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

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1 **Medium Term Survival of Pediatric Anterior Cruciate Ligament Reconstruction with Living**

2 **Donor Hamstring Tendon Graft**

3 **ABSTRACT**

4 **Background:**

5 It is well accepted that there is a higher incidence of repeat Anterior Cruciate Ligament (ACL) injury in the

6 pediatric population following ACL reconstruction (ACLR) with autograft tissue compared to adults. Hamstring

7 autograft harvest may contribute to the risk for repeat ACL injury in this high functional demand group. A

8 novel method is the use of a living donor hamstring tendon (LDHT) graft from a parent; however, there is

9 currently limited research on the outcomes of this technique, particularly beyond the short-term.

10 **Purpose/Hypothesis:** To determine the medium-term survival of the ACL graft and the contralateral ACL

11 (CACL) after primary ACLR with the use of a LDHT graft from a parent in those aged less than 18 years, and to

12 identify factors associated with subsequent ACL injury. It is hypothesised that ACLR with the use of a LDHT

13 provides acceptable midterm outcomes in pediatric patients.

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

15 **Methods:** Between 2005 and 2014, 247 (out of 265 eligible) consecutive patients in a prospective database

16 having undergone primary ACLR with the use of a LDHT graft aged less than 18 years were included. Outcomes

17 were assessed at a minimum of two years following surgery including collection of data on ACL re-injury,

18 International Knee Documentation Committee (IKDC) questionnaire, current symptoms and factors associated

19 with ACL re-injury risk were investigated.

20 **Results:** Patients were reviewed at a mean of 4.5 years (range 24-127 months (10.6years)) after ACLR with

21 LDHT graft. Fifty one patients (20.6%) sustained an ACL graft rupture, 28 patients (11.3%) sustained a CACL

22 rupture, and two patients sustained both an ACL graft and a CACL rupture (0.8%). Survival of the ACL graft was

23 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

24 years respectively. Survival of the ACL graft was favourable in those who were Tanner 1 and 2 stage of

25 development at the time of surgery versus Tanner stage 3-5 at 5 years (87% versus 69%, hazard ratio 3.7,

26 p=0.01).

27 **Conclusion:** After ACLR with a LDHT graft from a parent in those aged less than 18 years, second ACL injury

28 (ACL graft or CACL injury) occurred to 1 in 3 patients. The 5-year survival of the ACL graft was 76% and the

29 CACL 5-year survival was 86%. High IKDC scores and continued participation in sports were maintained over

30 the medium-term. Importantly, there was a favorable survival of the ACL graft in Tanner 1-2 patients

31 compared with Tanner 3-5 patients over 5 years. Tanner 1-2 patients also had a significantly lower incidence of

32 second ACL injury over 5 years compared to Tanner 3-5, occurring in 1 in 5 patients. Thus, the LDHT graft from

33 a parent is an appropriate graft for physically immature children.

35   **What is known about the subject:** Pediatrics are more likely to have a second ACL injury after ACLR compared

36   to adults, utilizing a hamstring tendon autograft. There is no literature on the incidence of re-injury in the

37   pediatric population with the use of hamstring tendon graft from a parent.

38   **What this study adds to existing knowledge:** This study documents the medium-term incidence of ACL graft

39   and CACL injury after ACLR in a large pediatric population with LDHT graft from a parent. Immature patients

40   (Tanner 1 and 2) had better outcomes than those at Tanner stages 3-5.

41   **INTRODUCTION**

42   It has been advocated that a non-operative approach to ACL injury for pediatric patients is to avoid iatrogenic

43   physeal disturbance. There is evidence that non-operative treatment can lead to intra-articular pathology and

44   poorer functional outcomes, particularly return to sport, when compared to operative management [2, 19, 30].

45   However, high level evidence on the outcomes following both non-operative and operative management for

46   the pediatric ACL is lacking.[31]. In recent years there has been increasing success and acceptance of operative

47   management for ACL injury in the pediatric population as it may protect their menisci and articular cartilage

48   from the classic pattern of injury seen in ACL deficiency, and can be performed without causing growth

49   disturbance [6, 39].

50   The incidence of ACL injury in pediatric patients is increasing [35], likely due to increased sports participation,

51   earlier sports specialization and the increased recognition of ACL injuries [24]. Furthermore, if the graft is injured

52   requiring revision ACLR, there is an association with poorer outcomes compared to primary ACLR[3, 52]. A recent

53   systematic review from Wiggins et al. [51] reported that athletes younger than 25 years of age, who return to

54   sport, have a 23% incidence of second ACL injury over 4.25 years (pooled mean). Morgan et al. [32] examined

55   patients 18 years or younger and reported a 31% incidence of second ACL injury over 15 years. These high

56   rates of reinjury have led some surgeons to consider alternative graft options for pediatric patients.

