Prevalence of Meniscal Extrusion and associated Knee Findings Detected by MRI in Patients with a History of Knee Trauma

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Abstract

Background and objectives: Meniscal extrusion is defined as the condition in which the meniscus is located outside the margin of the knee joint. This condition can lead to knee osteoarthritis, meniscal degeneration, and meniscal tears. Meniscal extrusion is broadly diagnosed through magnetic resonance imaging. The present study aimed to examine the prevalence of meniscal extrusion and the associated knee joint abnormalities in cases of trauma. Methods: The present cross-sectional study consisted of 122 cases (62 cases with knee injuries caused by falling on ground and 60 as a result of football playing) whom been referred to MR unit to undergo knee exam referred in the period from January to July 2019. A search for meniscus extrusion was performed, and once identified then checking for associated findings was performed. Results: The study group mean age was 31.77 years. Most of the cases (77%) were males. About one third of the cases (30.3) had meniscal extrusion, and almost half of them (48.4%) had meniscal tear. Meniscal root tear and complex tear of posterior horn of medial meniscus was the most frequent meniscal tear. About half of the cases (49.2%) had joint effusion. In both study subgroup, meniscal extrusion was significantly found in the medial meniscus, and it was significantly associated with medial meniscus tear, types of meniscal tear, and joint effusion (p<0.05). Age had a significant association with meniscal extrusion in the subgroup of trauma caused by falling on ground (p<0.05), the two groups were significantly different in terms of the meniscal extrusion distance (p<0.05). Conclusion: Medial meniscus and medial meniscus tear are the most significant risk factors for meniscal extrusion. Meniscal extrusion distance was shorter in individuals with knee trauma caused by football playing compared to those with knee injuries resulted from falling on ground.

Keywords: Meniscal extrusion; Joint abnormalities; Magnetic Resonance Imaging (MRI); Knee trauma

Introduction

The menisci refer to two fibro cartilaginous discs that are located laterally and medially between the surfaces of tibia and femur in the cavity of the knee joint.^[1] The menisci are highly significant because they stabilize the knee joint, reduce friction and shock during movement, and distribute the body weight across the knee joint. ^[2,3] According to the results of biomechanical studies, the menisci transmit a minimum of 50% of the knee joint compressive load.^[4] As a result, any change in the integrity and normal place of the menisci can lead to negative impacts on these important functions. As revealed by the results obtained from magnetic resonance imaging (MRI) tears or destruction of the menisci are quite common in the general population and rise with age.^[5,6]

One of the destructions in the menisci is labeled as meniscal extrusion (also referred to as meniscal subluxation) which is defined as a condition in which the peripheral border of the meniscus is remarkably located outside the margin of the knee joint.^[7,8] Meniscal extrusion has been reported to be associated

with the presence of knee osteoarthritis (OA), meniscal degeneration, and meniscal tears.^[9-13]

A study has shown that women experience meniscal extrusion more than men, which is attributed to the higher laxity of special knee structures like collateral ligaments in women compared to men.^[14] In addition to female sex, body mass index in the ranges of overweight and obesity can also cause meniscal extrusion to develop. ^[11] Furthermore, studies have indicated association between extrusion of the meniscus, osteoarthritis, and joint effusion. ^[15,16] Also, meniscal extrusion has been reported after knee trauma. ^[15,10]

According to what was mentioned above and given the

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significance of diagnosing meniscal extrusion and the associated knee abnormalities, the present study was aimed at determining the prevalence of meniscal extrusion and the associated knee joint abnormalities in two different subgroups of patients (falling on ground and football player), and making a comparison between these two subgroup findings.

Methods and Materials

Study design, setting, and sample

The present cross-sectional study was carried out on 122 cases with a history of knee trauma over a period of 6 months from January to July 2019. The patients were selected from those who referred to Rizgary Teaching Hospital in Erbil, the Kurdistan Region of Iraq. The study sample was chosen by a convenience sampling method. Patients with degenerative changes, claustrophobic patients, patients with contraindication to do MRI and failure to obtain appropriate image and sequences were crossed out of the study.

