ISSN: 2469-5718

Pringle et al. Int J Sports Exerc Med 2019, 5:153
DOI: 10.23937/2469-5718/1510153
Volume 5 | Issue 11
Open Access

International Journal of
Sports and Exercise Medicine

RESEARCH ARTICLE

Lady or Gentleman? Sex Differences in Osseous and Cartilaginous Structures of the Knee

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Abstract

Objective: To identify anatomic sex differences in the osseous and cartilage structures of the knee.

Materials and methods: We performed a comprehensive review of imaging investigations of knee morphology comparing male and female subjects using PUBMED, with search terms for CT/MRI, knee anatomy, and gender. Inclusion criteria were primary imaging investigations of knee osseous/cartilage anatomy (minimum 15 subjects); exclusion criteria were studies of post-operative patients, those with comorbid orthopedic conditions, and review articles. Sex differences in osseous/cartilage anatomy were extracted and aggregated.

Results: Of 1550 citations reviewed, 84 studies met inclusion criteria and fell into 5 categories: Bony axes of the knee (n = 21), morphology of the distal femur (n = 38), proximal tibia (n = 15) and patella (n = 8), and articular cartilage (n = 16). Knee axes studies suggested trochlear groove-tibial tuberosity distance and posterior tibial slope may be greater in females. Distal femur studies showed larger metrics in males, and narrower metrics in females with smaller intercondylar notch volumes. Regarding tibial morphology, females had smaller tibias (normalizing for height), with narrower tibial plateaus and deeper medial tibial plateaus. Female patellas were smaller and different enough in morphology to be accurate in predicting sex in forensic studies. Cartilage studies mostly suggested that articular cartilage thickness and volume were greater in males.

Conclusion: Sex differences in anatomic structures of the knee have been reported. Given the increasing emphasis on individualized medicine, the emergence of sex-based diagnosis and treatment protocols, radiologists should be aware of anatomic sex differences.

Introduction

Women's sports medicine is a growing field in the world, as research has shown that women are more susceptible to certain sports-related injuries and require tailored treatment and prevention programs. An understanding of anatomic sex differences is important in the recognition of sex-related injury patterns. In the knee, most researches have focused on the Anterior Cruciate Ligament (ACL), with orthopedic surgery, physical therapy, and other clinical sports medicine fields producing the majority of the research regarding the functional and biomechanical aspects of knee stability and ligament differences. Women are known to have 2-8 times more frequent non-contact ACL injuries than men. While the etiology and implications for this sex difference remained unclear, functional, hormonal and anatomic factors may play a role, and sex differences in bone anatomic features have been studied, as they relate to the ACL

Citation: Pringle LC, Tanaka MJ, Fayad LM (2019) Lady or Gentleman? Sex Differences in Osseous and Cartilaginous Structures of the Knee. Int J Sports Exerc Med 5:153. doi.org/10.23937/2469-5718/1510153

Accepted: November 09, 2019; **Published:** November 11, 2019

[1]. For example, sex differences had been suggested in the posterior tibial slope of injured knees, a parameter which had been shown to play a role in knee stability in addition to ACL injury [2,3], and differences in notch dimensions and lim alignment may be a causal factor in the developing of tears of the ACL [1]. However, there has been no systematic comparison of knee anatomy as it related to gender differences.

Another area of research relating to bone and cartilage sex differences has been performed outside the acute sports medicine practice, with the goal of personalizing arthroplasty components. Sex-specific implants are now being used clinically, despite some disagreement on whether the differences are truly related to sex or simply the size of the femur and tibia [4]. Additionally, whether sex-specific components improve outcomes after surgery is a controversial topic on its own [5].

Hence, we sought to evaluate the current literature to identify areas of agreement, controversy, and knowledge gaps that may better inform both radiologists and sports medicine clinicians about sex differences in the anatomy of the knee. If radiologists can accurately identify patients at risk of injury, can detect risk factors for post-operative complications, or help aid the clinical and surgical team in operative planning or rehabilitation planning by noting sex differences, the field of radiology will be invaluable in customizing care for patients moving forward. Thus, the purpose of this study was to perform a comprehensive review of the English literature for original scientific researches on sex differences in osseous and cartilage anatomy of the knee.

Materials and Methods

Search strategy

To identify original articles for this review, a computerized MEDLINE database search was performed through the PubMed service of the National Library of Medicine for articles in the English language with the search criteria listed (Figure 1). The search included articles published between 2001 and December 2016. Limiting the search to articles in English was done for practical reasons, but very few articles were eliminated using this filter. A manual search and perusing of reference lists was also performed in MEDLINE following the comprehensive search, to identify any potential additional primary studies. The search was performed on March 24, 2016.

Study selection

Inclusion criteria were primary investigations of cross-sectional imaging of knee anatomy by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) in males and females of all ages. We excluded studies with fewer than 15 subjects due to small sample size. Studies examining injury patterns, functional anatomy, anatomy of soft tissues (tendons, ligaments, muscles, menisci), and knee development were not included in this study. We also excluded studies focusing on modalities outside of CT/MR, such that studies examining differences based on radiography and nuclear medicine modalities were rejected. Studies reviewing joints other than the knee (e.g. the hip), studies in patients with comorbid conditions affecting the knee (example: Arthritis), studies in postsurgical patients and review articles