57   The influence of graft selection on the high rates of ACL re-injury in the pediatric population is poorly

58   understood and numerous alternative graft options have been investigated [25, 41]. Whilst autograft is a graft of

59   choice for ACLR, the key drawback is donor site morbidity. Patella tendon harvest is associated with anterior

60   knee pain, reduced knee extension strength [37] and an inability to kneel [18]. Similarly, hamstring tendon

61   autograft harvest is associated with persisting hamstring strength deficit which may adversely affect walking

62   and running [1, 34]. Furthermore, the hamstring tendons can be under-developed in the pediatric population,

63   leading to a small graft diameter for reconstruction [8].

64   To eliminate donor site morbidity and muscular deficit secondary to graft harvest, allograft tendons can be

65   used for ACLR. Allograft tissue was initially sterilised by irradiation, which alters the structural properties of the

66   collagen. Some evidence suggests that cadaveric allografts are associated with higher rates of graft rupture

67   compared to autografts in both pediatric and adult cohorts [14, 15, 26]. It is unclear if this is related to the graft

68 processing techniques. The LDHT graft from a parent, which is not frozen, irradiated or chemically treated,

69 provides an alternative graft choice that is similar to traditional allograft tissue, allows for flexibility in graft size

70 and avoids donor site morbidity. The graft size is particularly pertinent as there is an association between small

71 graft diameter and ACL reinjury [23]. Furthermore, it has been shown that soft tissue graft size is related to

72 height and weight and that the ACL graft in the very young increases in length but does not increase in

73 diameter[9, 10, 49]. Utilising a donor graft from a physically larger parent with mature hamstring tendons enables

74 a predictable graft diameter, which may reduce failure rates. The use of allograft (including LDHT) also allows

75 preservation of the hamstrings and use for potential revision cases in later life. Cadaveric allograft tissue has

76 been utilised in young patients where some authors have highlighted potential for disease transmission and

77 immune reactions with this graft choice [4, 25]. This can be more reliably screened in parental donors.
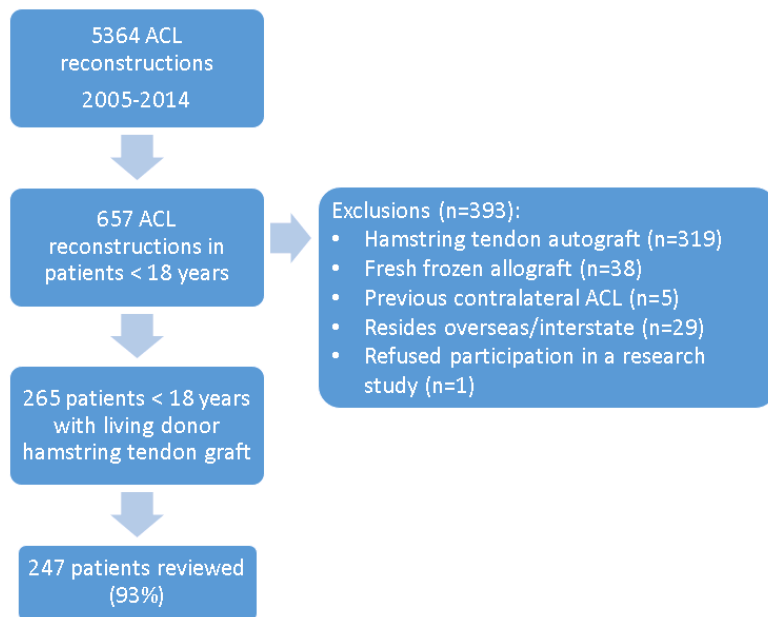
78 Conversely, there are unique considerations that may not favour the use of LDHT graft in the pediatric

79 population. Firstly, LDHT harvest adds surgical morbidity to a secondary party, who are typically older and have

80 a poorer anaesthetic risk profile. Goddard et al. [16] (2013) found that 28 out of the 29 parental donors for

81 juvenile ACLR reported no complications and would undergo the same procedure again if required. Secondly,

82 the cost associated with the procedure is greater than the traditional autograft method [16]. However, any

83 significant reduction in ACLR reinjury rate would greatly improve the overall burden on the patient and health

84 care system.

85 Only two previous studies have examined outcomes of ACLR after LDHT graft from a parent, but the cohorts in

86 these studies were small and restricted to two year follow-up[16, 17]. As such, there is currently no evidence on

87 the medium-term incidence of ACL re-injury with the use of LDHT graft. The aim of this study is to determine

88 the medium-term survival of ACLR with LDHT graft, and incidence of CACL rupture, and to identify the factors

89 that affect LDHT and CACL survival in a pediatric population post primary ACLR.

