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Generalised joint hypermobility increases ACL injury risk and is associated with inferior outcome after ACL reconstruction: a systematic review

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ABSTRACT

Objectives To investigate the association between generalised joint hypermobility (GJH) and ACL injury risk. Secondary aims involved evaluating associations between GJH and postoperative outcome (including graft-failure risk, knee laxity and patient-reported outcome). Furthermore, we aimed to compare the performance of different grafts in patients with GJH.

Methods Databases MEDLINE/PubMed, EMBASE and the Cochrane Library were searched, including 2760 studies. Two reviewers independently screened studies for eligibility. A modified version of the MINORS score was applied for quality appraisal. Studies assessing GJH while reporting the risk of ACL injury and/or postoperative outcome were included.

Results Twenty studies were included, using several different methods to determine GJH. There was consistent evidence showing that GJH is a risk factor for unilateral ACL injury in males, while in females, the results were conflicting. There was limited evidence associating GJH with increased knee laxity 5 years postoperatively. There was consistent evidence of inferior postoperative patient-reported outcome in patients with GJH. Moreover, there was limited yet consistent evidence indicating that patellar-tendon autografts are superior to hamstring-tendon autografts in patients with GJH in terms of knee laxity and patient-reported outcome. There was insufficient evidence to draw conclusions regarding the outcomes of bilateral ACL injury and graft failure.

Conclusions In men, GJH was associated with an increased risk of unilateral ACL injury. Moreover, GJH was associated with greater postoperative knee laxity and inferior patient-reported outcome. Based on the available evidence, a patellar-tendon autograft appears to be superior to a hamstring-tendon autograft in patients with GJH. However, the included studies were heterogeneous and there is a need for consensus in the assessment of GJH within sports medicine.

What is already known?

- ► Generalised joint hypermobility is associated with knee injuries in general.
- ► Generalised joint hypermobility is associated with articular pain and reduced quality of life in the general population.
- ► There have been conflicting reports associating the existence of generalised joint hypermobility with ACL injury, graft failure and postoperative outcome.

What are the new findings?

- ► Compared with normal joint mobility, men with generalised joint hypermobility have a greater risk of rupture of the ACL.
- ► Generalised joint hypermobility is associated with inferior patient-reported outcome after ACL reconstruction.
- ► Limited evidence indicates that patellar-tendon autografts are superior to hamstring-tendon autografts, in patients with generalised joint hypermobility, in terms of patient-reported outcome and postoperative knee laxity.

INTRODUCTION

The investigation of risk factors for ACL injury has been a subject of interest during the last few decades. Injuries to the ACL are caused by intricate interplay between intrinsic and extrinsic risk factors in combination with injury mechanisms.[1 2] One potential risk factor for ACL injury, which is attracting increasing interest, is generalised joint hypermobility (GJH). GJH has been shown to increase the risk of sustaining knee injuries in general,[3] and it has also been associated with ACL injury risk,[4] the risk of contralateral ACL injury[5] and inferior postoperative outcomes.[6] However, a recent study reported no association between GJH and ACL injury risk.[7] As a result, there is a need to evaluate the scientific evidence in this regard.

GJH is defined merely as hyperextensibility of the synovial joints with the ability to extend, passively and/or actively, beyond

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the normal physiological range of motion. GJH may be present in isolation, in combination with symptoms (eg, pain, fatigue or joint dislocations) or as a feature in a clearly defined syndrome, such as hereditary connective-tissue disorders. Previously, the term GJH has been used by several researchers within different subspecialised areas, although the definitions have differed between researchers. In 2017, a consensus statement and a clarification of hypermobility terminology were published in order to clearly define GJH and thus facilitate the more stringent use of this term forthwith.[8 9] In short, the statement suggests standardised testing procedures, and that individualised cut-off values should be used to define GJH, depending on the age, sex and maturity of the individuals. In specific conditions, a standardised questionnaire can be used.[10] The prevalence of GJH ranges from 2% to 57%, depending on the definition and methods used.[11–14] A large, recent study of a general Danish population found that the self-reported prevalence of GJH and knee joint hypermobility was 13% and 23%, respectively.[15] GJH is more common in young persons and in females and the prevalence varies with ethnic background.[11] Interestingly, sex and age have also been mentioned as individual risk factors for ACL injury.[16–18]

Previous systematic reviews have assessed risk factors for ACL injury, where GJH has been included.[2 3 19 20] However, the previous systematic review including most articles specifically assessing GJH in relation to ACL injury only included two studies in this respect.[2 3 19 20] Moreover, no review has evaluated the postoperative effects of GJH in patients with an ACL injury.

The primary purpose of this study was to investigate the influence of GJH on ACL injury risk. The secondary purpose was to investigate the influence of GJH on postoperative outcome (including graft-failure risk, knee laxity, patient-reported outcome) and to compare the performance of different graft types in patients with GJH.

METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[21]

Study eligibility

All original clinical studies, including prospective and retrospective studies, written in English and assessing GJH in relation to ACL injury, were considered for inclusion. Different methods are used to define GJH and, for this reason, all publications assessing GJH and relating to the primary or secondary purposes were included. The definition of GJH used by the authors of each individual study was also used to define hypermobility in this systematic review, but the authors had to report the summarised total score of GJH in order to be included. Postoperative clinical outcomes after ACL reconstruction (including graft-failure risk, knee laxity and patient-reported outcome) were not specified in detail in order to review all the possible data available. Studies reporting knee laxity or knee hypermobility alone were excluded. Review articles, expert opinions, cadaver studies, animal studies and case reports were excluded.