("Magnetic Resonance Imaging"[mh:noexp] OR "magnetic resonance imaging"[all] OR "magnetic resonance imagings"[all] OR "MRI"[all] OR "MR imaging"[all] OR "CT"[tiab] OR "Tomography, X-Ray Computed"[mh:noexp] OR "Four-Dimensional Computed Tomography"[mh] OR "Tomography, Spiral Computed"[mh] OR "Multidetector Computed Tomography"[mh] OR "computer assisted tomography"[all] OR "computed tomographic angiography"[all] OR "computed tomography"[all] OR "electron beam tomography"[all] OR "computer tomography"[all] OR "optical tomography"[all]) AND
("Knee injury"[all] OR "Knee anatomy"[all] OR "knee joint"[mh] OR "knee"[mh] OR "knee injuries"[mh:noexp] OR "tibial menisci"[all] OR "tibial meniscus"[all] OR "patellofemoral joint"[all] OR "patellofemoral joints"[all] OR "knee dislocation"[mh] OR "knee dislocation"[all] OR "knee dislocation"[all] OR "patellar dislocation"[mh] OR "patellar dislocation"[all] OR "anterior cruciate ligament"[mh] OR "anterior cruciate ligament"[all] OR "ACL"[all] OR "medial collateral ligament"[all] OR "MCL"[all] OR "lateral collateral ligament"[all] OR "LCL"[all] OR "posterior cruciate ligament"[mh] OR "PCL"[all] OR "posterior cruciate ligament"[all] OR "patellar ligament"[mh] OR "patellar ligament"[all] OR "patellofemoral ligament"[all] OR "patellar tendon"[all] OR "medial collateral ligament, knee"[mh] OR "lateral meniscus"[all] OR "medial meniscus"[all] OR "patella"[mh] OR "patella"[all] OR "patellar"[all] OR "tibial plateau"[all] OR "distal femur"[all] OR "intercondylar notch"[all] OR "femoral notch"[all] OR (("femur"[all] OR "femoral"[all] OR "knee"[all]) AND ("medial condyle"[all] OR "lateral condyle"[all] OR "trochlea"[all])) OR "tibial cartilage"[all] OR "femoral cartilage"[all] OR "patellar cartilage"[all] OR "knee cartilage"[all] OR (("meniscal tear"[all] OR "articular cartilage"[all]) AND "Knee"[all]) OR (("Fractures, Bone"[mh] OR "fracture"[all] OR "fractures"[all] OR "bone bruise"[all] OR "bone contusion"[all] OR "osteochondral defect"[all] OR "osteochondritisdissecans"[mh] OR "osteochondritisdissecans"[all]) AND ("knee"[all] OR "femur"[all] OR "femoral"[all] OR "patella"[all] OR "patellar"[all] OR "tibia"[all] OR "tibial"[all])) OR "quadriceps tendon"[all]) AND
(Gender[tw] OR "Sex"[mh] OR "sex"[all] OR ((Male[tiab]OR males[tw] OR men[tw] OR man[tw]) AND (female[tiab] OR females[tw] OR women[tw] OR woman[tw])) OR "sexual difference"[all] OR "sexual

Figure 1: Pubmed search strategy is shown.

were also excluded. The search also returned articles which were unrelated to the subject of interest (example: Treatment of tension pneumothorax) which were excluded as well.

Each citation was reviewed by one observer (LP) based on the inclusion and exclusion criteria, starting with title. If question of appropriateness of the study persisted, the abstract and finally the full text were reviewed prior to inclusion or exclusion of the study.

Extracted imaging features

Each eligible article was examined by one observer (LP), for imaging features that compared males and females on cross-sectional imaging, and the features were then divided into bony axes, distal femur morphology, proximal tibia morphology, patella morphology, and articular cartilage. If a study examined sex differences in multiple categories and/or subcategories, all applicable categories were assigned to that study.

Analysis

Each study was categorized as above, and anatomic features of males and females were extracted and tabulated. A descriptive analysis was performed. As the studies covered multiple categories of findings, with varied inclusion criteria, a meta-analysis could not be performed.

Results

Study selection

The literature search identified 1550 citations for consideration. A hand search yielded three additional articles satisfying inclusion criteria. Review of the article titles excluded 1104 citations, leaving 449 articles for further consideration. Finally, a full-text review excluded 365 studies, leaving 84 articles, as detailed in Figure 2. The range of sample sizes in the included investigations was as low as 17, to as large as 1062 subjects, as shown in Table 1.

Table 1: Study characteristics and categories.

First author	Year	Modality	Study category	Subcategory	Number females studied	Number males studied
Ariumi [11]	2010	CT	Axes	Flexion, rotation	24	21
Shabshin [9]	2004	MRI	Axes	Insall-salvati	134	128
Cinotti [36]	2013	MRI	Axes	mPTS, lPTS	35	45
Haddad [6]	2012	MRI	Axes	mPTS, lPTS	71	72
Hudek [7]	2011	MRI	Axes	mPTS, lPTS	31	24
Lustig [3]	2013	MRI	Axes	mPTS, lPTS	51	50
Ristic [44]	2014	MRI	Axes	mPTS, lPTS	11	49
Zhang [45]	2014	CT	Axes	mPTS, lPTS	40	40
Moghtadaei [46]	2015	CT	Axes	Rotation	54	96
Tao [12]	2010	CT	Axes	Rotation	19	20
Raju [47]	2015	MRI	Axes	Rotation	38	86
Dickschas [48]	2016	CT	Axes	TT-TG	36	19
Pandit [49]	2011	MRI	Axes	TT-TG	43	57
Skelley [50]	2015	MRI	Axes	TT-TG	57	59
Akagi [10]	2004	CT	Axes	Valgus	19	20
Han [51]	2016	MRI	Axes, femur	mPTS, lPTS, AP length, ML width, condyle height, PO	262	273
Van Diek [52]	2014	MRI	Axes, femur	mPTS, lPTS, ML width, notch	41	47
Cinotti [21]	2012	MRI	Axes, femur	mPTS, lPTS, PO	35	45
Alemparte [53]	2007	CT	Axes, femur	TT-TG, trochlea	30	30
Balcarek [37]	2010	MRI	Axes, femur, patella	TT-TG, trochlea, patella height	127	130
Hashemi [8]	2008	MRI	Axes, tibia	mPTS, lPTS, plateau depth	33	22