90 **MATERIALS AND METHODS**

91 <u>Patient Selection</u>

92 Patients included in the study were identified from a prospective database of knee surgery and had undergone

93 a primary ACLR with LDHT graft at least 2 years earlier. The participant flow is detailed in Figure 1. Patient

94 demographics were recorded in a prospective database which included information on the side of surgery,

95 age, gender, Tanner stage, physeal status, graft donor source, graft size and meniscal or articular cartilage

96 injury. Patients were sent an information sheet via post or email providing details of the project and inviting

97 them to participate. Subjective outcome data were obtained by contacting all patients meeting the inclusion

98 criteria via telephone or email. Those willing to participate in the study completed a telephone interview or

99 written questionnaire, which was returned via post or email. A research physiotherapist or an honours

100 medical student, both of whom had not been involved in the original surgery, performed the telephone

101 questionnaires. Ethical approval was granted by a local independent human ethics committee.

```
┌─────────────────┐
│   5364 ACL      │
│ reconstructions │
│    2005-2014    │
└─────────────────┘
         │
         ▼
┌─────────────────┐      ┌──────────────────────────────────────────┐
│   657 ACL       │─────▶│ Exclusions (n=393):                        │
│ reconstructions │      │ • Hamstring tendon autograft (n=319)       │
│   in patients   │      │ • Fresh frozen allograft (n=38)            │
│   < 18 years    │      │ • Previous contralateral ACL (n=5)         │
└─────────────────┘      │ • Resides overseas/interstate (n=29)       │
         │               │ • Refused participation in a research      │
         ▼               │   study (n=1)                              │
┌─────────────────┐      └──────────────────────────────────────────┘
│ 265 patients    │
│ < 18 years with │
│  living donor   │
│ hamstring tendon│
│     graft       │
└─────────────────┘
         │
         ▼
┌─────────────────┐
│  247 patients   │
│    reviewed     │
│     (93%)       │
└─────────────────┘
```

102

103   **Figure 1:** Participant Flow Chart

104   Subjective Evaluation

105   The questionnaire completed by patients included the full IKDC subjective knee evaluation form in addition to

106   questions relating to family history of ACL rupture, subsequent injury and/or surgery to either knee, whether

107   return to pre-injury level of sport was achieved and the current level of activity of the patient. Family history

108   was considered to be positive if the patient reported that a first degree relative (parents or sibling/s) had

109   sustained an ACL rupture at any time. A return to IKDC level 5 sports was defined as regular participation in

110   very strenuous activities involving cutting or pivoting type manoeuvres, as in basketball or soccer.

111   All patients who reported further injury to either knee that had not previously been documented were invited

112   to attend for further review. Graft rupture or CACL rupture was considered to have occurred only if one of the

113   following was present: (1) the patient had further knee reconstructive surgery (graft rupture) or primary

114   reconstruction (CACL) performed in our unit or by another orthopaedic surgeon; (2) had clinical examination

115   and/or an MRI scan reviewed by our unit to confirm ACL deficiency, (3) had reported another injury

116   characteristic of an ACL tear to either knee that had not been reviewed by us. For this last group, it was

117   assumed an ACL graft rupture or CACL rupture for the purposes of the survival analysis as a worst-case

118   scenario.

119   Operative Technique

120   ACLR was performed by one of two specialist knee surgeons (   ) in a single unit between the years

121   of 2005 and 2014. All patients and donors underwent preoperative blood testing including human

122   immodeficiency virus (HIV), hepatitis B and C, human papillomavirus (HPV), cytomegalovirus (CMV) and

123   syphilis testing. All patients underwent blood group testing including Rh status. Any Rh-negative female

124   patients were given the appropriate dose of Rh immunoglobulin on induction of anaesthesia to prevent

125   potential Rh sensitization.

126

127   Two fully staffed adjacent operating theaters were used and surgery was performed as day cases. In one

128   theatre, the gracilis and semitendinosus tendons were harvested from the parent donor. A tendon harvester

129   (Linvatec, Largo, Florida) was used to obtain a 22-cm tendon graft. Graft size was determined in regard to the

130   ACL footprint, to ensure a graft of adequate diameter but not one that would cause impingement at the

131   intercondylar notch. The tendons were wrapped securely in vancomycin soaked gauze and taken by the

132   surgeon to the adjacent operating theater. In the second operating theater, the child was already under

133   anesthesia and prepared and draped for surgery. Endoscopic transphyseal anatomic single-tunnel ACLR was

134   performed. The operative technique has been previously described in detail [16, 17].

135

136   From the 247 patients reviewed, there was 1 one-stranded, 30 two-stranded, 18 three-stranded, 191 four-

137   stranded, 6 five-stranded and 1 six-stranded LDHTs utilised. Femoral fixation included the round-headed Ti

138   cannulated interference screw (n = 167) (RCI, Smith & Nephew, Andover, Massachusetts), Endobutton (n = 49)

139   (Smith & Nephew), round-headed cannulated interference PEEK RCI screw (n = 29) (Signature Orthopaedics)

140   and staple (n = 2). Tibial fixation included the Ti RCI screw (n = 150) (Smith & Nephew), staple (n = 56), PEEK

141   RCI screw (n = 35) (Signature Orthopaedics), BioRCI screw (n=5) (Smith & Nephew), and post fixation (n = 1).

142   Routine radiographs were obtained postoperatively. Patients were allowed to bear full weight, and

143   commenced an early accelerated rehabilitation program [46]. At 9 to 12 months, an objective assessment of

144   rehabilitation goals was performed to assess readiness to return to competitive sports, especially those that

145   involved pivoting or side-stepping activity. Growth plate status was assessed from the immediate post

146   operative x-ray. Patients with open physes at the time of surgery obtained an annual x-ray of the knee. A long

147   leg alignment x-ray was also obtained at two years post operation, and then at 18 years of age. The long leg

148   alignment x-ray was assessed by the treating surgeon for growth disturbance or leg length discrepancy.

