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Allograft Donor Characteristics Significantly influence Graft Rupture after ACL Reconstruction in a Young, Active Population

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Summary Sentence: The age and sex of the allograft donor, and the morphology of the graft significantly influences the rate of ACL graft rupture in young active subjects. Tendons from female donors over the age of 50 should be avoided given the higher re-rupture rates compared to males of any age and younger females.

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Abstract

Background: Graft selection in anterior cruciate ligament surgery can be difficult in a young, active population given their high rates of reinjury. Allografts allow for control over graft size and reduce morbidity of autograft harvest. There are mixed results about the use of allograft in the literature, however, the influence of the properties of the allograft on outcomes has not been considered.

Hypothesis: ACL reconstruction with allografts from older donors will have a higher rate of graft rupture compared to allograft from young donors.

Study design: observational cohort study, Level 3 evidence

Methods: 211 subjects aged 13-25 underwent primary ACL reconstruction with fresh frozen allograft. Four graft types were used; patellar tendon (PT), Achilles tendon (AT), tibialis anterior (TA) and tibialis posterior (TP). Details were collected on allograft donor age and sex. At a minimum of 24 months subjects were evaluated for any further injuries and subjective analysis by IKDC questionnaire.

Results: ACL graft rupture rate occurred in 23.5%. When separated into single strand (PT and AT) and multi-strand (TA and TP) grafts, there was a significantly higher rate of re-injury in the single strand grafts compared to multi-strand grafts (29.9% vs. 11% p= 0.018). Grafts from female donors age 50 years and over had significantly higher rates of ACL graft rupture (52.6% p=0.004), with increased odds by 6.7 times compared to grafts from female donors under 50 years, or males of any age. There was no significant difference in mean IKDC scores between any of the groups based on age and sex of the allograft donor.

Conclusion: The age and sex of the allograft donor, and the morphology of the graft significantly influenced the rate of ACL graft rupture in young active subjects. Tendons from female donors over the age of 50 should be avoided given the higher re-rupture rates compared to males of any age and younger females.
Key terms: allograft, donor sex, donor age, anterior cruciate ligament reconstruction

Introduction

Young, active patients with anterior cruciate ligament (ACL) rupture are difficult to manage. They have high functional demands which require a strong and stable knee and have significantly high rate of re-injury [21, 25, 28]. Graft selection in the adolescent age group can be particularly difficult given they have not yet reached full maturity [19]. At our institute, as well as Australia wide, hamstring tendon autografts have been the preferred choice. They, however, are not without morbidity and may not be ideal in a young population.

Hamstring muscles are known to act as a secondary stabilizer of the knee. They offer a protective effect on the ACL to prevent anterior translation of the tibia, and play a role in knee proprioception. Following ACL reconstructive surgery, persistent hamstring atrophy and long-term deficits in strength and range of movement have been demonstrated [5, 17, 27]. Snow et. al found a reduction in hamstring volume of 50% a decade post operation, and reported a significant reduction in volume in the quadriceps muscles which correlated to decreased power [27]. This suggesting possible long-term muscle dysfunction and changes in knee biomechanics. The second issue with hamstring grafts in a young population is that the size may be insufficient to match their future development and functional demands [8]. Thus, allografts may be a good alternative; they avoid donor site morbidity and allow for better control over graft size. Furthermore, they result in a smaller wound, faster early recovery and reduced operative time.

There has been a reluctance to adopt allografts given their poor results in the literature [6, 9, 11, 12, 24]. Traditionally allografts were sterilized with gamma radiation. It is well recognized that ionizing radiation induces structural damage to the tissue and can limit cell potential to undergo a regenerative process [26]. The physical and biological influence of radiation could influence the strength of the graft when used in ACL reconstruction, resulting in higher failure rates. More recently a systematic review by Mascarenhas et. al, found no significant difference in ACL graft reinjury rate, postoperative laxity or patient reported outcomes in ACL reconstruction between autograft and non-irradiated allograft [20].

