2018

5-Year survival of pediatric anterior cruciate ligament reconstruction with living donor hamstring tendon grafts

Emma L. Heath

Lucy J. Salmon

Robert Cooper

Evangelos Pappas

Justin P. Roe

See next page for additional authors

This article was originally published as:
Heath, E. L., Salmon, L. J., Cooper, R., Pappas, E., Roe, J. P., & Pinczewski, L. (2018). 5-Year survival of pediatric anterior cruciate ligament reconstruction with living donor hamstring tendon grafts. *American Journal of Sports Medicine, 47* (1), 41-51.

Original article available here:
https://journals.sagepub.com/doi/10.1177/0363546518804502

Authors
Emma L. Heath, Lucy J. Salmon, Robert Cooper, Evangelos Pappas, Justin P. Roe, and Leo Pinczewski

Heath, E.L., Salmon, L.J., Cooper, R., Pappas, E., Roe, J.P., and Pinczewski, L.A. (2018) 5-Year survival of pediatric anterior cruciate ligament reconstruction with living donor hamstring tendon grafts. *American Journal of Sports Medicine, 47*(1), 41-51. doi: 10.1177/0363546518804502

Medium Term Survival of Pediatric Anterior Cruciate Ligament Reconstruction with Living Donor Hamstring Tendon Graft

ABSTRACT

Background:

It is well accepted that there is a higher incidence of repeat Anterior Cruciate Ligament (ACL) injury in the pediatric population following ACL reconstruction (ACLR) with autograft tissue compared to adults. Hamstring autograft harvest may contribute to the risk for repeat ACL injury in this high functional demand group. A novel method is the use of a living donor hamstring tendon (LDHT) graft from a parent; however, there is currently limited research on the outcomes of this technique, particularly beyond the short-term.

Purpose/Hypothesis: To determine the medium-term survival of the ACL graft and the contralateral ACL (CACL) after primary ACLR with the use of a LDHT graft from a parent in those aged less than 18 years, and to identify factors associated with subsequent ACL injury. It is hypothesised that ACLR with the use of a LDHT provides acceptable midterm outcomes in pediatric patients.

Study Design: Case series; Level of evidence, 4.

Methods: Between 2005 and 2014, 247 (out of 265 eligible) consecutive patients in a prospective database having undergone primary ACLR with the use of a LDHT graft aged less than 18 years were included. Outcomes were assessed at a minimum of two years following surgery including collection of data on ACL re-injury, International Knee Documentation Committee (IKDC) questionnaire, current symptoms and factors associated with ACL re-injury risk were investigated.

Results: Patients were reviewed at a mean of 4.5 years (range 24-127 months (10.6years)) after ACLR with LDHT graft. Fifty one patients (20.6%) sustained an ACL graft rupture, 28 patients (11.3%) sustained a CACL rupture, and two patients sustained both an ACL graft and a CACL rupture (0.8%). Survival of the ACL graft was 89%, 82% and 76% at 1, 2 and 5 years, respectively. Survival of the CACL was 99%, 94% and 86% at 1, 2 and 5 years respectively. Survival of the ACL graft was favourable in those who were Tanner 1 and 2 stage of development at the time of surgery versus Tanner stage 3-5 at 5 years (87% versus 69%, hazard ratio 3.7, p=0.01).

Conclusion: After ACLR with a LDHT graft from a parent in those aged less than 18 years, second ACL injury (ACL graft or CACL injury) occurred to 1 in 3 patients. The 5-year survival of the ACL graft was 76% and the CACL 5-year survival was 86%. High IKDC scores and continued participation in sports were maintained over the medium-term. Importantly, there was a favorable survival of the ACL graft in Tanner 1-2 patients compared with Tanner 3-5 patients over 5 years. Tanner 1-2 patients also had a significantly lower incidence of second ACL injury over 5 years compared to Tanner 3-5, occurring in 1 in 5 patients. Thus, the LDHT graft from a parent is an appropriate graft for physically immature children.

Keywords: graft rupture; juvenile; adolescent; pediatric; contralateral ACL; survivorship; medium-term.

What is known about the subject: Pediatrics are more likely to have a second ACL injury after ACLR compared to adults, utilizing a hamstring tendon autograft. There is no literature on the incidence of re-injury in the pediatric population with the use of hamstring tendon graft from a parent.

What this study adds to existing knowledge: This study documents the medium-term incidence of ACL graft and CACL injury after ACLR in a large pediatric population with LDHT graft from a parent. Immature patients (Tanner 1 and 2) had better outcomes than those at Tanner stages 3-5.

INTRODUCTION

It has been advocated that a non-operative approach to ACL injury for pediatric patients is to avoid iatrogenic physeal disturbance. There is evidence that non-operative treatment can lead to intra-articular pathology and poorer functional outcomes, particularly return to sport, when compared to operative management [2, 19, 30]. However, high level evidence on the outcomes following both non-operative and operative management for the pediatric ACL is lacking.[31]. In recent years there has been increasing success and acceptance of operative management for ACL injury in the pediatric population as it may protect their menisci and articular cartilage from the classic pattern of injury seen in ACL deficiency, and can be performed without causing growth disturbance [6, 39].

The incidence of ACL injury in pediatric patients is increasing [35], likely due to increased sports participation, earlier sports specialization and the increased recognition of ACL injuries [24]. Furthermore, if the graft is injured requiring revision ACLR, there is an association with poorer outcomes compared to primary ACLR[3, 52]. A recent systematic review from Wiggins et al. [51] reported that athletes younger than 25 years of age, who return to sport, have a 23% incidence of second ACL injury over 4.25 years (pooled mean). Morgan et al. [32] examined patients 18 years or younger and reported a 31% incidence of second ACL injury over 15 years. These high rates of reinjury have led some surgeons to consider alternative graft options for pediatric patients.

The influence of graft selection on the high rates of ACL re-injury in the pediatric population is poorly understood and numerous alternative graft options have been investigated [25, 41]. Whilst autograft is a graft of choice for ACLR, the key drawback is donor site morbidity. Patella tendon harvest is associated with anterior knee pain, reduced knee extension strength [37] and an inability to kneel [18]. Similarly, hamstring tendon autograft harvest is associated with persisting hamstring strength deficit which may adversely affect walking and running [1, 34]. Furthermore, the hamstring tendons can be under-developed in the pediatric population, leading to a small graft diameter for reconstruction [8].

To eliminate donor site morbidity and muscular deficit secondary to graft harvest, allograft tendons can be used for ACLR. Allograft tissue was initially sterilised by irradiation, which alters the structural properties of the collagen. Some evidence suggests that cadaveric allografts are associated with higher rates of graft rupture compared to autografts in both pediatric and adult cohorts [14, 15, 26]. It is unclear if this is related to the graft processing techniques. The LDHT graft from a parent, which is not frozen, irradiated or chemically treated, provides an alternative graft choice that is similar to traditional allograft tissue, allows for flexibility in graft size and avoids donor site morbidity. The graft size is particularly pertinent as there is an association between small graft diameter and ACL reinjury [23]. Furthermore, it has been shown that soft tissue graft size is related to height and weight and that the ACL graft in the very young increases in length but does not increase in diameter[9, 10, 49]. Utilising a donor graft from a physically larger parent with mature hamstring tendons enables a predictable graft diameter, which may reduce failure rates. The use of allograft (including LDHT) also allows preservation of the hamstrings and use for potential revision cases in later life. Cadaveric allograft tissue has been utilised in young patients where some authors have highlighted potential for disease transmission and immune reactions with this graft choice [4, 25]. This can be more reliably screened in parental donors.

