, and advances in treatment. Clin Anat 2015;28:269-87.
5. Makris EA, Hadidi P, Athanasiou KA. The knee meniscus: structure-function, pathophysiology, current repair techniques, and prospects for regeneration. Biomaterials 2011;32:7411-31.
6. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries osteoarthritis. The American journal of sports medicine 2007;35:1756-69.
7. Ding C, Martel-Pelletier J, Pelletier J-P, et al. Meniscal tear as an osteoarthritis risk factor in a largely non-osteoarthritic cohort: a cross-sectional study. The Journal of rheumatology 2007;34:776-84.
8. Englund M, Guermazi A, Roemer FW, et al. Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: The multicenter osteoarthritis study. Arthritis & Rheumatism 2009;60:831-9.
9. Englund M, Roemer FW, Hayashi D, Crema MD, Guermazi A. Meniscus pathology, osteoarthritis and the treatment controversy. Nat Rev Rheumatol 2012;8:412-9.
10. Beaufils P, Becker R, Kopf S, Matthieu O, Pujol N. The knee meniscus: management of traumatic tears and degenerative lesions. EFORT open reviews 2017;2:195-203.
11. Beaufils P, Becker R, Kopf S, et al. Surgical management of degenerative meniscus lesions: the 2016 ESSKA meniscus consensus. Knee Surg Sports Traumatol Arthrosc 2017;25:335-46.
12. Greis PE, Bardana DD, Holmstrom MC, Burks RT. Meniscal injury: I. Basic science and evaluation. J Am Acad Orthop Surg 2002;10:168-76.
13. Englund M, Guermazi A, Gale D, et al. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. N Engl J Med 2008;359:1108-15.
14. Meister K, Indelicato PA, Spanier S, Franklin J, Batts J. Histology of the torn meniscus: a comparison of histologic differences in meniscal tissue between tears in anterior cruciate ligament-intact and anterior cruciate ligament-deficient knees. Am J Sports Med 2004;32:1479-83.
15. Uysal M, Akpinar S, Bolat F, Cekin N, Cinar M, Cesur N. Apoptosis in the traumatic and degenerative tears of human meniscus. Knee Surg Sports Traumatol Arthrosc 2008;16:666-9.
16. Arner O, Lindholm A, Orell SR. Histologic changes in subcutaneous rupture of the Achilles tendon; a study of 74 cases. Acta chirurgica Scandinavica 1959;116:484-90.
17. Davidsson L, Salo M. Pathogenesis of subcutaneous tendon ruptures. Acta chirurgica Scandinavica 1969;135:209-12.
18. Jozsa L, Kannus P. Histopathological findings in spontaneous tendon ruptures. Scandinavian journal of medicine & science in sports 1997;7:113-8.
19. Kannus P, Jozsa L. Histopathological changes preceding spontaneous rupture of a tendon. A controlled study of 891 patients. J Bone Joint Surg Am 1991;73:1507-25.

20. Longo UG, Ronga M, Maffulli N. Acute ruptures of the achilles tendon. Sports medicine and arthroscopy review 2009;17:127-38.
21. Egger AC, Berkowitz MJ. Achilles tendon injuries. Current reviews in musculoskeletal medicine 2017;10:72-80.
22. Cook JL, Purdam CR. Is tendon pathology a continuum? A pathology model to explain the clinical presentation of load-induced tendinopathy. British journal of sports medicine 2009;43:409-16.
23. Pauli C, Grogan SP, Patil S, et al. Macroscopic and histopathologic analysis of human knee menisci in aging and osteoarthritis. Osteoarthritis Cartilage 2011;19:1132-41.
24. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. Journal of Chiropractic Medicine 2016;15:155-63.
25. Snoeker BA, Bakker EW, Kegel CA, Lucas C. Risk factors for meniscal tears: a systematic review including meta-analysis. J Orthop Sports Phys Ther 2013;43:352-67.
26. Mesiha M, Zurakowski D, Soriano J, Nielson JH, Zarins B, Murray MM. Pathologic Characteristics of the Torn Human Meniscus. The American Journal of Sports Medicine 2007;35:103-12.
27. Sun Y, Mauerhan DR, Kneisl JS, et al. Histological Examination of Collagen and Proteoglycan Changes in Osteoarthritic Menisci. The Open Rheumatology Journal 2012;6:24-32.
28. McDevitt CA, Webber RJ. The ultrastructure and biochemistry of meniscal cartilage. Clin Orthop Relat Res 1990:8-18.
29. Park DY, Min BH, Choi BH, et al. The Degeneration of Meniscus Roots Is Accompanied by Fibrocartilage Formation, Which May Precede Meniscus Root Tears in Osteoarthritic Knees. Am J Sports Med 2015;43:3034-44.
30. Jones JC, Burks R, Owens BD, Sturdivant RX, Svoboda SJ, Cameron KL. Incidence and Risk Factors Associated with Meniscal Injuries Among Active-Duty US Military Service Members. Journal of Athletic Training 2012;47:67-73.
31. Magnan B, Bondi M, Pierantoni S, Samaila E. The pathogenesis of Achilles tendinopathy: a systematic review. Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons 2014;20:154-9.
32. Ford GM, Hegmann KT, White GL, Holmes EB. Associations of body mass index with meniscal tears. American Journal of Preventive Medicine 2005;28:364-8.
33. Baker P, Coggon D, Reading I, Barrett D, McLaren M, Cooper C. Sports injury, occupational physical activity, joint laxity, and meniscal damage. The Journal of rheumatology 2002;29:557-63.
34. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. The Journal of clinical investigation 2011;121:2111-7.
35. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage 2013;21:16-21.
36. Sheehan TJ, DuBrava S, DeChello LM, Fang Z. Rates of weight change for black and white Americans over a twenty year period. 0000;27:498-504.
37. Zheng Y, Manson JE, Yuan C, et al. Associations of weight gain from early to middle adulthood with major health outcomes later in life. JAMA 2017;318:255-69.
38. Hutfless S, Maruthur NM, Wilson RF, et al. 2013.
39. Roos H, Adalberth T, Dahlberg L, Lohmander LS. Osteoarthritis of the knee after injury to the anterior cruciate ligament or meniscus: the influence of time and age. Osteoarthritis and Cartilage 1995;3:261-7.
40. Englund M. Meniscal tear--a feature of osteoarthritis. Acta Orthop Scand Suppl 2004;75:1-45, backcover.

41. Hunter DJ, Zhang YQ, Niu JB, et al. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis & Rheumatism 2006;54:795-801.
42. Sharma L, Eckstein F, Song J, et al. Relationship of meniscal damage, meniscal extrusion, malalignment, and joint laxity to subsequent cartilage loss in osteoarthritic knees. Arthritis Rheum 2008;58:1716-26.
43. Berthiaume M-J, Raynauld J-P, Martel-Pelletier J, et al. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Annals of the rheumatic diseases 2005;64:556-63.
44. Englund M, Roos EM, Lohmander LS. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: A sixteen-year followup of meniscectomy with matched controls. Arthritis & Rheumatism 2003;48:2178-87.