Procedures

The MR studies were performed on a 1.5 -T unit (Aera, Siemens, Erlangen, Germany), and a knee coil was used in all cases. The examination protocol included sagittal T1 weighted turbo spinecho sequence (TR range/TE range, 400-500/15-20), sagittal T2-weighted turbo spin-echo sequence (TR range/TE range, 2500-3000/74-130), axial, sagittal and coronal proton density turbo-spin echo sequences with fat suppression (TR range/TE range, 2000-2500/40-80) with a 3-mm section thickness and a 0.3 mm gap. The field of view was 20 cm, with a matrix size of 256×256 .

Image analysis

Two radiologists evaluated the MR images of a total of 122 cases. The study group was classified as sport injury (60 athletes, football player; all men) and trauma due to fall on ground (62 patients, 34 males, 28 females) that has been referred to MR unit from the orthopedic department.

To look for meniscus extrusion and its measurement, coronal plane was used as a reference, based on the technique described by Breitenseher et al. ^[17] Meniscus extrusion was defined as a distance of 3 mm or more between the peripheral edge of the meniscus and the central portion of the tibial plateau as measured in coronal plane [Figure 1]. A distance of less than 3 mm was not considered as meniscal extrusion. A search for other types of knee joint injuries was also made.

Meniscus tear was considered when an internal meniscal signal intensity is identified extending to the articular surfac. Meniscal extrusion was correlated with meniscal tear, joint effusion, and other knee joint injuries (like collateral ligaments, and PCL tear). Cases of mild, moderate and large joint effusion were enrolled in our study, while cases of small physiologic joint fluid were not considered in our study. Both low-grade and high-grade ACL tears were considered as tear in our study.

Statistical analysis

The collected data from the conducted examinations for each

patient were recorded using a special questionnaire designed for diagnosis, and they were later analyzed using SPSS version 23 and a Fisher's exact test was used to assess the significance of the associations between meniscal extrusion and knee joint abnormalities.

Ethical considerations

The study protocol was approved by the Ethical and Scientific Committee of Kurdistan Board for Medical Specialties. The purpose of the study was explained to each patient, and a verbal informed consent was obtained from them prior to their inclusion in the study.

Results

The final number of our study group was 122 cases, with mean age of $31.77 (\pm 9.18)$ years, most (73.8%) were adults (25-64 years), 23.8% were young (15-24 years), and 2.5% were children (<14 years). Of the 122 patients, 94 (77%) were males, and 28 (23%) females. The prevalence of meniscus extrusion was 30.3% (37 cases), and it was significantly higher in the medial than the lateral meniscus (P value of 0.001). A significant association was found between meniscus extrusion and meniscus tear, type of the tear, joint effusion and PCL tear, but no significant association was found to ACL, MCL and LCL tear. (The frequency of the mentioned data and their statistical correlation are shown in Tables 1 and 2.

Regarding the types of meniscal tear, the results showed that the most frequent meniscal tear was root tears in 14 cases (11.5%), followed by complex tear of posterior horn of medial meniscus (PH) in 11 cases (9%), horizontal tear of posterior horn of medial meniscus (PH) in 10 cases (8.2%), radial tear in 7 cases (5.7%), vertical tear of posterior horn of medial meniscus PH in 7 cases (5.7%), and bucket handle tear (BHT) in 3 cases (2.5%).

The group of knee trauma due to fall on ground

results of analyzing the data collected from 62 cases who had a history of knee trauma as a result of falling on ground showed that meniscus extrusion had a significant association with gender (more in female) (p=0.046), medial meniscus involvement, (p=0.001), meniscal tear (p=0.001), medial meniscus tear (p=0.001), types of meniscal tear (p=0.001), joint effusion (p=0.009), and age (p=0.006). But in this group of cases, there was no significant association between meniscal extrusion and lateral meniscus tear, lateral meniscus extrusion, or AC, PCL, MCL, and LCL tear (p>0.05).