Conversely, there are unique considerations that may not favour the use of LDHT graft in the pediatric population. Firstly, LDHT harvest adds surgical morbidity to a secondary party, who are typically older and have a poorer anaesthetic risk profile. Goddard et al. [16] (2013) found that 28 out of the 29 parental donors for juvenile ACLR reported no complications and would undergo the same procedure again if required. Secondly, the cost associated with the procedure is greater than the traditional autograft method [16]. However, any significant reduction in ACLR reinjury rate would greatly improve the overall burden on the patient and health care system.

Only two previous studies have examined outcomes of ACLR after LDHT graft from a parent, but the cohorts in these studies were small and restricted to two year follow-up[16, 17]. As such, there is currently no evidence on the medium-term incidence of ACL re-injury with the use of LDHT graft. The aim of this study is to determine the medium-term survival of ACLR with LDHT graft, and incidence of CACL rupture, and to identify the factors that affect LDHT and CACL survival in a pediatric population post primary ACLR.

MATERIALS AND METHODS

Patient Selection

Patients included in the study were identified from a prospective database of knee surgery and had undergone a primary ACLR with LDHT graft at least 2 years earlier. The participant flow is detailed in Figure 1. Patient demographics were recorded in a prospective database which included information on the side of surgery, age, gender, Tanner stage, physeal status, graft donor source, graft size and meniscal or articular cartilage injury. Patients were sent an information sheet via post or email providing details of the project and inviting them to participate. Subjective outcome data were obtained by contacting all patients meeting the inclusion criteria via telephone or email. Those willing to participate in the study completed a telephone interview or written questionnaire, which was returned via post or email. A research physiotherapist or an honours medical student, both of whom had not been involved in the original surgery, performed the telephone questionnaires. Ethical approval was granted by a local independent human ethics committee.

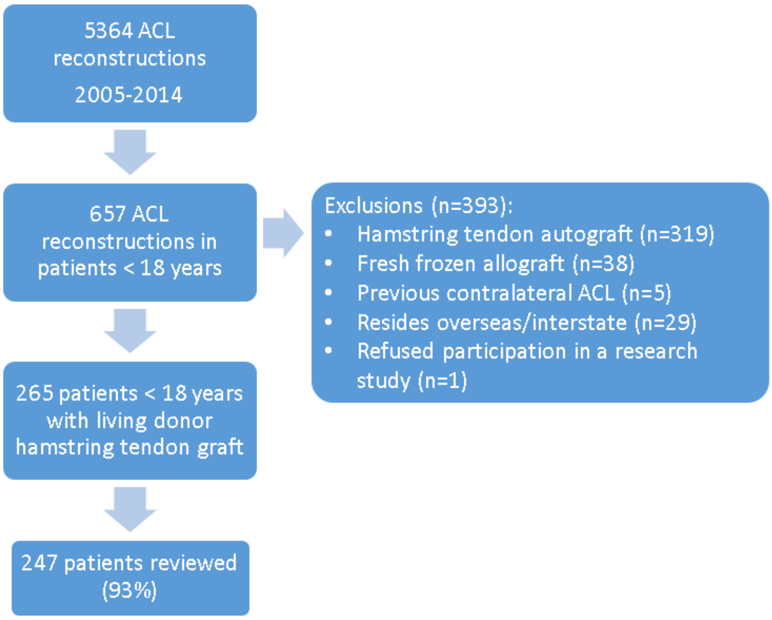

Figure 1: Participant Flow Chart

Subjective Evaluation

The questionnaire completed by patients included the full IKDC subjective knee evaluation form in addition to questions relating to family history of ACL rupture, subsequent injury and/or surgery to either knee, whether return to pre-injury level of sport was achieved and the current level of activity of the patient. Family history was considered to be positive if the patient reported that a first degree relative (parents or sibling/s) had sustained an ACL rupture at any time. A return to IKDC level 5 sports was defined as regular participation in very strenuous activities involving cutting or pivoting type manoeuvres, as in basketball or soccer.

All patients who reported further injury to either knee that had not previously been documented were invited to attend for further review. Graft rupture or CACL rupture was considered to have occurred only if one of the following was present: (1) the patient had further knee reconstructive surgery (graft rupture) or primary reconstruction (CACL) performed in our unit or by another orthopaedic surgeon; (2) had clinical examination and/or an MRI scan reviewed by our unit to confirm ACL deficiency, (3) had reported another injury characteristic of an ACL tear to either knee that had not been reviewed by us. For this last group, it was assumed an ACL graft rupture or CACL rupture for the purposes of the survival analysis as a worst-case scenario.

Operative Technique

ACLR was performed by one of two specialist knee surgeons ([redacted]) in a single unit between the years of 2005 and 2014. All patients and donors underwent preoperative blood testing including human immodeficiency virus (HIV), hepatitis B and C, human papillomavirus (HPV), cytomegalovirus (CMV) and syphilis testing. All patients underwent blood group testing including Rh status. Any Rh-negative female patients were given the appropriate dose of Rh immunoglobulin on induction of anaesthesia to prevent potential Rh sensitization.

Two fully staffed adjacent operating theaters were used and surgery was performed as day cases. In one theatre, the gracilis and semitendinosus tendons were harvested from the parent donor. A tendon harvester (Linvatec, Largo, Florida) was used to obtain a 22-cm tendon graft. Graft size was determined in regard to the ACL footprint, to ensure a graft of adequate diameter but not one that would cause impingement at the intercondylar notch. The tendons were wrapped securely in vancomycin soaked gauze and taken by the surgeon to the adjacent operating theater. In the second operating theater, the child was already under anesthesia and prepared and draped for surgery. Endoscopic transphyseal anatomic single-tunnel ACLR was performed. The operative technique has been previously described in detail [16, 17].

From the 247 patients reviewed, there was 1 one-stranded, 30 two-stranded, 18 three-stranded, 191 four-stranded, 6 five-stranded and 1 six-stranded LDHTs utilised. Femoral fixation included the round-headed Ti cannulated interference screw (n = 167) (RCI, Smith & Nephew, Andover, Massachusetts), Endobutton (n = 49) (Smith & Nephew), round-headed cannulated interference PEEK RCI screw (n = 29) (Signature Orthopaedics) and staple (n = 2). Tibial fixation included the Ti RCI screw (n = 150) (Smith & Nephew), staple (n = 56), PEEK RCI screw (n = 35) (Signature Orthopaedics), BioRCI screw (n=5) (Smith & Nephew), and post fixation (n = 1). Routine radiographs were obtained postoperatively. Patients were allowed to bear full weight, and commenced an early accelerated rehabilitation program [46]. At 9 to 12 months, an objective assessment of rehabilitation goals was performed to assess readiness to return to competitive sports, especially those that involved pivoting or side-stepping activity. Growth plate status was assessed from the immediate post operative x-ray. Patients with open physes at the time of surgery obtained an annual x-ray of the knee. A long leg alignment x-ray was also obtained at two years post operation, and then at 18 years of age. The long leg alignment x-ray was assessed by the treating surgeon for growth disturbance or leg length discrepancy.