Ding [35]	2003	MRI	Cartilage	G-vol	214	158
Nishimura [54]	2005	MRI	Cartilage	G-vol	31	37
Antony [55]	2015	MRI	Cartilage	T-vol	155	173
Berry [56]	2011	MRI	Cartilage	T-vol, p-vol	47	46
Caglar [57]	2014	MRI	Cartilage	T2	60	47
Joseph [58]	2015	MRI	Cartilage	T2	255	226
Mosher [59]	2004	MRI	Cartilage	T2	10	7
Eckstein [60]	2002	MRI	Cartilage	T2, thickness, SA	18	18
Draper [61]	2006	MRI	Cartilage	Thickness	30	20
Eckstein [62]	2010	MRI	Cartilage	Thickness	597	465
Cicuttini [63]	2002	MRI	Cartilage	Thickness, g-vol	96	70
Otterness [33]	2007	MRI	Cartilage	Thickness, SA, g-vol	40	57
Faber [34]	2001	MRI	Cartilage	Thickness, SA, g-vol	9	9
Beattie [64]	2008	MRI	Cartilage	Thickness, SA, t-vol	73	46
Eckstein [65]	2004	MRI	Cartilage	Thickness, SA, t-vol, p-vol, f-vol	14	15
Berry [66]	2008	MRI	Cartilage, patella	P-vol, patella bone volume	186	111
Li [67]	2012	CT	Femur	AP length, condyle height	39	51
Van den Heever [14]	2012	MRI	Femur	AP length, ML width	22	20
Cavaignac [15]	2016	CT	Femur	AP length, ML width	134	122
Cho [16]	2015	CT	Femur	AP length, ML width, condyle height, notch	114	88
Pinskerova [17]	2014	MRI	Femur	AP length, ML width, condyle height, trochlea	100	100
Barnes [68]	2010	CT	Femur	AP length, ML width, condyle ratios	39	27
Fehring [70]	2009	MRI	Femur	Condyle height	100	112
Yue [71]	2015	CT	Femur	Condyle height, condyle ratios	50	50
Rosenstein [72]	2008	MRI	Femur	Condyle ratios	50	50
Yan [43]	2014	CT	Femur	Condyle ratios, trochlea	50	50
Park [69]	2012	MRI	Femur	ML width, condyle ratios	79	147
Li [73]	2014	CT/ MRI	Femur	ML width, condyle height	65	96
Murshed [74]	2005	MRI	Femur	ML width, condyle height	100	100
Vrooijink [75]	2011	MRI	Femur	ML width, condyle ratios, notch	40	49
Anderson [76]	2001	MRI	Femur	ML width, notch	50	50
Van Eck [77]	2011	MRI	Femur	Notch	45	55
Van Eck [78]	2010	CT	Femur	Notch	10	10
Charlton [79]	2002	MRI	Femur	Notch	20	28
Dienst [80]	2007	MRI	Femur	Notch	10	10
Estes [81]	2015	MRI	Femur	Notch	23	49
Wang [20]	2014	CT	Femur	PO	50	50
Arslan [22]	2015	MRI	Femur	Red marrow	92	48
Biedert [82]	2009	MRI	Femur	Trochlea	68	84

Hasler [83]	2014	MRI	Femur	Trochlea	16	37
Kamath [84]	2013	MRI	Femur	Trochlea	183	146
Wang [42]	2012	CT	Femur	Trochlea	50	50
Voleti [4]	2015	MRI	Femur, cartilage	Condyle height, condyle ratios, PO, thickness	50	50
Lee [85]	2015	CT	Femur, patella	F-SA/vol, patella bone volume, patella SA	55	55
Cheng [40]	2010	CT	Femur, tibia	AP length, ML width, AP-t, ML-t	78	94
Lim [18]	2013	MRI	Femur, tibia	AP length, ML width, AP-t, ML-t, t-ratio	59	56
Bisson [19]	2010	MRI	Femur, tibia	AP length, ML width, plateau depth	40	40
Yue [13]	2011	CT	Femur, tibia	AP length, ML width, trochlea, AP-t, ML-t	20	20
Bellemans [86]	2010	CT	Femur, tibia	Condyle ratio, AP-t, ML-t, t-ratio	686	314
Huang [30]	2015	CT	Patella	Patella height, patella width, patella thickness	60	60
Shang [41]	2014	CT	Patella	Patella height, patella width, patella thickness	20	20
Yoo [87]	2007	MRI	Patella	Patella height, patella width, patella thickness	30	142
Mahfouz [32]	2006	CT	Patella	Patella morphology	95	133
Mahfouz [31]	2007	CT	Patella	Patella morphology	95	133
Scheffel [29]	2013	MRI	Tibia	ACL insertion site	68	70
Kucukdurmaz [88]	2014	MRI	Tibia	AP-t, ML-t	150	110
Erkocak [23]	2016	MRI	Tibia	AP-t, ML-t, t-ratio	138	88
Hartel [25]	2014	CT	Tibia	Master shape	38	79
Hartel [26]	2009	MRI	Tibia	Master shape	110	127
Hovinga [24]	2009	MRI	Tibia	ML-t	36	34
Stone [89]	2007	MRI	Tibia	ML-t	38	63
Tang [27]	2010	MRI	Tibia	Offset	25	25
Sun [28]	2014	CT	Tibia	Posterior proximal tibia	138	162

Legend: CT: Computed Tomography; MRI: Magnetic Resonance Imaging; TT-TG: Tibial Translation-Trochlear Groove Distance; mPTS: medial Posterior Tibial Slope; lPTS: Lateral Posterior Tibial Slope; AP: Anteroposterior; ML: Mediolateral; PO: Posterior Offset; Vol: Volume; G-vol: General volume; T-vol: Tibial volume; F-vol: Femoral volume; P-vol: Patellar volume; SA: Surface Area; F-SA: Femur Surface Area; AP-t: AP length of tibia; ML-t: ML width of tibia; T-ratio: Tibial ratio.