149

150   <u>Statistical Analysis</u>

151   Statistical analysis was performed using SPSS software. Statistical significance was set *a priori* at $p \leq 0.05$.

152   Groups were compared with t-tests for linear variables (mean IKDC scores) and chi square tests for categorical

153   data (gender, age, family history, growth plate status and Tanner stage).

154   The probability of failure (ACL graft rupture and/or CACL injury as well as second ACL injury) was estimated as

155   a function of time using the Kaplan-Meier (K-M) survival method. Survival tables at 1, 2 and 5 years were

156   collated. Comparisons of survival curves were made with univariate Cox proportional hazards. Factors

157   examined included age, sex, family history of ACL injury, growth plate status and Tanner score. Factors with p

158   ≤ 0.10 on univariate analysis were entered into a multivariate Cox regression analysis. Factors were then

159   eliminated in a stepwise fashion, until only the independent significant factors remained. Multiple imputation

160   was utilised for Tanner score to account for missing cases in the analysis by using the variables age and growth

161 plate status. Imputated and non-imputated raw Tanner data provided the same statistical significance for the

162 analysis. Non-imputated raw Tanner data are presented in the results section. Analysis was performed on the

163 whole group, and repeated for each gender independently.

164 **RESULTS**

165 Between January 2005 and December 2014, 5,364 patients underwent primary ACLR. Of these, 265 patients

166 were under 18 years of age, and in these cases a LDHT graft was harvested, thus forming the study cohort.

167 There were 247 (93%) patients that completed the subjective questionnaire at a mean of 4.5 years after

168 surgery (range 24 months – 127 months (10.6 years)). The participant flow is shown in Figure 1. Of the 247

169 patients, 166 (67%) had no subsequent ACL injuries and 81 (33%) sustained a further ACL injury. Of the

170 patients who sustained further ACL injuries, 51 patients (20.6%) sustained an ACL graft rupture, 28 patients

171 (11.3%) sustained a CACL injury and 2 patients (0.8%) sustained both an ACL graft and a CACL rupture.

172 Demographics (n=247)

173 There were 82 (33.2%) females and 165 (66.8%) males. The mean age at surgery was 14.6 years (range, 8-

174 17.9). There were 128 left-sided and 119 right-sided reconstructions. Surgery was performed in the acute

175 phase (within 3 weeks of injury) in 7 patients (2.7%), in the sub-acute phase (3-12 weeks) in 201 patients

176 (81.4%) and in the chronic phase (> 12 weeks) in 39 patients (15.8%). Tanner stage of development was

177 collected in a prospective manner at the time of surgery for 202 of the 247 patients. There were 23 Tanner 1,

178 24 Tanner 2, 29 Tanner 3, 79 Tanner 4 and 47 Tanner 5 patients (Figure 2). LDHT graft was obtained from the

179 father in 201 patients (81.4%) and the mother in 42 patients (17%). One step-father, one uncle, one brother

180 and one sister also donated a LDHT graft (.4%). The mean diameter of the LDHT graft was 7.5mm (range 4.5-

181 8.5mm). 153 patients (62%) had an isolated ACLR, without meniscal surgery. At the time of surgery, 12

182 patients (4.8%) required partial medial meniscectomy and 46 patients (18.6%) required partial lateral

183 meniscectomy. Meniscal sutures were used in 10 patients (4%) in the medial meniscus and 26 patients

184 (10.5%) in the lateral meniscus. The primary ACL rupture was most commonly sustained in the sports of rugby

185 and soccer, which accounted for 59% of injuries (see Figure 3).

186
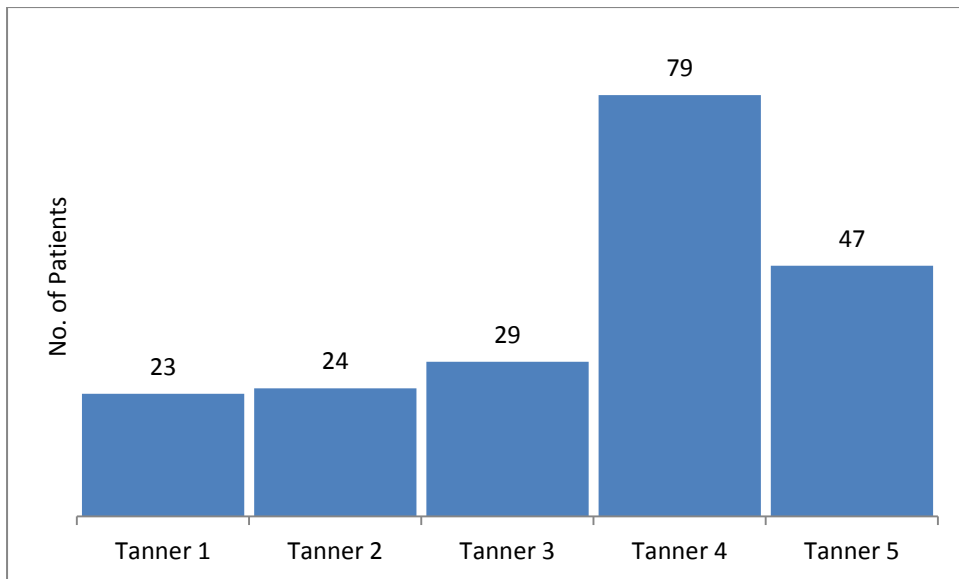
Figure 2: Tanner score at time of surgery in 202 of the 247 patients reviewed