Literature search

An expert medical librarian performed the literature search at the Biomedical Library in Gothenburg, Sweden, on 6 February 2018. An updated literature search was conducted on 11 January 2019 using a previously described method.[22] The MEDLINE/PubMed, EMBASE and the Cochrane Library databases were searched. Two general concepts were used to systematise the search. The first concept related to the ACL and ACL injury and the other concept pertained to hypermobility, accessible in the supplementary material (online supplementary table 1). The search was deliberately broad in an effort to include all relevant articles.

Study selection and data abstraction

Two authors (DS, LK) independently reviewed all the titles, abstracts and full-text articles. Data were abstracted by the medical librarian, in co-operation with the first author, and placed in an EndNote library (Clarivate Analytics, Philadelphia, USA). The publications were then extracted into the Rayyan web application for systematic reviews to facilitate the review process.[23] Publications were then read in full text for the assessment of eligibility. Consensus discussions were held in the event of disagreement.

Quality assessment

A critical appraisal of study quality was made using the Methodological Index for Non-Randomized Studies (MINORS).[24] Two authors (DS, AH) independently graded the quality of the included studies. Consensus discussions were held in the event of disagreement. Eight items relating to non-comparative studies and an additional 4, making 12 in total, were used for comparative studies. The MINORS assessment was originally used to assess longitudinal observational studies. However, the present systematic review includes several case–control studies, making items 6 and 7 irrelevant, and these items were therefore excluded for studies with a case–control study design. All items are graded on a scale ranging from 0 to 2. This gives a potential total of 16, 20 and 24 for non-comparative, case–control and comparative studies, respectively. For the interpretation of the results of non-comparative studies, the scores can be understood as follows: 0–4, very low quality; 5–8, low quality; 9–12, fair quality; and 13–16, high quality.[25] For comparative studies, the scores can be interpreted as 0–6, very low quality; 7–12, low quality; 13–18 fair quality and 19–24, high quality.[25] There is no consensus on predefined cut-offs for case–control studies using the MINORS score. The exact conditions for the distribution of the MINORS scores are specified in the online supplementary material.

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Table 1 Articles included in the final review

Authors	Year	Study group characteristics	Patients (male)	Mean age, years	Mean follow-up time, years	Percentage with non-contact injury	Patients with GJH, n (%)	Evaluation method
Akhtar *et al*[33]	2015	Primary ACL injury	139 (100)	28	NA	NI	52 (37)*	BS
		ACL revision	44 (29)	28	NA	NI	25 (57)*	
		Controls	70 (57)	33	NA	NA	11 (16)*	
Anderson *et al*[34]	1987	Unilateral ACL injury	17 (10)	23	NA	NI	NI	BS
		Bilateral ACL injury	14 (8)	26		NI	NI	
		Controls	17 (10)	27		NA	NI	
Astur *et al*[42]	2018	ACL injury	107 (82)	32.9 SD ±11.9	0.5	NI	17 (15.9)	BS
		ACL and meniscus injury	75 (60)		0.5		17 (36.2)	
		Meniscus injury	60 (54)		0.25		11 (25.6)	
Harner *et al*[29]	1994	Bilateral ACL injury	31 (22)	29	NA	100	NI	Modified and Horan method
		Controls	23 (13)	29	NA	NA	NI	
Kim *et al*[43]	2009	Single-bundle PT graft	32 (14)	29	2‡	NI	All patients	Beighton and Horan
		Double-bundle QT graft	29 (11)	25	2‡		All patients	
Kim *et al* (only subgroup with GJH presented)[44]	2008	Single-bundle PT graft	20 (7)	28	2‡	NI	All patients	Beighton and Horan
		Single-bundle HT graft	11 (3)	30	2‡		All patients	
Kim *et al*[30]	2009	Single-bundle PT graft or Single-bundle HT graft	272 (175)	29	2‡	NI	NA	Beighton and Horan
Kim *et al*[41]	2018	Non-hypermobile with PT graft	122 (97)§	29.9±10.6	2‡	NI	None	BS
		Non-hypermobile with HT graft	53 (42)§	31.1±10.6	2‡		None	
		Hypermobile with PT graft	41 (29)§	29.4±10.5	2‡		All	
		Hypermobile with HT graft	21 (15)§	28.5±8.0	2‡		All	
Kim *et al*[6]¶	2018	Hypermobile ACL reconstructed	27 (19)	29.5±10.2	8‡	NI	33	BS
		Non-hypermobile ACL reconstructed	81 (63)	28.7±10.4	8‡		67	
Kramer *et al*[31]	2007	ACL injury	33 (0)	21	NA	NI	NI	BS
		Controls	33 (0)	19	NA	NA	NI	
Larson *et al*[5]	2017	Hypermobile ACL reconstructed	41 (9)	23	5.7	NI	41	BS
		Non-hypermobile ACL reconstructed	142 (72)	28	6.2		0	
Motohashi[40]	2004	Unilateral ACL injury	161 (54)	19.8 (range 12–45)	3.3 (range 1.1–7.4)	NI	NA	Method according to Fukubayashi *et al*
		Bilateral ACL injury	10 (0)	18.2 (range 13–24)		90%	NA	
		Controls	95 (0)	15.6 SD ±1.4	NA	NA	NA	