Sport injury group

The results obtained from the 60 cases with knee injuries caused by sport (football playing) demonstrated a significant association between meniscal extrusion and medial meniscus involvement [Figure 2], meniscal tear, medial meniscus tear, and types of meniscal tear (p<0.05). However, there was no significant association between medial meniscal extrusion, ACL tear, PCL tear, MCL tear, LCL tear, age, and joint effusion (p>0.05). Table 3 shows the statistical correlation of both subgroups with the associated knee injuries. Table 4 shows the

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	Frequency	Percentage		Frequency	Percentag
	Meniscal Extrusion	-		Meniscal tear	-
Yes	37	30.3	Yes	59	48.4
No	85	69.7	No	63	51.6
Total	122	100.0	Total	122	100.0
1	Lateral meniscus extrusi	on		Medial Meniscal tear	
Yes	1	.8	Yes	56	45.9
No	121	99.2	No	66	54.1
Total	122	100.0	Total	122	100.0
	Medial meniscus extrusi	on		Lateral meniscal tear	
Yes	36	29.5	Yes	3	2.5
No	86	70.5	No	119	97.5
Total	122	100.0	Total	122	100.0
	Joint effusion			ACL tear	
Yes	60	49.2	No	59	48.4
No	62	50.8	High grade	31	25.4
	100	400.0	Low grade	32	26.2
Iotal	122	100.0	Total	122	100.0
	PCL tear			MCL tear	
No	110	90.2	Yes	5	4.1
High grade	1	.8	No	117	95.9
Low grade	11	9.0	Total	400	100.0
Total	122	100.0	Iotai	122	100.0
	LCL tear				
Yes	1	.8			
No	121	99.2			
Total	122	100.0			

Note: ACL: Anterior Cruciate Ligament, PCL: Posterior Cruciate Ligament. MCL: Medial Collateral Ligament, LCL: Lateral Collateral Ligament.

Table 2: The correlation between meniscal extrusion and associated knee findings.						
	Extrusion					
		Yes	No	Total	P-value	
Modial moniscus extrusion	Yes	36 (100.0)				
Medial meniscus extrusion	No	1 (1.2)	85 (98.8)	86 (100.0)	0.001	
Total		37 (30.3)	85 (69.7)	122 (100.0)	0.001	
Lateral meniscus	Yes	1 (100.0)	0 (0.0)	1 (100.0)		
Extrusion	No	36 (29.8)	85 (70.2)	121 (100.0)	0.30	
Total		37 (30.3)	85 (69.7)	122 (100.0)	0.00	
Moniscal toar	Yes	35 (59.3)	24 (40.7)	59 (100.0)		
Welliscal teal	No	2 (3.2)	61 (96.8)	63 (100.0)	0.001	
Total		37 (30.3)	85 (69.7)	122 (100.0)	0.001	
Modial moniscus toar	Yes	34 (60.7)	22 (39.3)	56 (100.0)		
medial meniscus teal	No	3 (4.5)	63 (95.5)	66 (100.0)	0.001	
Total		37 (30.3)	85 (69.7)	122 (100.0)		
Lateral menicous tear	Yes	1 (33.3)	2 (66.7)	3 (100.0)		
Lateral memocus tear	No	36 (30.3)	83 (69.7)	119 (100.0)	1 00	
Total		37 (30.3)	85 (69.7)	122 (100.0)	1.00	
loint offusion	Yes	27 (45.0)	33 (55.0)	60 (100.0)		
Joint endsion	No	10 (16.1)	52 (83.9)	62 (100.0)	0.001	
Total		37 (30.3)	85 (69.7)	122 (100.0)	0.001	
	No	21 (35.6)	38 (64.4)	59 (100.0)		
ACL tear	High grade	6 (19.4)	25 (80.6)	31 (100.0)		
	Low grade	10 (31.3)	22 (68.8)	32 (100.0)	0.279	
Total		37 (30.3)	85 (69.7)	122 (100.0)		
	No	30 (27.3)	80 (72.7)	110 (100.0)		
PCL tear	High grade	0 (0.0)	1 (100.0)	1 (100.0)		
	Low grade	7 (63.6)	4 (36.4)	11 (100.0)	0.033	
Total		37 (30.3)	85 (69.7)	122 (100.0)		

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MCL toor	Yes	3 (60.0)	2 (40.0)	5 (100.0)	
MCL lear	No	34 (29.1)	83 (70.9)	117 (100.0)	0 163
Total		37 (30.3)	85 (69.7)	122 (100.0)	0.105
	Yes	1 (100.0)	0 (0.0)	1 (100.0)	
LCL lear	No	36 (29.8)	85 (70.2)	121 (100.0)	0 303
Total		37 (30.3)	85 (69.7)	122 (100.0)	0.505



Figure 1: Fat saturated PD-weighted coronal image of left knee at midpoint in 40-year-old symptomatic female patient fell on ground shows medial meniscus extrusion of 4.5 mm. Meniscal extrusion distance measurement was taken from a perpendicular line to the edge of tibial plateau and edge of meniscus (white lines). Root tear of medial meniscus, high grade ACL tear and joint effusion are seen.