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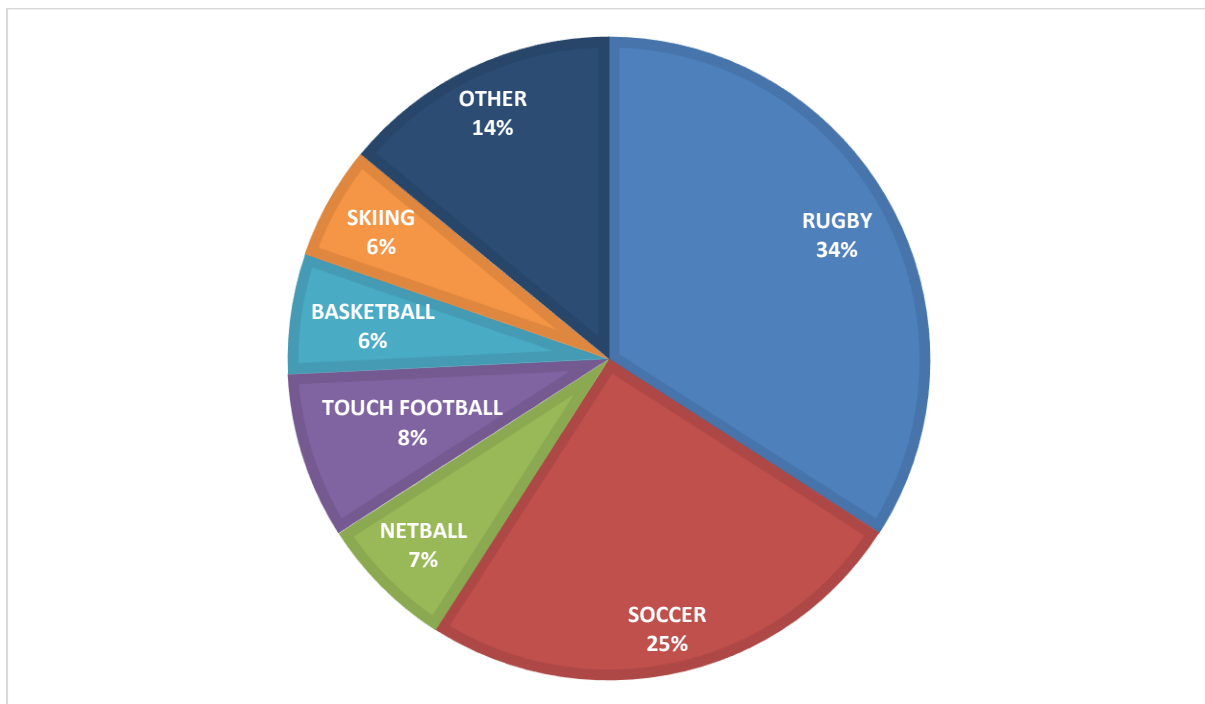
Figure 3: Sport of the primary ACL injury

Subjective Outcomes

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

196 the mean IKDC score between Tanner 1 and 2 patients versus Tanner 3-5 patients (92.3 v 91.9, p=.78), closed

197 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)

199 The incidence of ACLR graft injury was significantly higher than the incidence of CACL injury after

200 reconstruction (p=0.006). Tanner 3-5 patients had a significantly higher incidence of a second ACL injury

201 (38.1%) compared to Tanner 1 and 2 patients (21.3%) (p=0.03). There was a trend for patients aged 14 years or

202 more to have a higher incidence of second ACL injury compared to those less than 14 years of age (36.1%

203 versus 23.9% respectively; p=0.07). A positive family history was associated with a significantly higher

204 incidence of second ACL injury than patients without a positive family history (34.2% vs. 21.3%, p=0.04). There

205 was no significant difference in the incidence of second ACL injury between genders or growth plate status

206 (p=0.59 and p=0.46 respectively). A summary of second ACL injury can be seen in Table 1.

207 **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%	

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

ACL Graft Rupture

210 ACL graft rupture occurred in 53 (21.5%) patients (inclusive of the two patients that ruptured both their ACL

211 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

212 (range 1.5 – 60) post primary ACLR. One male patient reported a knee injury associated with instability but

213   was unable to attend for review; he was assumed to have sustained an ACL graft rupture. Patients who

214   reported characteristics of rupture in the questionnaire and had not undergone further reconstructive surgery

215   were examined in our unit to confirm ACL stability. All ACL ruptures occurred during sport and recreational

216   activities and soccer was the sport that accounted for the most ACL graft ruptures which can be seen in Table

217   2.