Extracted imaging features

The 84 included articles spanned 5 major categories shown in Table 1: Bony axes of the knee (21 papers), morphology of the distal femur (38 papers), morphology of the proximal tibia (15 papers), morphology of the patella (8 papers), and articular cartilage (16 papers). The axes category was divided into 7 subcategories (Table 2): Condylar angles, flexion, Insall-Salvati ratio (ratio of patellar length to patellar tendon length), Posterior Tibial Slope (PTS), tibial rotation, Tibial Tuberosity to Trochlear Groove (TT-TG) distance, and valgus. The distal femur category was divided into 9 subcategories (Table 3): Anteroposterior (AP) condylar length, mediolateral (ML) condylar width, condyle height, condyle ratios, notch, posterior offset, trochlea, red marrow, and surface area/volume. The proximal tibia category was divided into 8 subcategories (Table 4): Plateau depth, AP plateau diameter, ML plateau diameter, plateau ratio, tibial offset, master shape of the proximal tibia, posterior proximal tibia, and ACL insertion site in the proximal tibia. The patella category was divided into 7 subcategories (Table 5): Patella height, patella width, patella thickness, patella bone volume, patella surface area, patella width to thickness ratio, patella morphology sex

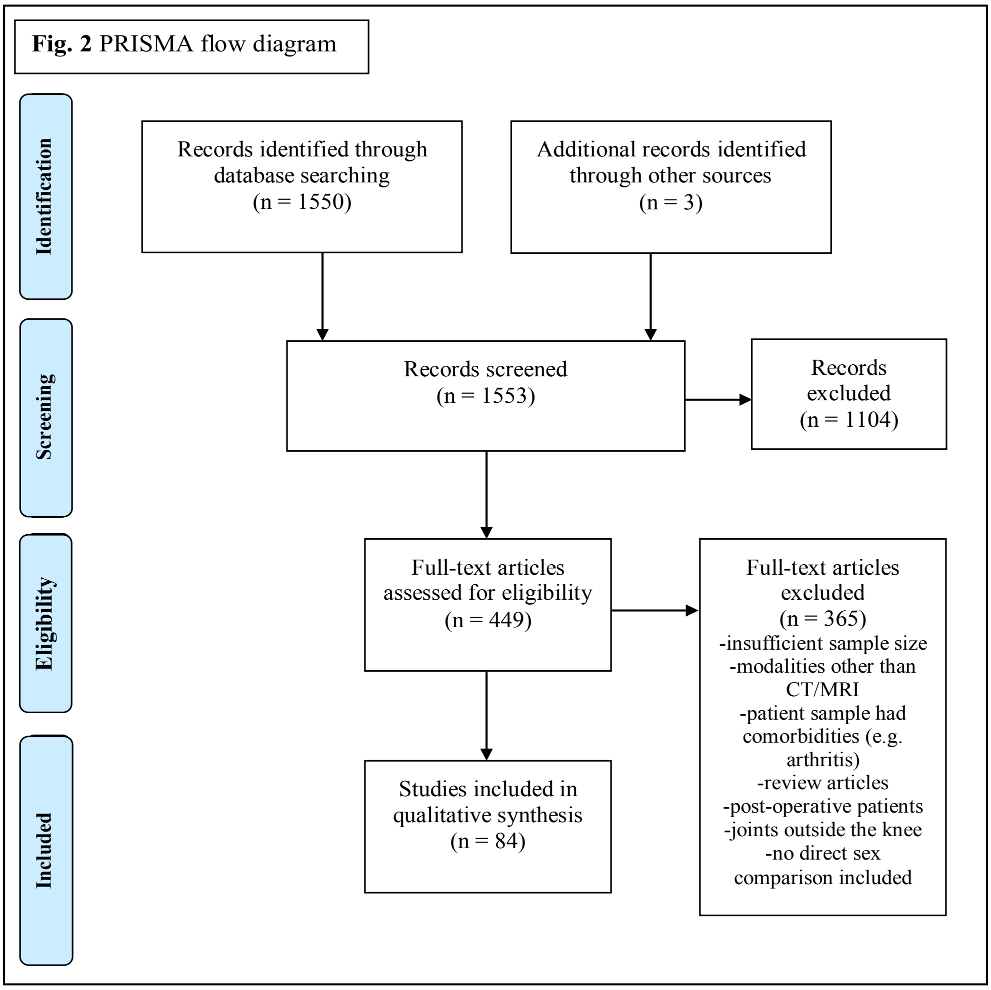

Figure 2: Diagram showing study inclusion and exclusion.

Table 2: A summary of investigations of the bony axes of the knee.

First author	TT-TG	Medial PTS	Lateral PTS	Flexion	Insall-salvati	Rotation	Valgus
Cinotti [36]		ND	ND				
Haddad [6]		F	F				
Hudek [7]		F	ND				
Lustig [3]		ND	ND				
Ristic [44]		ND	ND				
Zhang [45]		ND	ND				
Alemparte [53]	ND						
Dickschas [48]	ND						
Pandit [49]	ND						
Skelley [50]	F						
Ariumi [11]				M		ND	
Shabshin [9]					F		
Tao [12]						M[T]	
Akagi [10]							F
Han [51]		ND	ND				
Cinotti [21]		ND	ND				
Balcarek [37]	F						
Hashemi [8]		F	F				
Van Diek [52]		ND	ND				

Moghtadaei [46]						ND^{F}	
Raju [47]						ND^{F}	
SUMMARY	**Split between no sex difference and greater in females**	**7/10 studies say no sex difference**	**8/10 studies say no sex difference**	**Males exhibited greater degree of knee flexion**	**Females have different normal curve of Insall-Salvati ratio with higher values**	**No difference in femoral rotation; males have greater tibial rotation**	**Females have greater degree of knee valgus**

ND: No statistical difference; F: Greater/larger in females; M: Greater/larger in males; M^{T}: Greater tibial rotation in males; ND^{F}: No difference in femur rotation.