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Table 1 Continued

Authors	Year	Study group characteristics	Patients (male)	Mean age, years	Mean follow-up time, years	Percentage with non-contact injury	Patients with GJH, n (%)	Evaluation method
Ramesh *et al*[35]	2005	ACL injury	169 (137)	Range 18–34	NA	75.4%	72 (42.6)	BS
		Controls	65 (NI)	NI, age and gender matched	NA	NA	14 (21.5)	
Scerpella *et al*[38]	2005	ACL injury	36 (14)	Males: 22.7 SD ±3.4 Females: 21.5 SD ±2.5	NA	100	NA	BS and a modified version
		Controls	181 (89)	Males: 20.1 SD ±1.4 Females: 19.5 SD ±1.2	NA	NA	NA	
Shimozaki *et al*[7]	2018	ACL injury	12 (0)	15.4 SD ±0.3	3	12	NA**	BS
		Controls	156 (0)	15.5 SD ±0.3	3	NA	NA**	
Stijak *et al*[37]	2014	ACL injury	29 (29)	26.6	NA	100	NI	BS
		Controls	29 (29)	27.1	NA	NA	NI	
Stijak *et al*[39]	2014	ACL injury	12 (0)	24.2	NA	100	NI	BS
		Controls	12 (0)	24.8	NA	NA	NI	
Uhorchak *et al*[4]	2003	ACL injury	24 (16)	18.4 (range 17–23)	4 (both groups)	100	NA	BS
		Uninjured controls	835 (723)			NA	NA	
Vacek *et al*[32]	2016	ACL injury	109 (36)	NI	NA	100	NI	BS
		Controls	227	NI	NA	NA	NI	
Vaishya and Hasija[36]	2013	ACL injury group	210 (135)	24.6±0.9	NA	NI	127 (60.5)	BS
		Controls	90 (55)	NI. Matched for age and gender	NA	NA	23 (25.5)	

*Using the >4 cut-off limit.
†With modifications.
‡The exact follow-up time was not disclosed.
§The presented patients were followed up for 2 years, fewer patients were examined at the 5-year follow-up.
¶Only the patients in the 8-year follow-up were included, as the same patients from the 2-year and 5-year follow-ups appear to be presented in the following article by Kim *et al*.
**Patients not dichotomised into hypermobile/non-hypermobile.
BS, Beighton Score; GJH, generalised joint hypermobility; HT, hamstring tendon; NA, not applicable; NI, no information; PT, patellar tendon; QT, quadriceps tendon.

Data synthesis

Data synthesis was performed by presenting tables and summarising the results using a qualitative approach. Quantitative summarisation, using a meta-analysis, was considered, but it was ultimately not implemented owing to the heterogeneity of the data found in the included studies. The results section begins by summarising the methods used to assess GJH in the included studies. The results include the following sections: *Risk of ACL injury (main heading), Unilateral ACL injury* and *Bilateral ACL injury*. The postoperative results were presented as follows: *Postoperative outcomes (main heading), Graft failure, Knee laxity, Patient-reported outcome, Osteoarthritis* and *Graft choice in patients with GJH*.

RESULTS

The initial search generated 2760 articles that were screened by title and abstract and 59 of them were read in full text. Three studies analysed the influence of GJH on knee injuries in general, without any specific analysis of ACL injury risk, and they were therefore excluded from further analysis.[26–28] Finally, 20 articles contained relevant information and were included in the qualitative synthesis (table 1 and online supplementary figure 1).

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Appraisal of evidence

The mean (range) MINORS score were 9 (9–9), 13 (7–18) and 17 (13–19) for non-comparative studies, case–control studies and comparative studies, respectively. The quality of the non-comparative studies was interpreted as fair. For comparative studies, the quality ranged between fair and high, with a majority of studies of fair quality.

The principal methodological strengths overall include the reporting of a clearly stated aim (item 1), the inclusion of consecutive patients (item 2), the use of appropriate endpoints (item 4), a follow-up of more than 2 years (item 6) and the use of adequate and contemporary control groups (items 9 and 10).

The main methodological weaknesses involved the uneven reporting of the timing of data collection; if prospectively or retrospectively collected (item 3). Demographic baseline equivalence (item 11) was unevenly reported (table 2). Although not involved as a specific item in the MINORS score, the use of multivariable analysis in the assessment of ACL injury risk factors is important. Only six studies used multivariable, or partly multivariable analyses, considering the influence of potential confounders on the investigated outcome.[4 7 29–32] Furthermore, only eight studies used prospective power analysis (table 2) and one study appears to have performed a post hoc power analysis.[32]

Classification of GJH

Six principal methods were used to determine GJH, although minor differences existed within these groups. The scale of hypermobility scores ranged from 4 to 9 points among the methods, a difference partly due to whether tests were performed unilaterally or bilaterally. There was considerable variation in terms of how the authors of the included studies reported the method of executing the hypermobility tests. Methods that were deemed, by the authors of this review, as not easily reproducible can be found in online supplementary table 2. The most frequently implemented method was the Beighton Score (BS), using the 9-point scale, which was used in 12 studies. In these 12 studies, 4 different cut-offs were used to determine the presence of hypermobility and four studies did not use a cut-off at all (online supplementary table 2).