Statistical Analysis

Statistical analysis was performed using SPSS software. Statistical significance was set *a priori* at $p \leq 0.05$. Groups were compared with t-tests for linear variables (mean IKDC scores) and chi square tests for categorical data (gender, age, family history, growth plate status and Tanner stage).

The probability of failure (ACL graft rupture and/or CACL injury as well as second ACL injury) was estimated as a function of time using the Kaplan-Meier (K-M) survival method. Survival tables at 1, 2 and 5 years were collated. Comparisons of survival curves were made with univariate Cox proportional hazards. Factors examined included age, sex, family history of ACL injury, growth plate status and Tanner score. Factors with $p \leq 0.10$ on univariate analysis were entered into a multivariate Cox regression analysis. Factors were then eliminated in a stepwise fashion, until only the independent significant factors remained. Multiple imputation was utilised for Tanner score to account for missing cases in the analysis by using the variables age and growth plate status. Imputated and non-imputated raw Tanner data provided the same statistical significance for the analysis. Non-imputated raw Tanner data are presented in the results section. Analysis was performed on the whole group, and repeated for each gender independently.

RESULTS

Between January 2005 and December 2014, 5,364 patients underwent primary ACLR. Of these, 265 patients were under 18 years of age, and in these cases a LDHT graft was harvested, thus forming the study cohort. There were 247 (93%) patients that completed the subjective questionnaire at a mean of 4.5 years after surgery (range 24 months – 127 months (10.6 years)). The participant flow is shown in Figure 1. Of the 247 patients, 166 (67%) had no subsequent ACL injuries and 81 (33%) sustained a further ACL injury. Of the patients who sustained further ACL injuries, 51 patients (20.6%) sustained an ACL graft rupture, 28 patients (11.3%) sustained a CACL injury and 2 patients (0.8%) sustained both an ACL graft and a CACL rupture.

Demographics (n=247)

There were 82 (33.2%) females and 165 (66.8%) males. The mean age at surgery was 14.6 years (range, 8-17.9). There were 128 left-sided and 119 right-sided reconstructions. Surgery was performed in the acute phase (within 3 weeks of injury) in 7 patients (2.7%), in the sub-acute phase (3-12 weeks) in 201 patients (81.4%) and in the chronic phase (> 12 weeks) in 39 patients (15.8%). Tanner stage of development was collected in a prospective manner at the time of surgery for 202 of the 247 patients. There were 23 Tanner 1, 24 Tanner 2, 29 Tanner 3, 79 Tanner 4 and 47 Tanner 5 patients (Figure 2). LDHT graft was obtained from the father in 201 patients (81.4%) and the mother in 42 patients (17%). One step-father, one uncle, one brother and one sister also donated a LDHT graft (.4%). The mean diameter of the LDHT graft was 7.5mm (range 4.5-8.5mm). 153 patients (62%) had an isolated ACLR, without meniscal surgery. At the time of surgery, 12 patients (4.8%) required partial medial meniscectomy and 46 patients (18.6%) required partial lateral meniscectomy. Meniscal sutures were used in 10 patients (4%) in the medial meniscus and 26 patients (10.5%) in the lateral meniscus. The primary ACL rupture was most commonly sustained in the sports of rugby and soccer, which accounted for 59% of injuries (see Figure 3).