Table 3: A summary of investigations of the distal femur.

First author	AP condylar length	ML width (condyles, EW, BW)	Condyle height	Condyle ratios	Notch	PO	Trochlea	Red marrow	Femur surface area/volume
Van Diek [52]		M			ND				
Han [51]	M^{L} ND^{M}	M	M			M			
Balcarek [37]							F^{1,2} M^{3}		
Cinotti [21]						F^{a,M} ND			
Alemparte [53]							F^{1}		
Barnes [68]	M	M		F					
Fehring [70]			M^{M} ND^{E}						
Li [67]	M^{a,b}		M						
Li [73]		M	M						
Rosenstein [72]				F					
Van den Heever [14]	M	M							
Cho [16]	M^{b}	M^{b}	M^{b}		M^{b}				
Vrooijink [75]		M		ND	ND				
Pinskerova [17]	M	M	M				ND^{5} M^{3,4}		
Wang [42]				F			M^{9}		
Yan [43]				M			M^{4}		
Cavaignac [15]	M	M							
Murshed [74]		M	M						
Van Eck [77]					M				
Van Eck [78]					M^{NW} ND^{NWI}				
Charlton [79]					M^{b} ND^{a}				
Park [69]		M	M	ND	M				
Yue [71]			M	ND					
Dienst [80]					M^{a}				
Estes [81]					ND^{NWI}				
Anderson [76]		M^{b} ND^{a}			M^{b-NW} ND^{a-NW} ND^{NWI}				

Wang [20]						M[b] ND[a]			
Arslan [22]								F	
Biedert [82]							M[6]		
Hasler [83]							M[3,4] ND[2]		
Kamath [84]							ND[7]		
Voleti [4]			M	ND		M			
Lee [85]									M
Bellemans [86]				M					
Bisson [19]	F[a]	M							
Cheng [40]	M	M							
Lim [18]	M[M] ND[L]	M							
Yue [13]	M[M,a]	M[M,a]					ND[8]		
SUMMARY	Majority of studies showed males had greater unadjusted AP condylar dimensions. With adjustments, 2 studies demonstrate controversy.	Greater ML condylar width in males, although one paper suggested difference does not persist after adjustment	Majority show that males have greater condylar height	No consensus about condylar size/aspect ratios, although some papers focused on unique ratios or measured metrics differently than the others	Males had greater notch widths, although majority of studies showed this difference did not persist after adjustment/when evaluating NWI rather than simple NW	Males had greater offset with no adjustment; with adjustment, no difference or maybe slightly greater in females	Overall, findings suggest greater tendency towards trochlear dysplasia (metrics relating to shallow sulcus depth/asymmetry), although some characteristics showed no sex difference		

ND: No statistical difference; F: Greater/larger in females; M: Greater/larger in males; EW/BW: Epicondylar width/bicondylar width; X[a]: With adjustments (such as weight, height, BMI, bone length); X[b]: Without adjustments (such as weight, height, BMI, bone length); X[M]: Medial only; X[P]: Patella only; X[L]: Lateral only; X[E]: Elsewhere; X[1]: Sulcus angle; X[2]: Trochlear asymmetry; X[3]: Trochlear depth; X[4]: Trochlear and/or trochlear facet width; X[5]: Trochlear shape ratios (trochlear depth relative to trochlear width); X[6]: Trochlear height ratios (AP length of medial condyle relative to bicondylar width); X[7]: Trochlear inclination; X[8]: Trochlear groove orientation/location; X[9]: Trochlear groove 3D modeling with radius and arc length.

Table 4: A summary of investigations of the proximal tibia.

First author	Plateau depth	AP plateau	ML plateau	Plateau ratio	Offset	Master shape	Posterior prox tibia	ACL insertion site
Hashemi [8]	ND[M]							
Bellemans [86]		M	M	F ND				
Bisson [19]	F							
Cheng [40]		M[M]	M[M]					
Lim [18]		M	M	M				
Yue [13]		M[a] ND[b]	M[a] ND[b]					
Tang [27]					M[1]			

Erkocak [23]		M	M	M				
Hartel [25]						ND[2]		
Hartel [26]						ND[2]		
Hovinga [24]			M					
Kucukdurmaz [88]		ND						
Stone [89]			$M^{a,b}$					
Sun [28]							ND[3]	
Scheffel [29]								ND[4]
SUMMARY	½ studies say no difference, ½ showed greater depth in females	Majority show greater AP plateau depth in males	Majority show greater ML plateau width in males	2/3 studies showed greater aspect ratios in males; 1 showed greater or no difference in females	Greater offset in males	No sex difference in “master shape” of proximal tibia	No sex difference in posterior arc/ radius	No sex difference in tibial insertion site of ACL

ND: No statistical difference; F: Greater/larger in females; M: Greater/larger in males; X^a: With adjustments (such as weight, height, BMI, bone length); X^b: Without adjustments (such as weight, height, BMI, bone length); X^M: Medial only; X^1: Anterolateral tibial shaft offset relative to tibial plateau; X^2: Master shape of tibia plateau (model); X^3: Posterior proximal tibia arc angle/radius; X^4: Tibial ACL insertion site as % of total AP tibial plateau dimension.

Table 5: A summary of investigations of the patella.

First author	Patella height	Patella width	Patella thickness	Patella bone volume	Patella SA	Patella width to thickness ratio	Patella morphology sex model
Balcarek [37]	ND						
Berry [66]				M			
Lee [85]				M	M		
Huang [30]	M^a	M^a	M^a			ND	
Mahfouz [32]							93.51% accurate
Mahfouz [31]							96% accurate
Shang [41]	M	M	M				
Yoo [87]	M	M	M				
SUMMARY	Majority show greater height in males	All show greater width in males, even after adjustment	All show greater thickness in males, even after adjustment	Greater in males	Greater in males	No sex difference	3d modeling has high sex identification accuracy

ND: No statistical difference; F: Greater/larger in females; M: Greater/larger in males; X^a: With adjustments (such as weight, height, BMI, bone length); X^b: Without adjustments (such as weight, height, BMI, bone length).