GJH as a risk factor for ACL injury

Unilateral ACL injury

Eleven studies investigated the effect of GJH on the risk of primary ACL injury. Five of the studies presented the results for groups including individuals of both sexes,[4 33–36] all showing significant associations between GJH and ACL injury. Three of the studies with both sexes were either statistically adjusted for age and sex or the control subjects were matched to the cases during enrolment to the study.[33 34 36] One of the studies also analysed the relative risk of ACL injury in individuals with GJH, showing a relative risk of 2.8, 3.1 and 2.7, respectively, for all individuals, males only and females only.[4] In one of the five studies, including participants from both sexes, calculated the OR for the presence of hypermobility in patients with an ACL injury (OR 4.46, 95% CI 2.58 to 7.71).[36]

In four studies, males were analysed separately. In three of these studies, significant associations were found between ACL injury and GJH; all the studies were controlled for the age of the participants.[4 32 37] In the fourth study assessing males specifically, by Scerpella *et al*, two methods of evaluating GJH were used; one showed a significant association, while the other did not (details of the methods available in online supplementary table 2). However, in this study, there were age differences between the groups where the injured individuals were significantly older (table 3).[38]

Females were analysed separately in six studies. Two studies showed significant associations between GJH and ACL injury, one of which was controlled for age,[4] but in the other study it was unclear if the age of the participants was considered.[31] Two studies did not find a significant association[32 39] and another study found that a lower level of BS points was associated with an increased the risk of ACL injury.[7] However, when logistic regression analysis was used, GJH had no effect on ACL injury risk.[7] Finally, Scerpella *et al*[38] found that, using BS, there was no association with ACL injury. However, using the modified hypermobility score, with less strict limits for the degree of hyperextension, a significant association was observed (table 3).

Taken together, there was consistent evidence of association between GJH and the risk of unilateral ACL injury in males, while in females the results were conflicting.

Bilateral ACL injury

The occurrence of bilateral ACL injury was assessed in five studies. One study found that patients with bilateral ACL injuries had higher hypermobility scores when compared with patients with unilateral ACL injuries. This study consisted of only females, but the analysis was not adjusted for the difference in age.[40] The other four studies found no significant association between the incidence of bilateral/contralateral ACL injury and GJH (online supplementary table 3).[5 6 34 41]

Taken together, there was insufficient evidence to draw any conclusions regarding the influence of GJH on bilateral ACL injury risk.

Postoperative outcomes

Graft failure

In the current review, graft failure includes both failure due to rupture and due to a lax dysfunctional graft, owing to the underlying study material. Two studies reported only graft ruptures.[6 41] Two other studies used the definition graft failure, including failure both due to graft ruptures and due to increased graft laxity.[5 33] Thus, a total of four studies observed the occurrence of graft failure.

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Table 2 Quality appraisal of included studies according to minors assessment

Author	Journal	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Total	Available points
Akhtar *et al*[33]	*Knee*	2	2	1	2	0	NA	NA	2	2	0	0	1	12	20
Anderson *et al*[34]	*American Journal of Sports Medicine*	2	2	0	2	0	NA	NA	0	2	0	2	2	12	20
Astur *et al*[42]	*Acta Ortopédica Brasileira*	2	2	2	2	0	1	0	0	NA	NA	NA	NA	9	16
Harner *et al*[29]	*American Journal of Sports Medicine*	2	2	1	2	0	NA	NA	0	2	0	2	2	13	20
Kim *et al*[43]	*Journal of Bone and Joint Surgery, Am*	2	2	1	2	0	2	2	0	2	2	2	2	19	24
Kim *et al*[44]	*Journal of Bone and Joint Surgery, Am*	2	2	1	2	0	2	2	0	2	2	1	1	17	24
Kim *et al*[30]	*Clinical Orthopaedics and Related Research*	2	2	1	2	0	2	1	0	0	2	0	1	13	24
Kim *et al*[41]	*Knee Surgery Sports Traumatology Arthroscopy*	2	2	1	2	1	2	1	2	2	2	2	2	19	24
Kim *et al*[6]	*The Journal of Bone and Joint Surgery, Am*	2	2	1	2	0	2	1	2	2	2	2	2	18	24
Kramer *et al*[31]	*Journal of Sports Medicine and Physical Fitness*	2	0	1	2	2	NA	NA	0	2	0	1	1	11	20
Larson *et al*[5]	*Arthroscopy, The Journal of Arthroscopic and Related Research*	2	2	2	2	0	2	1	2	2	2	1	1	19	24
Motohashi[40]	*Journal of Orthopaedic Surgery*	1	2	0	2	0	2	0	0	2	2	1	1	13	24
Ramesh *et al*[35]	*Journal of Bone and Joint Surgery, Br*	1	2	1	2	0	NA	NA	0	0	0	0	1	7	20
Scerpella *et al*[38]	*Orthopaedics*	2	2	1	2	0	NA	NA	2	2	2	1	1	15	20
Shimozaki *et al*[7]	*Knee Surgery Sports Traumatology Arthroscopy*	2	2	2	2	0	NA	NA	2	2	2	2	2	18	20

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Table 2 Continued

Author	Journal	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Total	Available points
Stijak *et al*[37]	*Knee Surgery Sports Traumatology Arthroscopy*	2	2	0	2	0	NA	NA	2	2	2	2	2	16	20
Stijak *et al*[39]	*Knee Surgery Sports Traumatology Arthroscopy*	2	2	0	2	0	NA	NA	2	2	2	2	2	16	20
Uhorchak *et al*[4]	*American Journal of Sports Medicine*	2	2	2	2	0	2	1	0	2	2	2	2	19	24
Vacek *et al*[32]	*American Journal of Sports Medicine*	2	2	1	2	0	NA	NA	0	2	2	0	2	13	20
Vaishya and Hasija[36]	*Journal of Orthopaedic Surgery*	2	2	1	2	0	NA	NA	0	2	0	0	1	10	20

Items 6 and 7 were not applicable to case–control studies. Items 9 to 12 were not applicable to non-comparative studies.
NA, not applicable.