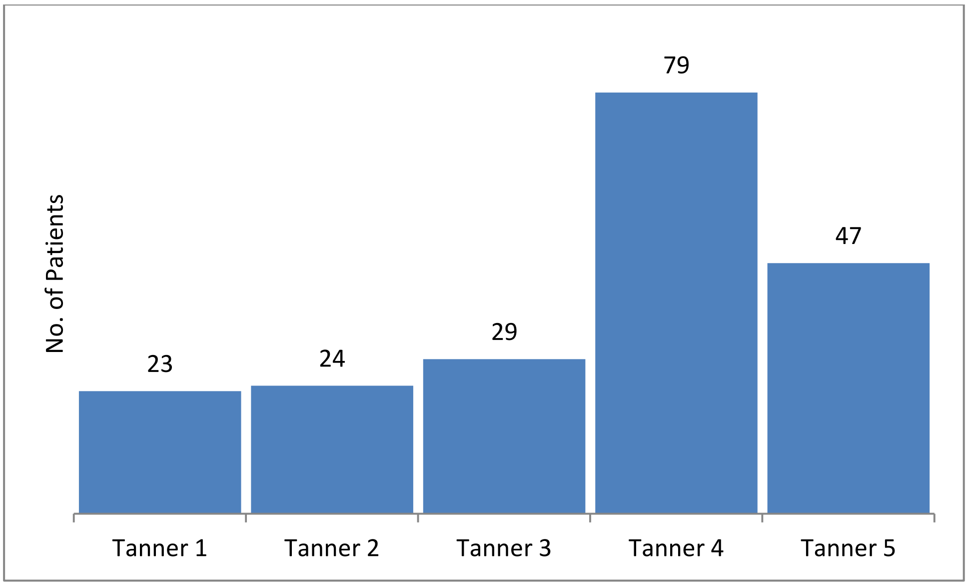

Figure 2: Tanner score at time of surgery in 202 of the 247 patients reviewed

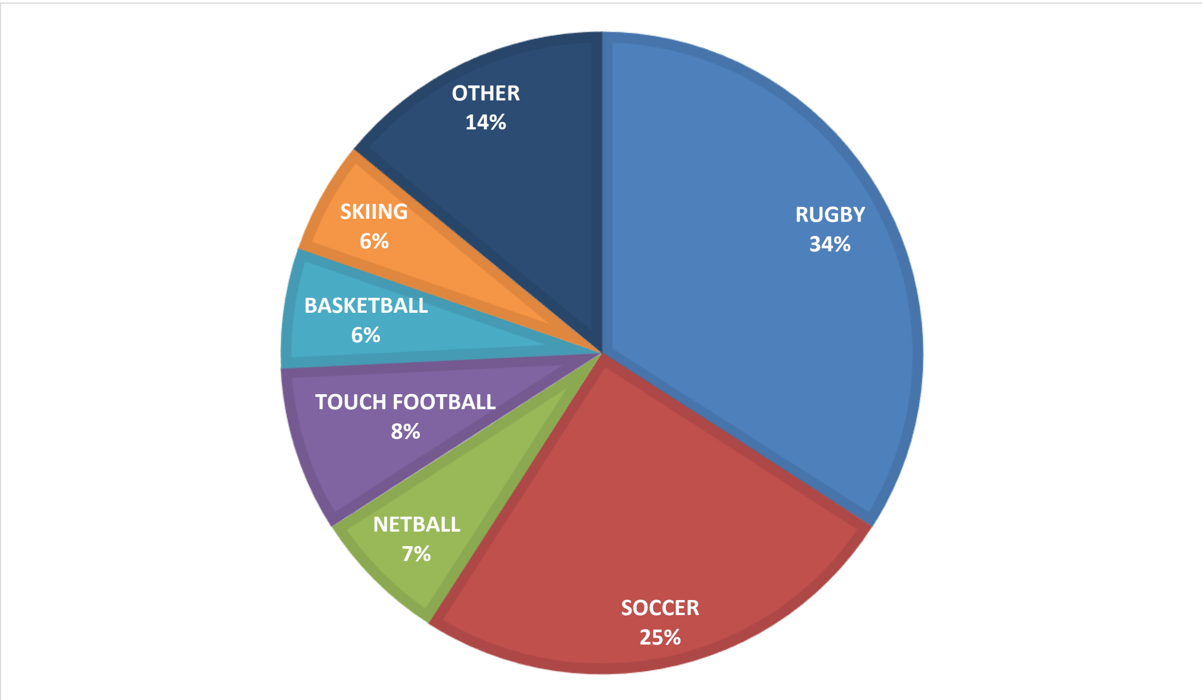

Figure 3: Sport of the primary ACL injury

<u>Subjective Outcomes</u>

Of the 247 patients with an intact ACL graft who completed the questionnaire, 146 (59.1%) reported returning to their pre-injury level of activity. Of the 101 who did not return to the pre-injury level of activity, 37 (15%) reported it was due to their operated knee and the remaining 64 patients (25.9%) cited other reasons. The mean overall IKDC score was 91.7 (range, 57-100). There was no significant difference between the mean subjective IKDC score between males and females (92.4 v 90.4, p=.25). There was no significant difference in the mean IKDC score between Tanner 1 and 2 patients versus Tanner 3-5 patients (92.3 v 91.9, p=.78), closed versus open growth plates (92.3 v 90.4, p=.17), or age < 14 or more versus ≥ 14 years (91.6 v 92.1, p=.72).

Incidence of Second ACL injury (ACL graft or CACL injury)

The incidence of ACLR graft injury was significantly higher than the incidence of CACL injury after reconstruction (p=0.006). Tanner 3-5 patients had a significantly higher incidence of a second ACL injury (38.1%) compared to Tanner 1 and 2 patients (21.3%) (p=0.03). There was a trend for patients aged 14 years or more to have a higher incidence of second ACL injury compared to those less than 14 years of age (36.1% versus 23.9% respectively; p=0.07). A positive family history was associated with a significantly higher incidence of second ACL injury than patients without a positive family history (34.2% vs. 21.3%, p=0.04). There was no significant difference in the incidence of second ACL injury between genders or growth plate status (p=0.59 and p=0.46 respectively). A summary of second ACL injury can be seen in Table 1.

TABLE 1 – Incidence of Second ACL Injury according to selected variables (ACL graft or CACL Injury)

Variable	No. of patients	ACL Graft or CACL Injury	% ACL Graft/CACL Injury	p value
Age at surgery, y				
< 14	67	16	23.9%	.07
≥ 14	180	65	36.1%	
Sex				
Male	165	56	33.9%	.59
Female	82	25	30.5%	
Family History of ACL injury				
Yes	76	26	34.2%	**.04**
No	141	30	21.3%	
Growth Plate Status				
Open	83	25	30.1%	.46
Closed	155	54	34.8%	
Tanner Stage				
1-2	47	10	21.3%	**.03**
3-5	155	59	38.1%	

Bolded p value indicates statistical significance (P ≤ .05). ACL, anterior cruciate ligament

ACL Graft Rupture

ACL graft rupture occurred in 53 (21.5%) patients (inclusive of the two patients that ruptured both their ACL graft and CACL) at a mean follow up of 4.5 years post ACLR. ACL graft injury occurred at a mean of 17.5 months (range 1.5 – 60) post primary ACLR. One male patient reported a knee injury associated with instability but was unable to attend for review; he was assumed to have sustained an ACL graft rupture. Patients who reported characteristics of rupture in the questionnaire and had not undergone further reconstructive surgery were examined in our unit to confirm ACL stability. All ACL ruptures occurred during sport and recreational activities and soccer was the sport that accounted for the most ACL graft ruptures which can be seen in Table 2.

TABLE 2 – Sports Associated with ACL Graft Rupture

Sport	No. of patients with ACL graft rupture (n=51)	Mean months to ACL failure
Soccer	18	21.6
Rugby or Australian Rules Football	15	22
Netball	3	11
Basketball	3	11.7
Playing at School	2	8
Fall/Jumping Fence	3	24
Dance	1	24
High Jump	1	10
Motorbike	1	16
Bicycle	1	13
Tee ball	1	4
Surfing	1	9
Skateboard	1	4

The ACL graft rupture was confirmed at the time of revision ACL surgery in 44 patients and by MRI and clinical examination in nine patients. Kaplan-Meier survival analysis for ACL graft rupture is shown in Figure 4 (A). ACL graft survival was 89%, 82% and 76% at 1, 2 and 5 years post reconstruction, respectively. The results of univariate analysis are shown in Table 3. Tanner score and age at surgery were entered into a multivariate Cox regression analysis and missing Tanner variables were accounted for with multiple imputation. On stepwise analysis, only Tanner Stage 3-5 remained significantly associated with poorer ACL graft survival with a hazard ratio of 3.7 (95% CI 1.34 – 10.39, p=0.01) (Multiple imputation data set hazard ratio of 3.0 (95% CI 2.06 – 4.54, p=<0.001). The Kaplan-Meier chart of ACL graft survival and Tanner Stage is shown in Figure 4 (B).

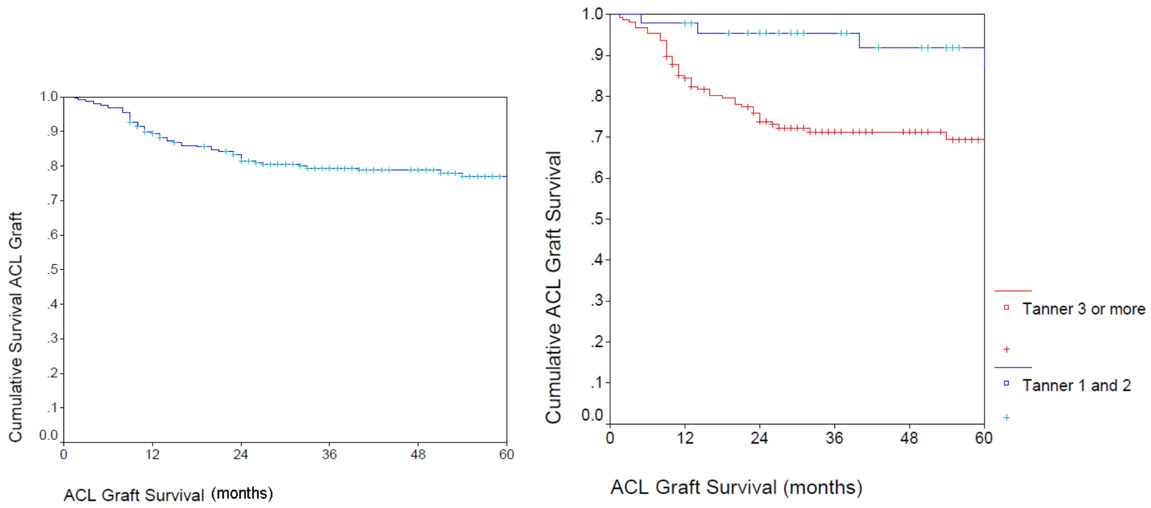

Figure 4: (A) Survivorship analysis of the ACL graft over time. (B) Survivorship analysis of the ACL graft in relation to Tanner Stage, p=.01.