218   **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

219

220   The ACL graft rupture was confirmed at the time of revision ACL surgery in 44 patients and by MRI and clinical

221   examination in nine patients. Kaplan-Meier survival analysis for ACL graft rupture is shown in Figure 4 (A). ACL

222   graft survival was 89%, 82% and 76% at 1, 2 and 5 years post reconstruction, respectively. The results of

223   univariate analysis are shown in Table 3. Tanner score and age at surgery were entered into a multivariate Cox

224   regression analysis and missing Tanner variables were accounted for with multiple imputation. On stepwise

225   analysis, only Tanner Stage 3-5 remained significantly associated with poorer ACL graft survival with a hazard

226   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,

227   p=<0.001). The Kaplan-Meier chart of ACL graft survival and Tanner Stage is shown in Figure 4 (B).
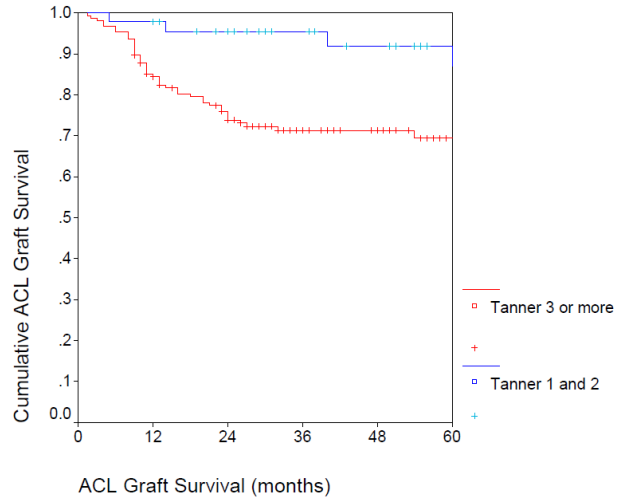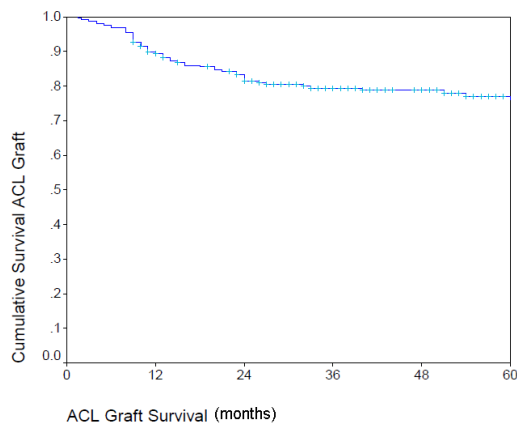
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229

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

232 **TABLE 3 - Survival of the ACL Graft with Univariate Hazard Ratios for the Examined Patients (N = 247**
233 **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 .51	
Closed	83	90	80	72		
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		

234

Contralateral ACL Injury

236 32 patients (12.9%) sustained a CACL rupture during the study period (inclusive of the two patients that
237 ruptured their ACL graft and CACL). CACL injury was confirmed at the time of CACL reconstruction in 30
238 patients, and clinical examination and MRI in our unit in 2 patients. CACL injury occurred at a mean of 37
239 months (range, 6-84) post primary ACLR (Figure 5A). CACL survival was 99%, 94% and 86% at 1, 2 and 5 years
240 respectively, post reconstruction. The results of univariate analysis are shown in Table 4. CACL survival was
241 not significantly associated with age, growth plate status, Tanner stage, graft diameter or femoral fixation.
242 Patients who had a positive family history of ACL injury displayed a non-significant trend to poorer CACL
243 survival compared to those without a positive family history (p=.09) (Figure 5B).

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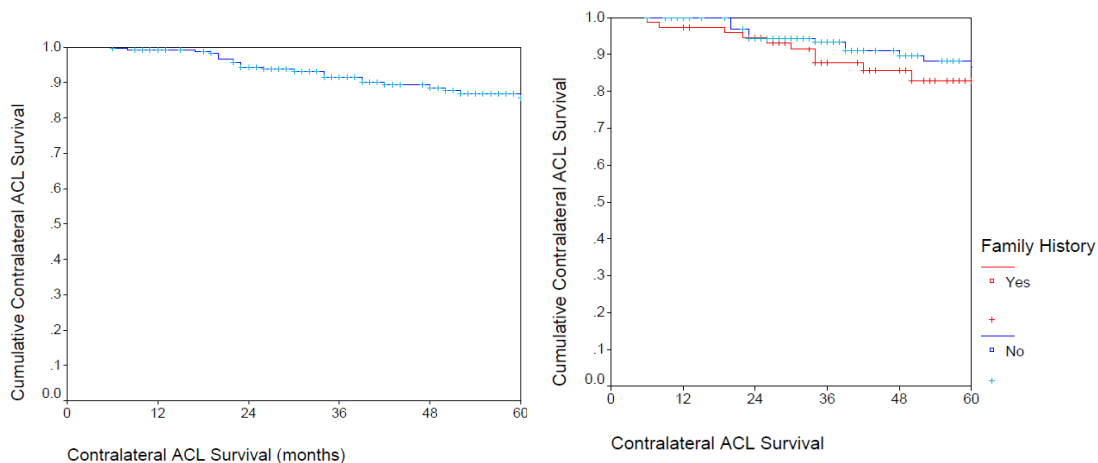
246 **Figure 5:** Survivorship analysis of the CACL over time. (B) Survivorship analysis of CACL in relation to family
247 history p=.09