Two studies, using a quadruple hamstring-tendon (HT) autograft, a patellar-tendon (PT) autograft, a fascia-lata autograft or an allograft found significant associations with hypermobility.[5 33] In the other two studies, the graft failure rate was consistently higher in the group with GJH, irrespective of graft type, though the results were not statistically significant. These two studies confirmed baseline equivalence in terms of sex and age, whereas the studies with a significant association did not (online supplementary table 4).

Taken together, there was insufficient evidence to draw conclusions in terms of the influence of GJH on graft failure risk.

Knee laxity

The Lachman test and the pivot-shift test were evaluated in two studies. At the 5-year[41] and 8-year[6] follow-ups, significantly increased anteroposterior laxity was observed in patients with GJH, using the Lachman test, irrespective of whether PT or HT grafts were used (table 4). Increased rotatory knee laxity, measured with the pivot-shift test, was observed in patients with PT grafts at the 5-year and 8-year follow-ups in patients with GJH[6 41] but not in patients with HT autografts.[41] The same surgical technique was used in both studies, with transtibial drilling of the femoral socket.

Anterior tibial translation was assessed in three studies. The mean side-to-side difference using the KT-2000 was significantly larger in patients with GJH at both the 5-year and 8-year follow-ups in two studies.[6 41] One study, using the KT-1000, found no significant difference in anterior tibial translation between groups at a mean of approximately 6 years postoperatively.[5]

Taken together, there was limited evidence associating GJH with increased anteroposterior knee laxity 5 and 8 years postoperatively. There was conflicting evidence in terms of the magnitude of rotatory knee laxity at 5 years and very limited evidence indicating increased rotatory knee laxity at 8 years postoperatively.

Patient-reported outcome

The Lysholm and International Knee Documentation Committee (IKDC) scores were evaluated in four comparative studies, showing inferior outcomes in patients with GJH after 2,[30 41] 5,[41] 6[5] and 8[6] years postoperatively. Inferior outcomes for patients with GJH were also reported using the Cincinnati knee rating system 6 years postoperatively.[5] The level of physical activity, using the Tegner Activity Scale, was assessed in one non-comparative study of patients with GJH. The follow-up time was only 6 months and no correlation between hypermobility and the level of activity was found (table 5).[42]

Taken together, there was limited but consistent evidence of inferior patient-reported outcome in patients with GJH and previous ACL reconstruction.

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Table 3 Risk of unilateral ACL injury

Author	Patients, n injury/control (male)	Mean hypermobility score *		Proportion of hypermobile patients (%)		Risk of ACL injury, OR (95% CI)	P value	Consideration for differences in sex and age
		ACL injury	Controls	ACL injury	Controls	Hypermobile		
Akhtar *et al*[33]	209 (157)	2.9	1.4				0.002	S and A matched
Anderson *et al*[34]	34 (20)	2.8	1.2				0.033	S and A matched
Kramer *et al*[31]	66 (0)	5.2	3.8				0.01	Similar age
Ramesh *et al*[35]	234 (NI)			42.6	21.5		<0.05	No
Scerpella *et al*[38]								
BS, males	103 (103)	1.6±1.6	1.1±1.4				NS	A difference‡
BS, females	114 (0)	2.5±2.1	2.5±1.7				NS	A difference‡
AHS, males	103 (103)	4.2±2.1	2.5±2.1				<0.05	A difference‡
AHS, females	114 (0)	5.4±2.6	4.3±2.2				<0.05	A difference‡
Shimozaki *et al*[7]	168 (0)	1.8±1.3	2.7±2.2				0.04	A matched
Stijak *et al*[37]	29 (29)	4§	2.3§				0.005	A matched
Stijak *et al*[39]	12 (0)	4.7§	5§				NS	A matched
Uhorchak *et al*[4]								
All patients	859 (739)	3.5±2.7	1.8±2.1				<0.001	A matched
Males	739 (739)	2.9±2.7	1.6±2.0				0.003	
Females	120 (0)	4.6±2.5	3.2±2.4				0.014	
Vacek *et al*[32]	336¶							
Males						1.3 (1.1 to 1.7)	0.025	A matched
Females						NI	NS	A matched
Vaishya and Hasija[36]	300 (190)			60.5	25.5		<0.01	S and A matched

*The particular method for each study of evaluation of hypermobility can be seen in the online supplementary table 2.
†Unclear if there was a statistical difference in age between the groups.
‡Statistical significant difference in age between the groups.
§Measured graphically using ImageJ from Figure 4 in the respective articles.
¶No information regarding the sex of the controls.
A, age; AHS, Adjusted Hypermobility Score; BS, Beighton Score; NI, no information; NS, not significant; S, sex.

Osteoarthritis

The development of osteoarthritis (OA) was evaluated, using radiography, in two comparative studies. No significant differences in terms of the incidence of OA between patients with and without GJH were found after 2, 5 or 8 years (online supplementary table 5).[6 41]

Taken together, there was limited evidence showing no effect of GJH on the development of OA in the short to mid-term follow-up. No evidence exists evaluating the influence of GJH in the long-term perspective.

Graft choice in patients with GJH

Four studies evaluated the effect of graft choice in ACL-reconstructed patients with GJH, all from the same research group.