TABLE 3 - Survival of the ACL Graft with Univariate Hazard Ratios for the Examined Patients (N = 247 Patients)

Variable	No. of patients	1 year survival (%)	2 year survival (%)	5 year survival (%)	Hazard Ratio (95% CI)	p value
All Patients	51/247 (20.6%)	89	82	76	-	-
Age at surgery, y						
< 14	67	96	90	84	1.9 (.94 – 3.94)	.07
≥ 14	180	87	78	73		
Sex						
M	165	88	80	73	1.4 (.78 – 2.65)	.24
F	82	91	84	82		
Family History of ACL injury						
Yes		93	87	81	1.5 (.72 – 3.10)	.29
No		94	90	87		
Growth Plate Status						
Open	155	88	84	79	1.2 (.68 – 2.19	
Closed	83	90	80	72	.51	
Tanner Stage						
1-2	47	98	95	87	3.7 (1.34 – 10.39)	**.01**
3-5	155	84	74	69		

Graft diameter						
≤7mm	69	93	85	83	1.5 (.78 – 2.83)	.23
>7mm	178	88	80	73		
Femoral Fixation						
Screw	194	89	80	74	.63 (.28 – 1.39)	.25
Endobutton	51	92	87	83		
Living Donor Hamstring Tendon						
Female Donor	43	79	74	74	1.3 (.69-2.6)	.39
Male Donor	205	96	91	83		

Contralateral ACL Injury

32 patients (12.9%) sustained a CACL rupture during the study period (inclusive of the two patients that ruptured their ACL graft and CACL). CACL injury was confirmed at the time of CACL reconstruction in 30 patients, and clinical examination and MRI in our unit in 2 patients. CACL injury occurred at a mean of 37 months (range, 6-84) post primary ACLR (Figure 5A). CACL survival was 99%, 94% and 86% at 1, 2 and 5 years respectively, post reconstruction. The results of univariate analysis are shown in Table 4. CACL survival was not significantly associated with age, growth plate status, Tanner stage, graft diameter or femoral fixation. Patients who had a positive family history of ACL injury displayed a non-significant trend to poorer CACL survival compared to those without a positive family history (p=.09) (Figure 5B).

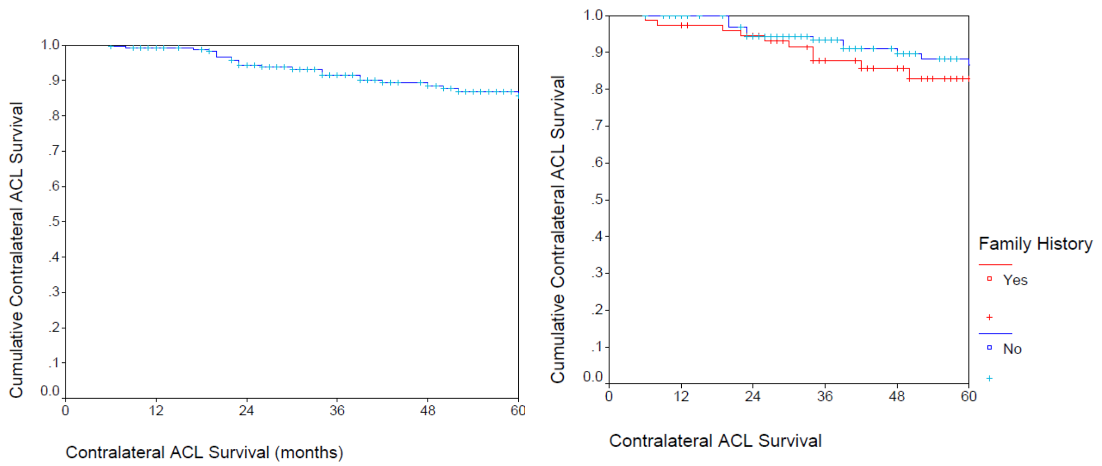

Figure 5: Survivorship analysis of the CACL over time. (B) Survivorship analysis of CACL in relation to family history p=.09

TABLE 4

Survival of the contralateral ACL with univariate hazard ratios for the examined variables (N = 247 Patients)

Variable	No. of patients	1 year survival (%)	2 year survival (%)	5 year survival (%)	Hazard Ratio (95% CI)	p value
All patients	28/247 (11.3%)	99	94	86	-	-
Age at surgery, y						
< 14	67	96	90	84	1.3 (.57 – 3.13)	.51
≥ 14	180	87	78	73		
Sex						
M	165	99	94	87	.89 (.42 – 1.87)	.76
F	82	97	95	82		
Family History of ACL injury						
Yes	76	96	95	83	1.9 (.91 – 3.99)	.09
No	141	87	94	87		
Growth Plate Status						
Open	83	98	95	90	1.1 (.51 – 2.39	.80
Closed	155	99	94	82		
Tanner Stage						
1-2	47	98	93	93	1.1 (.45 – 2.94)	.78
3-5	155	99	95	80		
Graft diameter						
≤7mm	69	99	92	86	1.0 (.47 – 2.17)	.99
>7mm	178	99	95	85		
Femoral Fixation						
Screw	194	99	96	87	1.3 (.54 – 3.27)	.53
Endobutton	51	96	89	86		

Gender Analysis

14 (17.1%) females and 39 males (23.6%) had an ACL graft rupture; however, there was no significant difference between males and females in survival of the ACL graft or CACL at 5 years post surgery (p=.24 and p=.76 respectively; see Table 3 and 4). Eleven females (13.4%) and 19 males (11.5%) had a CACL injury. In male patients, there was a significant association between ACL graft rupture with positive family history (p=0.01) and Tanner stage 3-5 (p=.01); there was also a non-significant trend toward graft rupture for patients aged less

than 14 years (p=.06). When both genders were pooled, there was no significant association between the variables Tanner stage, age or growth plates status for ACL graft rupture or CACL injury (see Table 5(a) & 5(b)).

TABLE 5a. Survival of the ACL graft with Univariate Hazard Ratios for the Examined Patients by Gender

	Male Gender			Female Gender		
	Odds Ratio	95% confidence interval	P	Odds Ratio	95% confidence interval	P
Positive Family History	2.95	1.3-6.9	**.01**	0.21	.0-11.1	.23
Tanner Stage 3 or more	3.53	1.2-9.9	**.02**	0.4	.0-68.7	.40
Age 14 or more years	.47	.2-1.9	.06	1.6	.36-7.2	.54
Open Growth Plates	.79	.4-1.5	.49	2.67	.35—20.5	.35

Table 5b. Survival of the CACL with Univariate Hazard Ratios for the Examined Patients by Gender

	Male Gender			Female Gender		
	Odds Ratio	95% confidence interval	P	Odds Ratio	95% confidence interval	P
Positive Family History	2.27	.87-5.89	.09	1.3	.42-4.56	.59
Tanner Stage 3 or more	1.12	.40-3.38	.77	1.04	.12-8.70	.97
Age 14 or more years	.71	.25-7.98	.50	1.15	.25-5.34	.86
Open Growth Plates	.79	.32-2.00	.63	0.75	.16-3.52	.71

Open Growth Plates

There were no growth disturbances noted on x-ray or long leg alignment films by the treating surgeons at a mean of 37 months (range 5-102 months) post surgery in the 83 skeletally immature patients in this series.