Figure 2: Fat saturated PD-weighted coronal image of right knee in 34-year-old symptomatic male athlete shows medial meniscus extrusion of 4.1mm, joint effusion and bony contusion of medial tibial plateau.

distribution of the associated meniscus tear types.

Discussion

The present study was an investigation into the prevalence of meniscal extrusion and associated knee joint abnormalities in patients with a history of knee trauma. The prevalence of meniscus extrusion in our overall study sample was 30.3%, athletes showed 13.3% prevalence versus 46.8% in non-athlete trauma group, while Rennie and Finlay (2006) reported 48% prevalence in athletes versus 30% in the control subjects. ^[18]

Most of the study sample were adults with an age range of 25-64 years. Similarly, Guermazi et al. reported a higher prevalence of knee trauma among adults compared to other age groups.^[5] It was also seen that most of the patients (77%) were males. This finding is not in line with the reports by Shultz et al. who stated meniscal extrusion is more prevalent among women than men, due to the higher laxity of special knee structures like collateral ligaments in women compared to men.^[14] This difference can be attributed to the fact that the present study was participated by a remarkably higher number of men than women.

It was observed that meniscus extrusion was significantly more common in the medial than the lateral meniscus and this finding is in good agreement with the study conducted by Puig et al. who reported medial and lateral extrusion respectively in 68.5% and 18.8% of the studied patients.^[19]

Regarding the association between meniscus extrusion, meniscus tear and its type, a statistically significant association was noticed, and this is in line with several studies which referred to as tear of medial menisci as the most important risk factor for meniscal extrusion. ^[18, 20-22] Root type tear was the most prevalent in our study group, followed by complex tear posterior horn of medial meniscus, and horizontal tear posterior horn of medial meniscus. Similar results were reported by other previously conducted studies. ^[23-25]

Our study showed a significant relationship between gender and meniscal extrusion. This finding is not in agreement with the one reported in the study conducted by Ding et al. who concluded that age, sex and family history of OA do not have a significant association with baseline medial meniscal extrusion. ^[26] This difference can be attributed to the fact that the present study was participated mostly by males (77%), while the number of females in the study carried out by Ding et al. as more than males (58% vs. 42%).

Moreover, there was a significant relationship between meniscal extrusion and types of meniscal tear. In this regard, meniscal root tears were found to be quite prevalent in cases with meniscal extrusion. Similarly, Carreau et al. reported that tear of the meniscus root can lead to meniscal extrusion.^[27] Joint effusion was also significantly associated with meniscal extrusion. In addition, posterior cruciate ligament tear was found to be significantly associated with meniscal extrusion. In line with these two findings, Crema et al. showed a significant association between meniscal extrusions, joint effusion and posterior cruciate ligament tear.^[15] A significant relationship was also observed between age and development of meniscal extrusion, such that meniscal extrusion was more prevalent among adults. Similar results were reported by Englund et al.