Knee laxity was assessed using four different methods. Using the Lachman test, a double-bundle (DB) quadriceps-tendon (QT) autograft produced less knee laxity compared with a PT autograft in one study (table 6).[43] The difference between PT and HT autografts was evaluated in two studies, showing less knee laxity for the PT in one study[44] at 2 years postoperatively, but, at 5 years postoperatively, there was no difference between the grafts.[41] Evaluating the pivot-shift test, one study reported less rotatory knee laxity using PT autografts compared with HT autografts at 2 years postoperatively.[44] Using the KT-2000, one study reported less intrumented anteroposterior knee laxity using DB-QT autografts compared with PT autografts.[43] Consistently less instrumented anteroposterior knee laxity was reported using the PT autograft in studies compared with the HT autograft,[43 44] although, in one of the studies, no statistical analysis was performed (table 6).[30]

There was no difference in the Lysholm score between DB-QT autografts and PT autografts.[43] However, higher Lysholm scores were reported for patients receiving the PT autograft, at 2 and 5 years, compared with patients receiving the HT autograft.[41 44] The two studies assessing the Hospital for Special Surgery and the IKDC (classified as A, B, C and D) scores were unable to find any differences with regard to graft type.[43 44] The IKDC score was, however, higher in patients receiving the PT autograft compared with patients with the HT autograft in one study, both 2 and 5 years postoperatively (table 6).[41]

There was limited, yet consistent evidence that PT autografts were superior to HT autografts in patients with GJH, with PT autografts showing a reduced risk of

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Table 4 Postoperative knee laxity in relation to the presence of GJH

Authors	Patients (male)	Test	Type of graft	Follow-up time, mean years (minimum)	Result sorted by presence of GJH: GJH	Non-GJH	P value
Kim *et al*[41]*	237 (183)	Lachman test (% with 0, 1, 2, 3)	PT	2 (2)	66, 27, 7, 0	85, 13, 2, 0	NS
				5	55, 33, 9, 3	81, 16, 3, 0	0.034
			HT	2 (2)	52, 33, 14, 0	83, 15, 2, 0	NS
				5	35, 47, 18, 0	81, 15, 5, 0	0.040
Kim *et al*[6]	108 (82)		PT	8	52, 33, 11, 4	80, 16, 4, 0	0.010
Kim *et al*[41]*	237 (183)	Pivot shift test (% with 0, 1, 2, 3)	PT	2 (2)	73, 20, 7, 0	87, 12, 2, 0	NS
				5	58, 30, 12, 0	86, 12, 2, 0	0.013
			HT	2 (2)	62, 29, 10, 0	89, 9, 2, 0	NS
				5	50, 39, 11, 0	85, 12, 2, 0	NS
Kim *et al*[6]	108 (82)		PT	8	56, 33, 11, 0	84, 14, 3, 0	0.007
Kim *et al*[41]	237 (183)	KT-2000, mean side-to-side difference	PT	2 (2)	2.7±1.4	2.1±1.0	NS
				5	3.2±1.8	2.2±1.2	0.001
			HT	2 (2)	3.5±1.4	2.3±0.9	<0.001
				5	4.4±1.8	2.3±0.9	<0.001
Kim *et al*[6]	108 (82)		PT	8	3.3±2.0	2.2±1.2	0.001
Larson *et al*[5]	183 (81)	KT-1000 ATT, mean MMT side-to-side difference (range)	Various‡	5.7/6.2 (2)	1.6 (3.5–8)	1.0 (5–5.5)	NS

*The p values of the Bonferroni correction analysis are presented for this publication.
†The exact follow-up time was not disclosed.
‡PT autograft (46), PT allograft (43), quadrupled HT autograft (85), tibialis anterior allograft (9).
ATT, anterior tibial translation; GJH, generalised joint hypermobility; HT, hamstring tendon; MMT, manual maximum test side-to-side difference with a force of 134 N; NS, not significant; PT, patellar tendon.

increased anteroposterior laxity and improved patient-reported outcome. Very limited evidence suggests that DB-QT autografts produce less knee laxity, but with no difference in patient-reported outcome, in comparison with PT autografts.

DISCUSSION

The most important finding in this review was that there is an increased risk of ACL injury in individuals with GJH. This is similar to a previous meta-analysis assessing the influence of GJH on knee injuries in general,[3] although, since the publication of that particular meta-analysis, additional studies have reported conflicting results.[26 45] The increased risk of primary ACL injury in individuals with GJH found in this review could not be established when analysing female individuals separately. In females, the results were more ambiguous. This is surprising, since female sex[16 46] and GJH are regarded as important risk factors for ACL injury and hypermobility is more common in females.[11] Because of this, we hypothesised that part of the reason for the increased risk of ACL injury, seen in females, could be attributed to hypermobility. However, in females, other possible risk factors, such as reduced neuromuscular control,[47–50] a narrow femoral notch[4 51] or hormonal factors, could be of greater significance.[52]

Postoperative outcomes

The results showing increased postoperative laxity, with no difference at 2 years but an increase in the group with GJH at 5 and 8 years, are interesting. It appears that the GJH has a greater impact on postoperative knee laxity after 2 years have passed, beyond the immediate rehabilitation phase. Possibly, repetitive strain on the ACL graft has a different effect on the collagen tissue in the graft in patients with GJH. GJH is related to alterations and impairment of the extracellular matrix, primarily collagen, elastin and fibrillin.[53] Interestingly, one study has demonstrated that biological failures were associated with GJH.[33] Biological failures were, by the authors, defined as faliures where no technical cause could be identified and where no traumatic injury had occurred. In 74% of the cases in the group with biological failures, the patients' grafts were intact but lax (non-functional according to the authors). Thus, increasing joint hypermobility may be associated with increased risk of biological failure, as defined above, with the difference becoming more obvious after the first 2 years after ACL reconstruction.