DISCUSSION

The 5 year survival rate of the ACL graft and CACL post primary ACLR with the use of a LDHT graft was 76% and 86% respectively. Survival of the ACL graft was favourable in those who were Tanner stage 1 and 2 at the time of surgery compared with Tanner 3-5 patients by a factor of 3.1. The use of a LDHT graft for ACLR offers acceptable 5 year survival for skeletally immature patients.

There is limited research on the use of a LDHT for ACLR other than those that have published from our group with a smaller sample size and shorter follow up than this current series.[16, 17] Furthermore, there are few studies with a patient cohort as young as our current series and, to our knowledge, no large scale studies available on the medium-term outcome of ACLR with LDHT graft for comparison. Direct comparison of the cohort of living donor patients with traditional autograft patients is difficult due to the differences in the patient population and length of follow up in the published literature. In a previous study of patients 18 years or less with an ACLR performed at the same institution, utilising autologous hamstring tendon, ACL graft survival was 88% at five years and 83% at 15 years [32]. However the population of this autograft series were older than our current series (mean age 16 years versus mean age of 14.6 years). If we compare the outcomes according to age, the five year ACL graft survival in those 14 or less was 84% with LDHT graft and 78% with hamstring tendon autograft. For those age >14 years ACL graft survival was 73% with the LDHT graft and 90% with the hamstring tendon autograft. Direct comparison of these two cohorts is limited by the consecutive nature of the series, particularly the effect of evolving rehabilitation protocols; however the two cohorts are from the same institution and involved the same surgeons. In the absence of a randomised series, our results suggest that the use of a LHDT graft may be considered reasonable in patients aged 14 year or less, but we cannot conclude that it reduces the incidence of graft rupture in adolescents when compared to a hamstring autograft.

<u>Lower second ACL injury in Tanner 1 and 2 pediatrics</u>

A lower rate of second ACL injury was noted in physically immature patients. Tanner 1 and 2 patients had a one in five incidence of second ACL injury compared with Tanner 3 – 5 patients who had just over a one in three incidence of second ACL injury (21.3% versus 38.1%) at a mean of 4.5 years post surgery. The reasons for this lower rate of re-injury in the immature patients may be multi-factorial. Socially, juveniles may be protected from second ACL injury compared with the adolescents due to increased parental supervision. Adolescents may have more freedom to play at a higher level, and participation in competitive sports is often more aggressive, which potentially increases their likelihood of re-injury. Furthermore, adolescents have a greater body mass as they grow, generating larger moments and greater inertia during sports. According to Barber-Westin et al. (2006)[5] these factors highlight the need for continued neuromuscular control training throughout adolescence. In prepubescent patients, neuromuscular control issues may be offset by their lower body mass and reduced movement velocities[5]. Distinctive cellular responses may also contribute to the lower rate of secondary ACL injury in younger patients; animal studies in minipigs have suggested that there may be a faster healing response and increased cellularity in the skeletally immature ACL, compared to adults [27, 28]. It has been demonstrated that fibroblasts from the ACLs of immature pigs and sheep grow faster and migrate faster than adolescent cells [28, 33]; however equivalent human studies are currently lacking [22]. It remains to be determined whether Tanner 1 and 2 patients will go on to have elevated risk once they move into adolescence. While the factors contributing to second injury are likely to be multifactorial and frequently theoretical, it can be concluded that the adolescents have the greatest risk of second ACL injury compared to both juveniles and adults.

Patients with open growth plates

There were no measurable growth disturbances or varus/valgus mal-alignment noted on radiographs in the 83 skeletally immature patients in this series with open growth plates at a mean of 37 months post surgery (range 5-102 months). This finding is consistent with the growing literature base confirming ACLR utilising a transphyseal approach as a safe procedure with no significant episodes of growth disturbance or varus/valgus alignment when carefully performed [11, 29, 40, 47]. The surgical technique used in this series respects the important principles that only soft tissue grafts should be used, that the tibial and femoral tunnel diameter must be less than five percent of the physeal cross-sectional area, and that graft fixation is placed away from the open physis to avoid growth disturbance[20, 38, 53].

Gender differences

In this series of patients, there was no significant difference between males and females in terms of survival of the ACL graft or CACL which is consistent with findings in the literature [42, 44, 48]. Webster et al. [50] examined a series of patients younger than 20 years post ACLR with autologous hamstring grafts, and the subgroup of patients less than 18 years had a second ACL injury rate of 44.3% in males and 31.8% in females (our LDHT graft series 33.9% and 30.5% respectively) at 5 years. When analysing males independently, there was a statistically significant association between ACL graft rupture and a positive family history, and Tanner stage 3-5 (compared with Tanner stage 1-2). These differences were not present in females. This could be due to differing cohort sizes in this series (165 males, 82 females). Further investigation into gender differences between sexes in the young is warranted.

Gender of the LDHT graft also demonstrated no significant difference in terms of survival of the ACL graft at 5 years (p=.39). However at 2 years, there was a 74% ACL graft survival in female living donor patients compared to 91% in male donors. The lack of statistical significance may be reflective of the smaller sample size of female versus male living donors (n=43 vs n=205). Further studies into the gender of living donors is warranted.

Graft Selection

Graft selection in ACLR is controversial. The ideal graft recreates the anatomical and biomechanical properties of the native ligament, provides rapid biological integration, reduces recovery time and donor site morbidity [12, 21]. Integration time of allograft versus autograft tissue is well documented in numerous animal studies involving goats, sheep, and rabbits for example [13, 36, 45]. However, it is difficult to extrapolate animal data to humans directly. Nevertheless, there is support deeming that cadaveric allograft tissue is slower to incorporate than autograft [7, 20]. This documented slower incorporation rate is unknown in the situation of the fresh graft harvest from a living donor. Further research into graft incorporation in the unique case of LDHT graft is required to know whether its incorporation rate is similar to an autograft.

Study Limitations

Due to the retrospective nature of the study design there was incomplete data that must be considered when interpreting results. Firstly, Tanner stage was collected in 202 of the 247 patients. The missing data is due to the overlap period before our institution collected Tanner stage as a variable. The multiple imputation statistical technique was also utilised to account for the missing Tanner stage data and the findings continued to highlight a significant ACL graft survival difference between Tanner 1-2 and Tanner stage 3 or more. Secondly, family history was successfully obtained in 217 of the 247 patients so there is missing data for this variable that also needs to be considered.

Furthermore, choice of soft tissue graft in ACLR remains debated [43], and in our cohort of patients a variety of femoral fixation devices were utilised including interference screw, endobutton and staple fixation. This variation in fixation highlights another weakness of the retrospective study design however caution was taken in all cases to ensure fixation was situated away from the physes in patients with open growth plates. Despite the studies weaknesses, the retrospective study design has allowed the collection of data on 247 patients that provides sufficient statistical power to investigate outcomes in a particular sub-cohort of patients with ACLR.