Table 3: Correlation between subgroups and the associated knee injuries.							
Trauma		Extr	usion	Total	P-valuo		
Tauna		Yes	Νο	Total	I -value		
Gender	Male	12 (35.3)	22 (64.7)	34 (100.0)			
Total	Female	17 (60.7)	11 (39.3)	28 (100.0)	0.046		
Iotai	Voc	29 (40.8)	33 (53.2)	62 (100.0) 28 (100.0)			
Medial meniscus extrusion	No	20 (100.0)	33 (97 1)	28 (100.0) 34 (100.0)	0.001		
Total		29 (46.8)	33 (53.2)	62 (100.0)	0.001		
	Yes	1 (100.0)	0 (0.0)	1 (100.0)			
Lateral meniscus extrusion	No	28 (45.9)	33 (54.1)	61 (100.0)	0.468		
Total		29 (46.8)	33 (53.2)	62 (100.0)			
Moniscal toar	Yes	27 (75.0)	9 (25.0)	36 (100.0)			
Meniscal teal	No	2 (7.7)	24 (92.3)	26 (100.0)	0.001		
Total		29 (46.8)	33 (53.2)	62 (100.0)			
Medial meniscus tear	Yes	26 (76.5)	8 (23.5)	34 (100.0)			
	No	3 (10.7)	25 (89.3)	28 (100.0)	0.001		
Total		29 (46.8)	33 (53.2)	62 (100.0)			
Lateral meniscus tear	Yes	1 (50.0)	1 (50.0)	2 (100.0)	4.000		
Tatal	No	28 (46.7)	32 (53.3)	60 (100.0)	1.000		
Iotai	Vee	29 (40.8)	33 (53.2) 12 (28.2)	62 (100.0)			
Joint effusion	res	21 (01.0)	13 (30.2) 20 (71.4)	34 (100.0) 28 (100.0)	0.000		
Total	NO	29 (46 8)	20 (71.4)	20 (100.0) 62 (100.0)	0.009		
Total	No	18 (48.6)	19 (51 4)	37 (100.0)			
ACL tear	High grade	4 (44 4)	5 (55 6)	9 (100.0)			
	Low grade	7 (43.8)	9 (56.3)	16 (100.0)	0.937		
Total	Ū	29 (46.8)	33 (53.2)	62 (100.0)			
	No	22 (42.3)	30 (57.7)	52 (100.0)			
PCL tear	Low grade	7 (70.0)	3 (30.0)	10 (100.0)	0 167		
					0.107		
Total		29 (46.8)	33 (53.2)	62 (100.0)			
MCL tear	Yes	2 (100.0)	0 (0.0)	2 (100.0)			
	No	27 (45.0)	33 (55.0)	60 (100.0)	0.215		
Total		29 (46.8)	33 (53.2)	62 (100.0)			
LCL tear	Yes	1 (100.0)	0 (0.0)	1 (100.0)	0.469		
Total	NO	20 (45.9)	33 (54.1) 32 (52.2)	67 (100.0)	0.400		
Total		29 (40.0) Extr	usion	02 (100.0)			
Athletes		Yes	No	Total	P-value		
	Yes	8 (100.0)	0 (0.0)	8 (100.0)			
Medial meniscus extrusion	No	0 (0.0)	52 (100.0)	52 (100.0)	0.004		
Total		8 (13.3)	52 (86.7)	60 (100.0)	0.001		
Manipool toor	Yes	8 (34.8)	15 (65.2)	23 (100.0)			
Meniscal tear	No	0 (0.0)	37 (100.0)	37 (100.0)	0.001		
Total		8 (13.3)	52 (86.7)	60 (100.0)	0.001		
Medial meniscus tear	Yes	8 (36.4)	14 (63.6)	22 (100.0)			
	No	0 (0.0)	38 (100.0)	38 (100.0)	0.001		
Total		8 (13.3)	52 (86.7)	60 (100.0)			
Lateral meniscus tear	Yes	0 (0.0)	1 (100.0)	1 (100.0)			
Tatal	NO	8 (13.6) 8 (13.0)	57 (86.4)	59 (100.0) 60 (100.0)	1.000		
IOCAI	Voc	0 (13.3) 6 (75.0)	J∠ (00.7)	26 (100.0)			
Joint effusion	No	2 (25 0)	20 (30.3)	20 (43.3) 34 (56 7)			
Total		8 (100 0)	52 (100 0)	60 (100 0)	0.06*		
	No	3 (13.6)	19 (86.4)	22 (100.0)			
ACL tear	High grade	2 (9.1)	20 (90.9)	22 (100.0)			
	Low grade	3 (18.8)	13 (81.3)	16 (100.0)	0.730		
Total	-	8 (13.3)	52 (86.7)	60 (100.0)			

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	No	8 (13.8)	50 (86.2)	58 (100.0)	
PCL tear	High grade	0 (0.0)	1 (100.0)	1 (100.0)	
	Low grade	0 (0.0)	1 (100.0)	1 (100.0)	1.000
Total		8 (13.3)	52 (86.7)	60 (100.0)	
	Yes	1 (33.3)	2 (66.7)	3 (100.0)	
MCL tear	No	7 (12.3)	50 (87.7)	57 (100.0)	*0 354
Total		8 (13.3)	52 (86.7)	60 (100.0)	0.554