There was considerable agreement between studies showing that GJH has a negative influence on postoperative patient-reported outcome in patients with previous

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Table 5 Postoperative patient-reported outcome in relation to presence of generalised joint hypermobility

Authors	Patients (male)	Test	Type of graft	Follow-up time, mean years (minimum)	Result sorted by presence of GJH			P value
					Correlation with GJH (r)	GJH	Non-GJH	
Kim *et al*[41]*	237 (183)	Lysholm score	PT	2 (2)		88.9±4.9	91.1±4.2	NS
				5		86.6±6.1	91.4±3.6	<0.001
			HT	2 (2)		84.1±3.6	91.6±5.6	<0.001
				5		81.2±4.2	91.1±4.4	<0.001
Kim *et al*[6]	108 (82)		PT	8		85.9±6.2	90.5±3.6	<0.001
Larson *et al*[5]	183 (81)		Various‡	5.7/6.2		83.1	92.4	<0.001
Kim *et al*[30]	272 (175)		PT or HT	2 (2)	−0.116			0.013
Kim *et al*[41]*	237 (183)	IKDC score	PT	2 (2)		86.3±8.8	89.5±7.3	NS
				5		82.4±10.3	88.6±6.8	<0.001
			HT	2 (2)		81.1±3.5	90.1±4.5	<0.001
				5		79.2±4.7	89.2±4.5	<0.001
Kim *et al*[6]	108 (82)		PT	8		82.1±10.8	88.9±7.6	<0.001
Larson *et al*[5]	183 (81)		Various‡	5.7/6.2		78.3	87.4	0.003
Kim *et al*[30]	272 (175)		PT or HT	2 (2)	−0.193			0.001
Larson *et al*[5]	183 (81)	Cincinnati knee rating system	Various‡	5.7/6.2		82.3	91.7	0.001
Astur *et al*[42]	242 (196)	TAS, ACL	HT	0.5	−17.6%			NS
		TAS, ACLM	HT	0.5	−1.6%			NS

*The p values of the Bonferroni correction analysis are presented for this publication.
†The exact follow-up time was not disclosed.
‡PT autograft (46), PT allograft (43), quadrupled HT autograft (85), tibialis anterior allograft (9).
ACLM, combination of ACL and meniscus injury; GJH, generalised joint hypermobility; HT, hamstring tendon ; IKDC, International Knee Documentation Committee; NS, not significant; PT, patellar tendon; TAS, Tegner Activity Scale.

ACL reconstruction. Using patient-reported outcome measurements is important in order to quantify patient satisfaction. The subgroup of patients with GJH are already at a disadvantage preinjury, as is illustrated by a recent study of 1006 non-injured Danish adults demonstrating that patients with GJH or knee joint hypermobility had a twofold probability of reporting symptoms such as knee pain, inferior performance of usual activity and reduced health-related quality of life.[15] It is therefore especially important to optimise both surgical interventions and rehabilitation in this group of patients.

In this systematic review, OA was evaluated in two studies with ACL-injured patients showing no difference in OA at short-term to mid-term follow-ups with respect to the presence of GJH. Previous studies have assessed the association between OA and GJH in the general population with inconclusive results.[54–56] It has been suggested that cross-sectional investigations of both OA and GJH at older ages may be difficult to interpret, as hypermobility might be a marker of fitness, associated with less OA.[55] More studies, with longer follow-ups beyond 10 years, are needed to draw definite conclusions. In line with the argument above, it is recommended to assess GJH in these patients preoperatively, with a subsequent long-term follow-up to avoid misinterpretation of the results.

Should the presence of GJH influence graft choice?

The choice of graft might be particularly important in patients with GJH. This review reported that patients receiving HT autografts had increased instrumented anteroposterior laxity and inferior Lysholm and IKDC scores compared with patients receiving PT autografts. In the general population, previous systematic reviews have reported that PT autografts produce less anteroposterior laxity but with poorer results regarding postoperative complications, including anterior knee pain and kneeling pain, compared with HT autografts.[57–59] In terms of laxity, the same results were found in this review for the subset of patients with GJH. However, in contrast to the general ACL-reconstructed population,[60] patients with GJH receiving the PT autograft also benefited from superior subjective outcomes, according to the results of the present review. With the knowledge available at present, a PT autograft appears to be the better alternative compared with HT autografts in patients with GJH.