Conclusions

We present the largest pediatric series of all arthroscopic transphyseal single bundle ACLR with LDHT with follow up to a mean of 4.5 years post surgery. ACL injury after ACLR in juveniles and adolescents remains a challenging problem. ACLR using a LDHT graft is associated with good subjective outcomes. Tanner 1 and 2 stage patients have a lower incidence of repeat ACL injury compared to adolescents. Thus, using a LDHT graft for ACLR may be an appropriate graft to consider for the skeletally immature. However, for those adolescents who are skeletally mature, we are unable to advocate the use of LDHT for ACLR.

References

1. Abourezk MN, Ithurburn MP, McNally MP, et al. Hamstring Strength Asymmetry at 3 Years After Anterior Cruciate Ligament Reconstruction Alters Knee Mechanics During Gait and Jogging. *The American Journal of Sports Medicine.* 2017;45(1):97-105.

2. Aichroth PM, Patel DV, Zorrilla P. The natural history and treatment of rupture of the anterior cruciate ligament in children and adolescents: A prospective review. *J Bone Joint Surg Br.* 2002;84-B(1):38-41.

3. Anand BS, Feller JA, Richmond AK, Webster KE. Return-to-Sport Outcomes After Revision Anterior Cruciate Ligament Reconstruction Surgery. *The American Journal of Sports Medicine.* 2016;44(3):580-584.

4. Asselmeier MA, Caspari RB, Bottenfield S. A review of allograft processing and sterilization techniques and their role in transmission of the human immunodeficiency virus. *The American Journal of Sports Medicine.* 1993;21(2):170-175.

5. Barber-Westin SD, Noyes FR, Galloway M. jump-land characteristics and muscle strength development in young athletes a gender comparison of 1140 athletes 9 to 17 years of age. *The American Journal of Sports Medicine.* 2006;34(3):375-384.

6. Beynnon B, Johnson R, Abate J, Fleming B, Nichols C. Treatment of Anterior Cruciate Ligament Injuries, Part 2. *Am J Sports Med.* 2005;33(11):1751-1767.

7. Bhatia S, Bell R, Frank RM, et al. Bony incorporation of soft tissue anterior cruciate ligament grafts in an animal model: autograft versus allograft with low-dose gamma irradiation. *The American Journal of Sports Medicine.* 2012;40(8):1789-1798.

8. Bickel BA, Fowler TT, Mowbray JG, Adler B, Klingele K, Phillips G. Preoperative Magnetic Resonance Imaging Cross-Sectional Area for the Measurement of Hamstring Autograft Diameter for Reconstruction of the Adolescent Anterior Cruciate Ligament. *Arthroscopy: The Journal of Arthroscopic & Related Surgery.* 2008;24(12):1336-1341.

9. Boisvert C, Aubin M, DeAngelis N. Relationship between anthropometric measurements and hamstring autograft diameter in anterior cruciate ligament reconstruction. *Am J Orthop.* 2011;40:293-295.

10. Bollen S, Pease F, Ehrenraich A, Church S, Skinner J, Williams A. Changes in the four-strand hamstring graft in anterior cruciate ligament reconstruction in the skeletally-immature knee. *J Bone Joint Surg Br.* 2008;90(4):455-459.

11. Calvo R, Figueroa D, Gili F, et al. Transphyseal anterior cruciate ligament reconstruction in patients with open physes: 10-year follow-up study. *The American Journal of Sports Medicine.* 2015;43(2):289-294.

12. Cerulli G, Placella G, Sebastiani E, Tei MM, Speziali A, Manfreda F. ACL Reconstruction: Choosing the Graft. *Joints.* 2013;1(1):18.

13. Dustmann M, Schmidt T, Gangey I, Unterhauser F, Weiler A, Scheffler S. The extracellular remodeling of free-soft-tissue autografts and allografts for reconstruction of the anterior cruciate ligament: a comparison study in a sheep model. *Knee Surgery, Sports Traumatology, Arthroscopy.* 2008;16(4):360-369.

14. Ellis HB, Matheny LM, Briggs KK, Pennock AT, Steadman JR. Outcomes and revision rate after bone–patellar tendon–bone allograft versus autograft anterior cruciate ligament reconstruction in patients aged 18 years or younger with closed physes. *Arthroscopy: The Journal of Arthroscopic & Related Surgery.* 2012;28(12):1819-1825.

15. Engelman GH, Carry PM, Hitt KG, Polousky JD, Vidal AF. Comparison of Allograft Versus Autograft Anterior Cruciate Ligament Reconstruction Graft Survival in an Active Adolescent Cohort. *The American Journal of Sports Medicine.* 2014;42(10):2311-2318.

16. Goddard M, Bowman N, Salmon LJ, Waller A, Roe JP, Pinczewski LA. Endoscopic Anterior Cruciate Ligament Reconstruction in Children Using Living Donor Hamstring Tendon Allografts. *The American Journal of Sports Medicine.* 2013;41(3):567-574.

17. Hui C, Roe J, Ferguson D, Waller A, Salmon L, Pinczewski L. Outcome of Anatomic Transphyseal Anterior Cruciate Ligament Reconstruction in Tanner Stage 1 and 2 Patients With Open Physes. *Am J Sports Med.* 2012;40(5):1093-1098.

18. Kartus J, Movin T, Karlsson J. Donor-site morbidity and anterior knee problems after anterior cruciate ligament reconstruction using autografts. *Arthroscopy.* 2001;17(9):971-980.

19. Lawrence JTR, Argawal N, Ganley TJ. Degeneration of the Knee Joint in Skeletally Immature Patients With a Diagnosis of an Anterior Cruciate Ligament Tear:Is There Harm in Delay of Treatment? *The American Journal of Sports Medicine.* 2011;39(12):2582-2587.

20. Li H, Tao H, Cho S, Chen S, Yao Z, Chen S. Difference in Graft Maturity of the Reconstructed Anterior Cruciate Ligament 2 Years Postoperatively A Comparison Between Autografts and Allografts in Young Men Using Clinical and 3.0-T Magnetic Resonance Imaging Evaluation. *The American Journal of Sports Medicine.* 2012;40(7):1519-1526.

21. Macaulay AA, Perfetti DC, Levine WN. Anterior cruciate ligament graft choices. *Sports Health: A Multidisciplinary Approach.* 2012;4(1):63-68.

22. Magarian EM, Vavken P, Murray MM. Human anterior cruciate ligament fibroblasts from immature patients have a stronger in vitro response to platelet concentrates than those from mature individuals. *The Knee.* 2011;18(4):247-251.

23. Magnussen R, Lawrence J, West R, Toth A, Taylor D, WE. G. Graft Size and Patient Age Are Predictors of Early Revision After Anterior Cruciate Ligament Reconstruction With Hamstring Autograft. *Arthroscopy.* 2012;28:526-531.

24. Mall NA, Chalmers PN, Moric M, et al. Incidence and trends of anterior cruciate ligament reconstruction in the United States. *The American Journal of Sports Medicine.* 2014;42(10):2363-2370.

25. Mariscalco MW, Magnussen RA, Mehta D, Hewett TE, Flanigan DC, Kaeding CC. Autograft Versus Nonirradiated Allograft Tissue for Anterior Cruciate Ligament Reconstruction A Systematic Review. *The American Journal of Sports Medicine.* 2014;42(2):492-499.