Table 6: A summary of investigations of the articular cartilage.

First author	T2 value	Thickness	SA	General volume	Tibial volume	Patellar volume	Femur volume
Caglar [57]	ND						
Joseph [58]	F^{MF} ND^{E}						
Mosher [59]	ND						
Draper [61]		M					
Eckstein [62]		M					
Eckstein [60]	ND	ND	M				
Antony [55]					M		
Berry [56]					M	M	
Ding [35]				M			

Nishimura [54]				M^{b} ND^{a}			
Cicuttini [63]		M^{a}		M^{a}			
Otterness [33]		M^{a}	M^{a}	M^{a}			
Beattie [64]		M	M		M		
Eckstein [65]		ND^{P,LT}	M		M	M	M
Faber [34]		M^{b} ND^{a}	M^{b} ND^{a}	M^{b} ND^{a}			
Berry [66]						M	
SUMMARY	Majority show no sex difference	Most show greater thickness in males, although 3/8 studies suggest no difference	Mostly show greater surface area in males, although controversial after adjustment	Greater in males without adjustment; 50% say greater in males with adjustment vs. no difference	Greater in males	Greater in males	Greater in males

ND: No statistical difference; F: Greater/larger in females; M: Greater/larger in males; X^{a}: With adjustments (such as weight, height, BMI, bone length); X^{b}: Without adjustments (such as weight, height, BMI, bone length); X^{MF}: Medial femur only; X^{P}: Patella only; X^{LT}: Lateral tibia only; X^{E}: Elsewhere.

model (3D-CT modeling for forensic sex analysis with a single patella). The articular cartilage category was divided into 7 subcategories (Table 6): T2 cartilage values, thickness, surface area, general volume, tibial volume, patellar volume, and femur volume.

Analysis

Bony axes of the knee: Although there were some common results, most of the metrics studied in articles investigating bony axes of the knee showed controversy with regards to sex differences, and some articles investigated unique metrics not evaluated in other articles. Studies evaluating the TT-TG showed either no sex difference (3/5 studies), or greater values in females, particularly with a history of patellar instability (2/5 studies showing 14.1-19.5 mm in females vs. 12.6-17.0 mm in males). The majority of studies examining PTS showed no sex difference in either the medial (7/10 studies) or lateral tibial plateau (8/10 studies), although the remaining studies showed a greater slope in females (2/10 studies for lateral tibial plateau; 3/10 studies for medial tibial plateau), with females having a mean medial PTS ranging from 4.9 - 6.3 degrees compared to 3.0 - 5.1 degrees in males [6-8], and a mean lateral PTS ranging from 6.3 - 7.0 degrees in females compared with 4.8 - 5.4 degrees in males [6,8]. Females had greater average Insall-Salvati ratios (1.0878 in females vs. 1.0032 in males) and valgus angles at the knee (mean of 5.3 degrees in females vs. 3.1 degrees in males), although these metrics were only described in one study each [9,10]. Males exhibited a greater degree of flexion at the knee, also only described in one study [11]. Femoral rotation was described in three studies, which showed no sex difference; however, one study showed greater tibial rotation in males [12].

Morphology of the distal femur: This group of studies had the largest volume of articles and metrics investigated. Examples of distal femur metrics studied are seen in Figure 3. In nearly all femoral size metrics (including metrics such as epicondylar width, AP diameter of each condyle, height of the condyles, surface area of the distal femur etc.), males had greater unadjusted values. For example, unadjusted measurements of the AP dimensions of the medial condyle ranged from 55-64 mm in females with significantly greater dimensions in males in most papers, ranging from 61-70 mm [13-18]. Unadjusted AP measurements of the lateral condyle were also greater in males, ranging from 58-66 mm in females compared with 65-72 mm in males [13-17]. However, when adjustments for height, weight, femoral length, leg length, etc., were performed, many of these sex differences decreased or disappeared, or disagreement existed within the investigations. For example, one study showed statistically greater mean AP medial femoral condyle measurements in females (77 mm compared to 74 mm) and greater mean AP lateral femoral condyle measurements in males (79 mm compared to 74 mm) when normalized to the transepicondylar width of the femur [19]. Condylar aspect ratios were also controversial, with some studies showing no sex difference, some showing greater aspect ratios in males, and some showing greater aspect ratios in females. Studies also looked specifically at the intercondylar notch and found that while males have greater unadjusted notch widths, when using the notch width index or adjusting for other factors, the sex difference often decreased or disappeared.

Three studies looked at posterior femoral offset and two thirds of the studies found greater femoral offset in males. Two of the studies looked at posterior