Table 6 Graft type in patients with generalised joint hypermobility

	Authors	Test	Follow-up time, mean years (minimum)	Result sorted by graft type			P value
				Double-bundle QT	PT autograft	HT autograft	
Knee laxity tests	Kim *et al*[43]	Lachman test (% with 0, 1, 2, 3)	2*	69, 31, 0, 0	38, 56, 6, 0		0.032
	Kim *et al*[44]		2 (2)*		40, 50, 10, 0	27, 46, 27, 0	0.024
	Kim *et al*[41]		2 (2)*		66, 27, 7, 0	52, 33, 14, 0	NS
			5*		55, 33, 9, 3	35, 47, 18, 0	NS
	Kim *et al*[43]	Pivot shift test (% with 0, 1, 2, 3)	2*	100, 0, 0, 0	91, 9, 0, 0		NS
	Kim *et al*[44]		2 (2)*		95, 5, 0, 0	82, 9, 9, 0	0.013
	Kim *et al*[41]		2 (2)*		73, 20, 7, 0	62, 29, 10, 0	NS
			5*		58, 30, 12, 0	50, 39, 11, 0	NS
	Kim *et al*[43]	KT-2000 mean SSD±SD	2*	2.03±1.11	3.37±1.8		0.02
	Kim *et al*[44]		2 (2)*		3.4±1.5	4.5±2.0	0.036
	Kim *et al*[41]		2 (2)*		2.7±1.4	3.5±1.4	0.043
			5*		3.2±1.8	4.4±1.8	0.034
	Kim *et al*[30]		2 (2)*		3.44±1.2	4.64±1.3	†
Patient-reported outcome	Kim *et al*[43]	Lysholm score mean±SD	2*	91.1±6.8	89.4±7.3		NS
	Kim *et al*[44]		2 (2)*		89±7	79±12	0.015
	Kim *et al*[41]		2 (2)*		88.8±4.9	84.1±3.6	0.004
			5*		86.6±6.1	81.2±4.2	0.005
	Kim *et al*[43]	HSS mean±SD	2*	92.1±6.1	90.8±6.7		NS
	Kim *et al*[44]	IKDC (% with A, B, C, D)	2 (2)*		15, 65, 10, 10	18, 46, 9, 27	†
	Kim *et al*[41]	IKDC subjective score	2 (2)*		86.3±8.8	81.1±3.5	0.013
			5*		82.4±10.3	79.2±4.7	0.005
Radiography		IKDC radiographic grade (% with A, B, C, D)	2 (2)*		93, 7, 0, 0	95, 5, 0, 0	NS
			5*		73, 24, 3, 0	67, 28, 6, 0	NS

All patients in the diagram have been determined as hypermobile by the corresponding authors.
*The exact follow-up time was not disclosed.
†No statistical analysis performed.
HSS, Hospital for Special Surgery Score; HT, hamstring tendon; IKDC, International Knee Documentation Committee; NS, not significant; PT, patellar tendon; QT, quadriceps tendon; SSD, side-to-side difference.

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Limitations and strengths

A few limitations relate to the overall quality of the studies included in this review. First, several methods were used to assess GJH using different cut-offs for the definition of hypermobility. Consequently, no general recommendations could be given in terms of aspects of treatment related to a specific degree of hypermobility; only general statements can be made.

Second, the lack of an a priori sample-size calculation of the involved studies raises concerns about a type-II error possibly being present in several of the studies in this review.

Third, the heterogeneity of the assessment methods for definition of GJH and the multiple confounding variables limits the ability to pool data for a quantitative analysis. This review focused in particular on the confounders sex and age, as female sex and younger age are risk factors for primary ACL injury and ACL revision[16 61] and GJH is more common at younger ages and in females.[11] However, there are many other important potential confounders, such as extrinsic and intrinsic risk factors and injury mechanisms, that were not acknowledged in the majority of the studies. One of the studies in this review conducted both multivariable adjusted and unadjusted analyses. When the authors adjusted for known confounders, this changed the regression coefficients by at least 10%, emphasising the importance of considering potential confounders in analyses of risk factors for ACL injury.[62]

Last, one first author (Dr Sung-Jae Kim) contributed with five of the studies (22%) eligible for this review. His research group provided the majority of or all the available evidence on the following aspects of this review: radiography, postoperative knee laxity, postoperative clinical outcome and the effect of graft type in patients with GJH. This limits the generalisability of our conclusions since joint hypermobility varies among ethnic groups[11] and there is an ongoing debate concerning the possible association between ACL injury and genetic variations/polymorphisms.[63]

Considering a lack of studies and the limitations listed above, there was insufficient evidence to draw any definitive conclusions at present for the following analyses; bilateral ACL injuries, graft failure and return to physical activity.

Particular strong points include the homogeneous primary end-point, ACL injury, in contrast to more vaguely defined knee injury assessed in a previous systematic review.[3] Moreover, this review includes primary ACL injury risk, graft-failure risk and postoperative outcome, giving a comprehensive overview of the scientific evidence relating to the association between the ACL-injured athlete and GJH.

Future perspectives

With respect to future studies, there are some aspects that could improve the quality and between-study comparisons in the future. Several methods with different cut-offs were used to establish the diagnosis of GJH. It is important to standardise the definition of GJH across all subspecialised fields in order to create comparable data. The recommendation is to use the definition of GJH presented in the consensus document by Malfait *et al* in 2017, presenting cut-offs as follows: ≥6 for pre-pubertal children and adolescents, ≥5 for pubertal males and females up to the age of 50, and ≥4 for those >50 years of age.[8] In the ACL-injured individual, the use of the 5-point questionnaire[8 10] or an *injury allowance point*[64] is recommended to mitigate the bias of the disturbed range of motion of the ACL-injured knee. Moreover, the use of grafts should be meticulously considered in patients with GJH. Future randomised controlled studies are needed to draw definite conclusions regarding the preferred use of grafts and the use of surgical techniques in these patients. On current evidence, we recommend the use of PT autografts.

CONCLUSIONS

In males, GJH was associated with an increased risk of unilateral ACL injury. Moreover, GJH was associated with increased postoperative knee laxity and inferior patient-reported outcome. Based on the available evidence, a PT autograft appears to be superior to a HT autograft in patients with GJH. However, the included studies were heterogeneous and there is a need for consensus in the assessment of GJH in sports medicine.

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