26. Mascarenhas R, Erickson BJ, Sayegh ET, et al. Is there a higher failure rate of allografts compared with autografts in anterior cruciate ligament reconstruction: a systematic review of overlapping meta-analyses. *Arthroscopy: The Journal of Arthroscopic & Related Surgery.* 2015;31(2):364-372.

27. Mastrangelo A, Haus B, Vavken P, Palmer M, Murray M. Immature animals have denser anterior cruciate ligament wound site cell repopulation than adolescent or adult animals. *J Orthop Res.* 2009.

28. Mastrangelo AN, Magarian EM, Palmer MP, Vavken P, Murray MM. The effect of skeletal maturity on the regenerative function of intrinsic ACL cells. *Journal of Orthopaedic Research.* 2010;28(5):644-651.

29. McConkey MO, Bonasia DE, Amendola A. Pediatric anterior cruciate ligament reconstruction. *Current Reviews in Musculoskeletal Medicine.* 2011;4(2):37.

30. Mizuta H, Kubota K, Shiraishi M, Otsuka Y, Nagamoto N, Takagi K. The conservative treatment of complete tears of the anterior cruciate ligament in skeletally immature patients. *J Bone Joint Surg Br.* 1995;77-B(6):890-894.

31. Moksnes H EL, Risberg MA. The Current Evidence for Treatment of ACL Injuries in Children Is Low: A Systematic Review. *J Bone Joint Surg Am.* 2012;94(12):1112-1119.

32. Morgan MD, Salmon LJ, Waller A, Roe JP, Pinczewski LA. Fifteen-Year Survival of Endoscopic Anterior Cruciate Ligament Reconstruction in Patients Aged 18 Years and Younger. *The American Journal of Sports Medicine.* 2016;44(2):384-392.

33. Murray MM, Magarian EM, Harrison SL, Mastrangelo AN, Zurakowski D, Fleming BC. The effect of skeletal maturity on functional healing of the anterior cruciate ligament. *The Journal of Bone & Joint Surgery.* 2010;92(11):2039-2049.

34. Nakamura N, Horibe S, Sasaki S, et al. Evaluation of active knee flexion and hamstring strength after anterior cruciate ligament reconstruction using hamstring tendons. *Arthroscopy: The Journal of Arthroscopic & Related Surgery.* 2002;18(6):598-602.

35. Parkkari J, Pasanen K, Mattila VM, Kannus P, Rimpelä A. The risk for a cruciate ligament injury of the knee in adolescents and young adults: a population-based cohort study of 46 500 people with a 9 year follow-up. *British Journal of Sports Medicine.* 2008;42(6):422-426.

36. Pauzenberger L, Syré S, Schurz M. "Ligamentization" in hamstring tendon grafts after anterior cruciate ligament reconstruction: a systematic review of the literature and a glimpse into the future. *Arthroscopy: The Journal of Arthroscopic & Related Surgery.* 2013;29(10):1712-1721.

37. Petersen W, Taheri P, Forkel P, Zantop T. Return to play following ACL reconstruction: a systematic review about strength deficits. *Archives of Orthopaedic and Trauma Surgery.* 2014;134(10):1417-1428.

38. Pierce TP, Issa K, Festa A, Scillia AJ, McInerney VK. Pediatric anterior cruciate ligament reconstruction: a systematic review of transphyseal versus physeal-sparing techniques. *The American Journal of Sports Medicine.* 2017;45(2):488-494.

39. Ramski D, Kanji W, Franklin C, Baldwin K, Ganlet T. Anterior Cruciate Ligament Tears in Children and Adolescents A Meta-analysis of Non-operative Versus Operative Treatment. . *Am J Sports Med.* 2014;42(11):2769-2776.

40. Redler LH, Brafman RT, Trentacosta N, Ahmad CS. Anterior cruciate ligament reconstruction in skeletally immature patients with transphyseal tunnels. *Arthroscopy: The Journal of Arthroscopic & Related Surgery.* 2012;28(11):1710-1717.

41. Reinhardt KR, Hetsroni I, Marx RG. Graft selection for anterior cruciate ligament reconstruction: a level I systematic review comparing failure rates and functional outcomes. *Orthopedic Clinics of North America.* 2010;41(2):249-262.

42. Ryan J, Magnussen RA, Cox CL, Hurbanek JG, Flanigan DC, Kaeding CC. ACL reconstruction: do outcomes differ by sex?: a systematic review. *JBJS.* 2014;96(6):507-512.

43. Saccomanno MF, Shin JJ, Mascarenhas R, et al. Clinical and functional outcomes after anterior cruciate ligament reconstruction using cortical button fixation versus transfemoral suspensory fixation: a systematic review of randomized controlled trials. *Arthroscopy: The Journal of Arthroscopic & Related Surgery.* 2014;30(11):1491-1498.

44. Salmon LJ, Refshauge KM, Russell VJ, Roe JP, Linklater J, Pinczewski LA. Gender differences in outcome after anterior cruciate ligament reconstruction with hamstring tendon autograft. *Am J Sports Med.* 2006;34(4):621-629.

45. Scheffler S, Dustmann M, Gangey I, Schulz T, Unterhauser F, Weiler A. The biological healing and restoration of the mechanical properties of free soft-tissue allografts lag behind autologous ACL reconstruction in the sheep model. *Trans Orthop Res.* 2005;30.

46. Shelbourne KD, Nitz P. Accelerated rehabilitation after anterior cruciate ligament reconstruction. *Am J Sports Med.* 1990;18(3):292-299.

47. Streich NA, Barié A, Gotterbarm T, Keil M, Schmitt H. Transphyseal reconstruction of the anterior cruciate ligament in prepubescent athletes. *Knee Surgery, Sports Traumatology, Arthroscopy.* 2010;18(11):1481-1486.

48. Tan SHS, Lau BPH, Khin LW, Lingaraj K. The Importance of Patient Sex in the Outcomes of Anterior Cruciate Ligament Reconstructions: A Systematic Review and Meta-analysis. *Am J Sports Med.* 2015;44(1):242-254.

49. Treme G, Diduch D, Billante M, Miller M, Hart J. Hamstring Graft Size Prediction. *Am J Sports Med.* 2008;36:2204-2209.

50. Webster K, Feller J. Exploring the High Reinjury Rate in Younger Patients Undergoing Anterior Cruciate Ligament Reconstruction. *American Journal of Sports Medicine.* 2016.

51. Wiggins AJ, Grandhi RK, Schneider DK, Stanfield D, Webster KE, Myer GD. Risk of Secondary Injury in Younger Athletes After Anterior Cruciate Ligament Reconstruction A Systematic Review and Meta-analysis. *Am J Sports Med.* 2016;44(7):1861-1876.

52. Wright R, Spindler K, Huston L, et al. Revision ACL reconstruction outcomes: MOON cohort. *The Journal of Knee Surgery.* 2011;24(04):289-294.

53. Yoo WJ, Kocher MS, Micheli LJ. Growth plate disturbance after transphyseal reconstruction of the anterior cruciate ligament in skeletally immature adolescent patients: an MR imaging study. *Journal of Pediatric Orthopaedics.* 2011;31(6):691-696.