	Table 4: The distribution	on of the associated	l meniscus tears typ	es.	
	Athlata	Extrusion		-	Durahua
Athletes		Yes	No	Iotai	P-value
	No	0 (0.0)	37 (71.2)	37 (61.7)	
	BHT	0 (0.0)	3 (5.8)	3 (5.0)	
	Complex tear of AH, BHT	ear of AH, BHT 0 (0.0) 1		1 (1.7)	
	Complex tear of PH	0 (0.0)	3 (5.8)	3 (5.0)	
Type of meniscal tear	Complex tear of PH, BHT	0 (0.0)	1 (1.7)	1 (1.7)	
	Horizontal tear of PH	1 (12.5)	4 (7.7)	5 (8.3)	0.001
	Radial tear	2 (25.0)	0 (0.0)	2 (3.3)	
	Root tear	4 (50.0)	0 (0.0)	4 (6.7)	
	Vertical tear of PH	1 (12.5)	3 (5.8)	4 (6.7)	
	Total	8 (100.0)	52 (100.0)	60 (100.0)	
	Trauma		Extrusion		Duralua
			No	Iotai	P-value
	No	0 (0.0)	24 (100.0)	24 (100.0)	
	Complex tear of PH	5 (62.5)	3 (37.5)	8 (100.0)	
	Horizontal tear of AH	0 (0.0)	1 (100.0)	1 (100.0)	
	Horizontal tear of PH	2 (40.0)	3 (60.0)	5 (100.0)	
	Intra-substance degeneration	2 (100.0)	0 (0.0)	2 (100.0)	
	Radial tear	5 (100.0)	0 (0.0)	5 (100.0)	
Type of meniscal tear	Radial tear , BHT	2 (100.0)	0 (0.0)	2 (100.0)	0.004
	Root tear	10 (100.0)	0 (0.0)	10 (100.0)	0.001
	Root tear , BHT	2 (100.0)	0 (0.0)	2 (100.0)	
	Vertical tear of PH	1 (33.3)	2 (66.7)	3 (100.0)	
	Total	29 (46.8)	33 (53.2)	62 (100.0)	
Note: PH: Posterior Horn	, AH: Anterior Horn, BHT: Bucket-Han	dle Tear.			

^[6] The results revealed that meniscal extrusion did not have a significant relationship with ACL, MCL, and LCL tears. This finding is supported by the study conducted by Hulet et al. ^[28]

Meniscus extrusion and trauma groups: analyzing the association between meniscal extrusion and the studied variables in the group who had knee trauma due to falling, similar significant association was found as for all of the 122 cases, except for the association between meniscal extrusion and posterior cruciate ligament tear (PCL), which was significant for the 122 cases (62 cases with knee injury from falling on ground and 60 from football playing). However, this association was not significant for the cases that had knee trauma as a result of falling on ground. Although this association was not significant, meniscal extrusion was seen in 42.3% of the cases without PCL tear. This finding is in line with the study carried out by Crema et al. ^[15]

Meniscus extrusion and trauma by football playing group: the results obtained for the cases with knee trauma caused by football playing indicated almost similar results as obtained for all of the 122 cases and the of knee injuries from falling on ground, except for the non-significant correlation of meniscal extrusion with posterior cruciate ligament tear, joint effusion, and age. Although the association between meniscal extrusion and joint effusion was not significant, 75% of the cases with joint effusion had experienced meniscal extrusion; our result was not in line with Rennie and Finlay who reported a significant association between meniscal extrusion and joint effusion in athletes.^[18]The results also showed that the group with knee trauma caused by falling on ground and the group with knee injury as a result of football playing were significantly different in terms of their age and meniscal extrusion distance, such that the mean age of cases with knee injuries from falling on ground was 35 years, while that of the athletes was 28.43 years. Moreover, the meniscal extrusion distance was shorter in athletes compared to the other group, such that meniscal extrusion distance was 2.28 and 3.21 mm in the athletes and trauma group respectively. This finding is almost similar to the one reported by Rennie and Finlay.^[18]

Conclusion

Prevalence of meniscal extrusion is high among cases with knee injuries whether due to falling on ground or football playing, medial meniscus involvement is much more commonly affected, with a significant association between meniscus extrusion and meniscus tear, root type tear, joint effusion and PCL tear. Medial meniscus tear is the most significant risk factors for meniscal excursion. Athletes experience a shorter meniscal extrusion distance compared to the non-athletes.

Competing Interests

The authors declare that they have no competing interests.

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