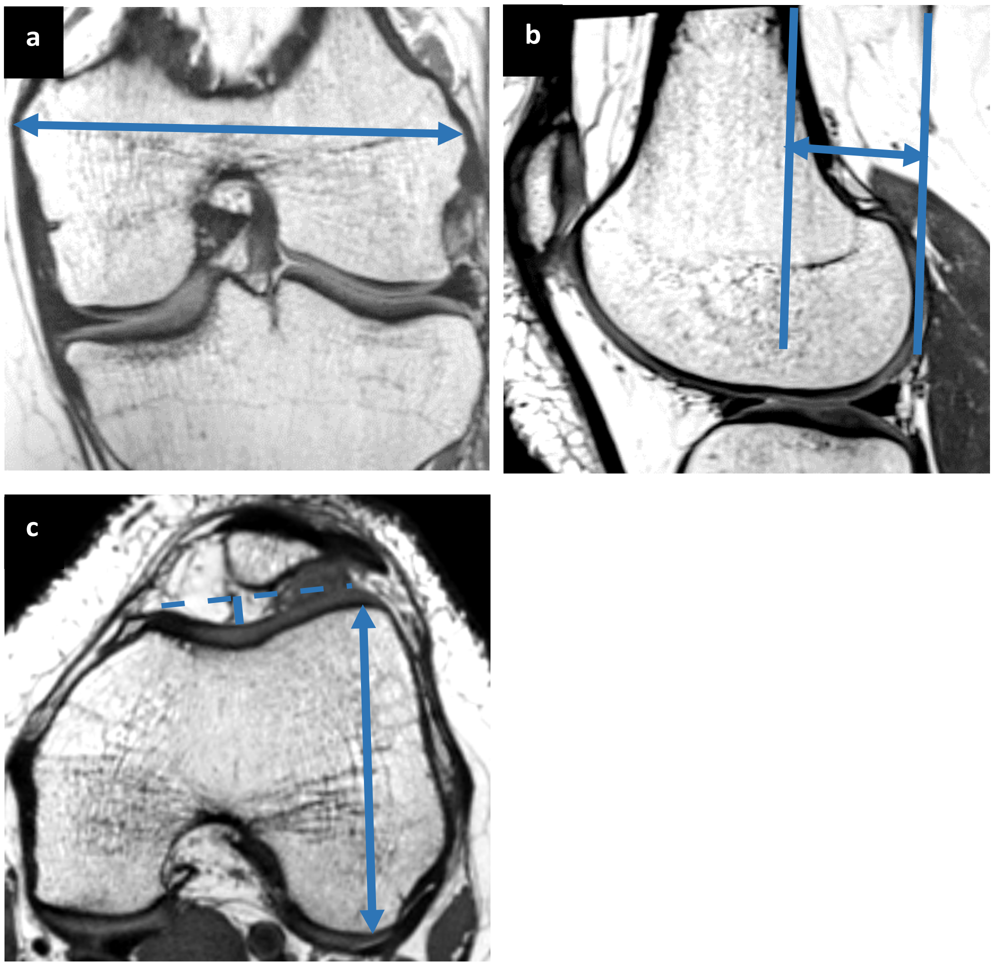

Figure 3: (a) Example figures showing distal femur metrics. Transepicondylar width is an example of a mediolateral (ML) metric; (b) Posterior offset of the femur; (c) Trochlear depth (solid line) and lateral condyle height (solid arrow).

offset as a ratio to femoral size; however, one study calculated the ratio based on AP diameter of the distal femoral condyles, finding no sex difference, while the other study used the diameter of the femoral diaphysis, finding the medial condyle ratio to be greater in females, but not different in the lateral compartment [20,21].

The trochlea was evaluated in 10 different studies, which showed a general trend (with some exceptions) towards more metrics suggesting trochlear dysplasia in females (such as shallower sulcus/greater sulcus angle, or greater asymmetry). One final unique study evaluated anatomical sex differences in the femur, finding greater residual red marrow in females than males [22].

Morphology of the proximal tibia: The majority of studies showed greater proximal tibial metrics in males (such as plateau depth, and AP/ML diameter of the tibia), often persisting with adjustment for body height and weight. For example, unadjusted mediolateral tibial plateau widths were larger in males, measuring 77-81 mm in males compared to 69-70 mm in females [23,24]. Tibial plateau ratios were less conclusive, with 2/3 studies showing greater or no difference between sexes.

There were 5 studies evaluating unique sex differences of the proximal tibia: Two studies were performed by the same group at the same institution which evaluated a master shape of the proximal tibia produced through a contour detection algorithm, finding no sex differences [25,26]. One study looked at the anterolateral offset of the tibial shaft relative to the tibial plateau, which was greater in males [27]. Another study evaluated the morphology of the posterior aspect of the proximal tibia, finding no sex difference in either the arc angle or radius of the arc forming the posterior contour [28]. Finally, another study calculated the tibial insertion site of the ACL as a percentage of the AP tibial plateau dimension and found that there were no significant sex differences in this percentage [29].

Morphology of the patella: The majority of studies evaluating the patella showed greater metrics in males, which usually persisted after adjustment for height and weight. However, one paper evaluated the patella width to thickness ratio and found no sex difference [30]. Interestingly, two studies from the same institution looked at 3D forensic modeling using CT and found that the patellar morphology was able to be modeled with at least 93% accuracy when predicting sex of the donor [31,32].

Articular cartilage: We found articles that discussed T2 cartilage metrics (thickness, area, and volumes) as well as T2 signal characteristics. Not all studies adjusted findings for patient height and weight. Males had greater cartilage size metrics when no adjustments were made. When adjusting for height and weight, two studies found that females had less cartilage volume, thickness, and joint surface area, while two other studies found no sex discrepancy in cartilage metrics. For example, in two studies that showed statistically greater total knee cartilage volume in males (mean ranging from 23-27 cc) compared to females (mean 18 cc) [33,34], statistical significance was lost after adjusting for patient height/weight [34]. The other study showed greater cartilage volume in males, to a lesser degree after normalizing to weight (male to female volume difference decreasing from 9 cc to 5 cc) or height (difference decreasing from 9 cc to 7 cc) [33]. Of potential importance, one of the two studies which showed the sex difference also described a faster cartilage loss in females with aging relative to males, and this was not evaluated in other studies in our sample [35]. Finally, four studies looked at sex differences in T2 signal characteristics, and only one found statistically significant higher T2 values in females, only in the medial femur cartilage.

Discussion

This was the first report comprehensively assessing the existing literature to identify differences in the osseous and cartilage structures of the knee between the sexes. While sex differences in the knee had been previously documented, they had largely focused on the ACL anatomy, injury rates and outcomes. The sex differences of bone and cartilage were less well understood, and this comprehensive review demonstrated that there were some well-established sex differences, some trends toward differences in anatomy, and that other sex differences still require further investigation.