248

249

250   **TABLE 4**

251   **Survival of the contralateral ACL with univariate hazard ratios for the examined variables**

252   **(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		

253

254   <u>Gender Analysis</u>

255   14 (17.1%) females and 39 males (23.6%) had an ACL graft rupture; however, there was no significant

256   difference between males and females in survival of the ACL graft or CACL at 5 years post surgery (p=.24 and

257   p=.76 respectively; see Table 3 and 4). Eleven females (13.4%) and 19 males (11.5%) had a CACL injury. In male

258   patients, there was a significant association between ACL graft rupture with positive family history (p=0.01)

259   and Tanner stage 3-5 (p=.01); there was also a non-significant trend toward graft rupture for patients aged less

260 than 14 years (p=.06). When both genders were pooled, there was no significant association between the

261 variables Tanner stage, age or growth plates status for ACL graft rupture or CACL injury (see Table 5(a) & 5(b)).

262 **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

263

264 **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

265

266 <u>Open Growth Plates</u>

267 There were no growth disturbances noted on x-ray or long leg alignment films by the treating surgeons at a

268 mean of 37 months (range 5-102 months) post surgery in the 83 skeletally immature patients in this series.

269 **DISCUSSION**

270 The 5 year survival rate of the ACL graft and CACL post primary ACLR with the use of a LDHT graft was 76% and

271 86% respectively. Survival of the ACL graft was favourable in those who were Tanner stage 1 and 2 at the time

272 of surgery compared with Tanner 3-5 patients by a factor of 3.1. The use of a LDHT graft for ACLR offers

273 acceptable 5 year survival for skeletally immature patients.

274 There is limited research on the use of a LDHT for ACLR other than those that have published from our group

275 with a smaller sample size and shorter follow up than this current series.[16, 17] Furthermore, there are few

276 studies with a patient cohort as young as our current series and, to our knowledge, no large scale studies

277 available on the medium-term outcome of ACLR with LDHT graft for comparison. Direct comparison of the

278 cohort of living donor patients with traditional autograft patients is difficult due to the differences in the

279 patient population and length of follow up in the published literature. In a previous study of patients 18 years

280 or less with an ACLR performed at the same institution, utilising autologous hamstring tendon, ACL graft

281 survival was 88% at five years and 83% at 15 years [32]. However the population of this autograft series were

282 older than our current series (mean age 16 years versus mean age of 14.6 years). If we compare the outcomes

283 according to age, the five year ACL graft survival in those 14 or less was 84% with LDHT graft and 78% with

284 hamstring tendon autograft. For those age >14 years ACL graft survival was 73% with the LDHT graft and 90%

285 with the hamstring tendon autograft. Direct comparison of these two cohorts is limited by the consecutive

286 nature of the series, particularly the effect of evolving rehabilitation protocols; however the two cohorts are

287 from the same institution and involved the same surgeons. In the absence of a randomised series, our results

288 suggest that the use of a LHDT graft may be considered reasonable in patients aged 14 year or less, but we

289 cannot conclude that it reduces the incidence of graft rupture in adolescents when compared to a hamstring

290 autograft.

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

292 A lower rate of second ACL injury was noted in physically immature patients. Tanner 1 and 2 patients had a

293 one in five incidence of second ACL injury compared with Tanner 3 – 5 patients who had just over a one in

294 three incidence of second ACL injury (21.3% versus 38.1%) at a mean of 4.5 years post surgery. The reasons for

295 this lower rate of re-injury in the immature patients may be multi-factorial. Socially, juveniles may be

296 protected from second ACL injury compared with the adolescents due to increased parental supervision.

297 Adolescents may have more freedom to play at a higher level, and participation in competitive sports is often

298 more aggressive, which potentially increases their likelihood of re-injury. Furthermore, adolescents have a

299 greater body mass as they grow, generating larger moments and greater inertia during sports. According to

300 Barber-Westin et al. (2006)[5] these factors highlight the need for continued neuromuscular control training

301 throughout adolescence. In prepubescent patients, neuromuscular control issues may be offset by their lower

302 body mass and reduced movement velocities[5]. Distinctive cellular responses may also contribute to the lower

303 rate of secondary ACL injury in younger patients; animal studies in minipigs have suggested that there may be

304 a faster healing response and increased cellularity in the skeletally immature ACL, compared to adults [27, 28]. It

305 has been demonstrated that fibroblasts from the ACLs of immature pigs and sheep grow faster and migrate

306 faster than adolescent cells [28, 33]; however equivalent human studies are currently lacking [22]. It remains to be

307 determined whether Tanner 1 and 2 patients will go on to have elevated risk once they move into

308 adolescence. While the factors contributing to second injury are likely to be multifactorial and frequently

309 theoretical, it can be concluded that the adolescents have the greatest risk of second ACL injury compared to

310 both juveniles and adults.