As women's sports medicine is still an emerging field, we uncovered investigations of anatomic sex differences that utilized varied and non-uniform anatomic metrics and study methods. In particular, many of the studies did not normalize the metrics to patient size (such as patient height, weight, femur length etc), or did not normalize the metrics to patient size in a standard way (such as to a particular bone diameter). In addition, in some studies, sex comparisons were secondary objectives rather than the primary endpoint of the investigation, perhaps resulting in a study design that less optimally assessed sex differences. Another factor that might explain some of the varied results observed was the potential for measurement error in many of the metrics utilized; whether measurements were made by hand or with an automated tool, inter-observer reliability statistics were not available in many investigations. Hence, this comprehensive review yielded a heterogeneous group of studies, upon which a meta-analysis could not be performed; rather, we aimed to accurately summarize current knowledge and gaps in information.

Overall, the literature indicated that unadjusted size metrics in the knee, including various femoral, tibial, patellar, and cartilage metrics, were larger in males than females. However, once adjustments were made for factors such as subject height, weight, and total femur length, some of the sex differences in anatomic metrics did not persist. This phenomenon was particularly true in many distal femur, proximal tibia, and articular cartilage metrics. Thus, adjusting for body size factors was critical to determining whether observed sex differences were innate, or whether they were due solely to the patient size.

The majority of studies showed no sex differences in measurements of the bony axes of the knee, although in studies where a difference was observed, females were shown to have larger metrics (including in the TT-TG, the Insall-Salvati, the PTS PTS, and the valgus angulation). Alterations in such metrics had been posed as potential risk factors for sports injuries in females. For example, sex differences in the PTS were thought to be a risk factor in developing ACL and meniscus tears, due to accompany altered biomechanics [36]. Given the known female predilection for ACL tears, such investigations of anatomic differences in the PTS may provide important insight into why this female predilection existed, and when designing a treatment plan, anatomic differences might play an important role in therapy and future prevention.

Another area of interest that was explored in this study was the trochlear morphology. Unfortunately, the studies found in our search were fewer in number and heterogeneous, resulting in limited conclusive power. Included studies that analyzed trochlear morphology suggested a trend towards a more shallow trochlea in females with lesser trochlear depth, greater sulcus angle, and greater asymmetry in the trochlea, all important anatomic features to further exploring the diagnosis of trochlear dysplasia and its predisposition to patellar maltracking. Our findings regarding the trochlea were therefore consistent with observations in sports medicine, that females had higher rates of patellar instability (including patellofemoral pain and sensation of patellar subluxation),higher rates of primary dislocation during the high-risk adolescent period (age 10-17), and higher rates of recurrent dislocations in patients with instability symptoms [37,38].

Other than the trochlea, most measures of the distal femur, when adjusting for height, weight and other confounding factors, were not significantly different between males and females (including aspect ratios and notch width). However, one measure that reported important in the assessment of knee arthroplasty functionality was the posterior femoral offset. This measurement was found to be greater in males than females in two of three anatomic studies. Hence, customized arthroplasties designed with attention to the offset were probably important to subsequent restoration of function in patients requiring surgery, and care was often taken to consider this factor in treatment planning [39].

In the patella, it appeared that sex differences likely persisted after adjusting for confounding factors, with males had generally larger and exaggerated morphology compared to females. Additionally, it was very interesting that the sex differences of the patella were enough that a trained neural network in forensic CT modeling can identify patient sex with a high degree of accuracy [32,32]. These findings might have clinical implications to both developing injury (also potentially contributing to patellar instability/dislocation in addition to trochlear morphology), and to arthroplasty design and surgical treatment. Similarly, in the tibia, males tended to have larger tibias with more pronounced features (such as greater depth or greater anteroposterior to lateral diameter). These proximal tibial differences likely had clinical implications, with resulting alterations to the biomechanics and stability of the knee joint, shear forces (and therefore injury risk) on the intra-articular soft tissues such as cruciate ligaments, articular cartilage and menisci might be different between the sexes as a consequence.

Our comprehensive review had limitations. We excluded studies that were not written in the English language, which limited the scope of our search. We included studies focusing on certain ethnic/racial populations, such as studies looking specifically at Chinese subjects only [12,20,27,28,40-44]. Such a specific patient population focus might limit the generalizability of the findings; we did not adjust for ethnicity, race or age, as not enough data was available to do so. Also, as already mentioned, the study populations, research methodology and outcome measures were highly variable between investigations; due to the heterogeneity of studies, a quality assessment tool could not be utilized to capture quality differences and a meta-analysis could not be performed. In addition, measurement from different studies made by different modalities could influence the results, but there was no inter-modality comparison available to determine the accuracy and interplay between modalities.

In conclusion, while a robust understanding of the bony and cartilaginous sex differences in the knee were still emerging, we had provided a compendium of current knowledge in this important field. Such information was valuable to potentially providing a customized radiology interpretation for individual patients of different sexes and identifying patients at risk of injury. In this way, imaging metrics of sex differences might help promote better surgical outcomes and post-operative care, as an understanding of the sex differences continues to be elucidated. Finding metrics that had no sex difference would also be beneficial in directing resources away from sex-specific approaches in sports medicine, to those that were influenced by patient sex. Radiology was uniquely positioned to study these anatomic differences in a noninvasive manner with continually improving imaging techniques, including high-resolution and increasingly fast acquisitions, which can improve the standardization of measurements and findings. Moving forward, investigations looking at sex differences should conduct rigorous, reproducible measurements that were normalized to patient height, weight, and femur length at a minimum, so that any sex differences discovered can be attributable to sex rather than patient size alone.

Acknowledgments

Individuals who are not authors: We thank Katie Lobner, clinical informationist at the Johns Hopkins Welch Medical library, for her assistance in developing/refining our search strategy and assistance in collecting the articles reviewed for this project.

Grants/Funding

None.

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