311   <u>Patients with open growth plates</u>

312   There were no measurable growth disturbances or varus/valgus mal-alignment noted on radiographs in the 83

313   skeletally immature patients in this series with open growth plates at a mean of 37 months post surgery (range

314   5-102 months). This finding is consistent with the growing literature base confirming ACLR utilising a

315   transphyseal approach as a safe procedure with no significant episodes of growth disturbance or varus/valgus

316   alignment when carefully performed [11, 29, 40, 47]. The surgical technique used in this series respects the

317   important principles that only soft tissue grafts should be used, that the tibial and femoral tunnel diameter

318   must be less than five percent of the physeal cross-sectional area, and that graft fixation is placed away from

319   the open physis to avoid growth disturbance[20, 38, 53].

320   <u>Gender differences</u>

321   In this series of patients, there was no significant difference between males and females in terms of survival of

322   the ACL graft or CACL which is consistent with findings in the literature [42, 44, 48]. Webster et al. [50] examined a

323   series of patients younger than 20 years post ACLR with autologous hamstring grafts, and the subgroup of

324   patients less than 18 years had a second ACL injury rate of 44.3% in males and 31.8% in females (our LDHT

325   graft series 33.9% and 30.5% respectively) at 5 years. When analysing males independently, there was a

326   statistically significant association between ACL graft rupture and a positive family history, and Tanner stage 3-

327   5 (compared with Tanner stage 1-2). These differences were not present in females. This could be due to

328   differing cohort sizes in this series (165 males, 82 females). Further investigation into gender differences

329   between sexes in the young is warranted.

330   Gender of the LDHT graft also demonstrated no significant difference in terms of survival of the ACL graft at 5

331   years (p=.39). However at 2 years, there was a 74% ACL graft survival in female living donor patients compared

332   to 91% in male donors. The lack of statistical significance may be reflective of the smaller sample size of female

333   versus male living donors (n=43 vs n=205). Further studies into the gender of living donors is warranted.

334

335   <u>Graft Selection</u>

336   Graft selection in ACLR is controversial. The ideal graft recreates the anatomical and biomechanical properties

337   of the native ligament, provides rapid biological integration, reduces recovery time and donor site morbidity [12,

338   21]. Integration time of allograft versus autograft tissue is well documented in numerous animal studies

339   involving goats, sheep, and rabbits for example [13, 36, 45]. However, it is difficult to extrapolate animal data to

340   humans directly. Nevertheless, there is support deeming that cadaveric allograft tissue is slower to incorporate

341   than autograft [7, 20]. This documented slower incorporation rate is unknown in the situation of the fresh graft

342   harvest from a living donor. Further research into graft incorporation in the unique case of LDHT graft is

343   required to know whether its incorporation rate is similar to an autograft.

344   <u>Study Limitations</u>

345   Due to the retrospective nature of the study design there was incomplete data that must be considered when

346   interpreting results. Firstly, Tanner stage was collected in 202 of the 247 patients. The missing data is due to

347   the overlap period before our institution collected Tanner stage as a variable. The multiple imputation

348   statistical technique was also utilised to account for the missing Tanner stage data and the findings continued

349   to highlight a significant ACL graft survival difference between Tanner 1-2 and Tanner stage 3 or more.

350   Secondly, family history was successfully obtained in 217 of the 247 patients so there is missing data for this

351   variable that also needs to be considered.

352   Furthermore, choice of soft tissue graft in ACLR remains debated [43], and in our cohort of patients a variety of

353   femoral fixation devices were utilised including interference screw, endobutton and staple fixation. This

354   variation in fixation highlights another weakness of the retrospective study design however caution was taken

355   in all cases to ensure fixation was situated away from the physes in patients with open growth plates. Despite

356   the studies weaknesses, the retrospective study design has allowed the collection of data on 247 patients that

357   provides sufficient statistical power to investigate outcomes in a particular sub-cohort of patients with ACLR.

358   <u>Conclusions</u>

359   We present the largest pediatric series of all arthroscopic transphyseal single bundle ACLR with LDHT with

360   follow up to a mean of 4.5 years post surgery. ACL injury after ACLR in juveniles and adolescents remains a

361   challenging problem. ACLR using a LDHT graft is associated with good subjective outcomes. Tanner 1 and 2

362   stage patients have a lower incidence of repeat ACL injury compared to adolescents. Thus, using a LDHT graft

363   for ACLR may be an appropriate graft to consider for the skeletally immature. However, for those adolescents

364   who are skeletally mature, we are unable to advocate the use of LDHT for ACLR.

365

366   <u>References</u>

367

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