To the best of our knowledge, the influence of donor characteristics and tendon type used as the graft on the outcome of ACL reconstruction with allograft material has never been evaluated. The purpose of this study was to evaluate outcomes at a minimum of 24 months with fresh frozen allograft in ACL reconstruction in young patients and to assess the influence of allograft tendon type, donor characteristics and mode of preparation. The primary outcome variable was ACL graft rupture rate and secondary outcome was subjective patient reported outcomes. We predicted that ACL graft rupture rates with allografts may be influenced by the characteristics of the donor, with higher rates of ACL graft rupture in tendons from older donors. We hypothesized that there would be no difference in ACL graft rupture rates based on the type of tendon used or the method of preparation.

Methods

From January 2014 to June 2017, 211 subjects between the ages of 13-25 underwent primary ACL reconstruction with fresh frozen allograft. All subjects reported participating in their respective sport at a competitive level. Inclusion and exclusion criteria are listed on Table 1. Ethical approval was sought and granted by a local human ethics committee (St. Vincent's Hospital, Sydney, Australia).

Table 1: Inclusion and Exclusion Criteria

Inclusion	**Exclusion**
Age 25 years or under Isolated ACL injury Primary reconstruction Nil injury to contralateral knee Consent to use of use of non-irradiated fresh-frozen allograft	Age over 25 years Other significant ligamentous injury to index knee Previous ACL injury to either knee Subjects seeking compensation for their injury

Allografts were obtained from Tissue bank Victoria or Tissue bank Queensland, government regulated bodies. The tissue banks provided details on the donor including age and sex. None of the grafts were prepared with irradiation. The sterilization process included either a 0.5% chlorhexidine and 70% alcohol wash performed three times or 320ug/ml gentamicin wash stored for 24 hours at 4 degrees Celsius. Both banks used sampling techniques and control swabs to ensure sterility. Additionally, donors were screened prior to organ donation for potential infectious diseases. Grafts were stored at -40 degrees Celsius until time of use.

Both tissue banks supplied all types of grafts. Four graft types were available: tibialis anterior and tibialis posterior with soft tissue alone, and patellar tendon and Achilles tendon with bone blocks. The type of graft used in each patient was not randomly allocated but dependent on availability from the tissue bank as well as what the surgeon felt was most appropriate for the patient. The consensus was to avoid patellar tendon allografts in smaller female patients as the bone blocks result in drilling larger tunnels. Similarly, patellar tendon grafts were avoided in skeletally immature patients, to avoid possible disruption of the physis. Thus, Achilles tendon, tibialis posterior and tibialis anterior tendon were preferentially selected for female patients or smaller males and patellar tendons tended to be reserved for larger males.

At time of surgery the graft was removed from the freezer and defrosted in warm 0.9% sterile saline. The tibialis grafts were measured and cut to approximately 22cm and folded in half over a No 5. suture to form a two-stranded (multi-strand) graft. This suture was used as the leading strand to pull the graft through the tunnel. The two ends of the graft where then sutured using a No. 1 Vicryl whipstitch for approximately 20mm. The patellar tendon grafts were made from the central third of the tendon with bone blocks on either end. At either end of the tendon a 20-25mm trapezoidal bone block was excised and a 10mm wide strip of tendon was cut. The bone blocks where then fashioned to pass through a round graft sizer. Achilles grafts were removed from the bone block and tubularized at both ends with Vicryl whipstitch in an identical fashion to the tibialis tendons. They however, remained single stranded at the intra-articular component. The grafts where all placed in vancomycin soaked gauze until ready for use.

All operations were performed by two orthopedic surgeons (L.P, J.R) using identical technique. The knee was prepared and femoral tunnel was marked with an awl at 5mm anterior to the posterior capsule insertion at the 11-o'clock or 1-o'clock position for the right and left knee respectively. The femoral tunnel was drilled with the knee in full flexion to the size of the tendon or the bone block previously measured. The tibial tunnel was prepared with a drill guide placed at the footprint of the ACL, one-third of the way along a line from the anterior horn of the lateral meniscus and the medial tibial spine. Fixation at the femur and tibia was with a PEEK RCI HA screw (Smith & Nephew, Andover, Massachusetts) with the screw 5-10mm from the aperture. All patients underwent a standard accelerated rehabilitation protocol used for all ACL reconstructions at our institute, with post-operative day one weight bearing and range of movement exercises. Readiness to return to sport was determined following assessment by the surgeon and physiotherapist, typically at 12 months post-surgery.

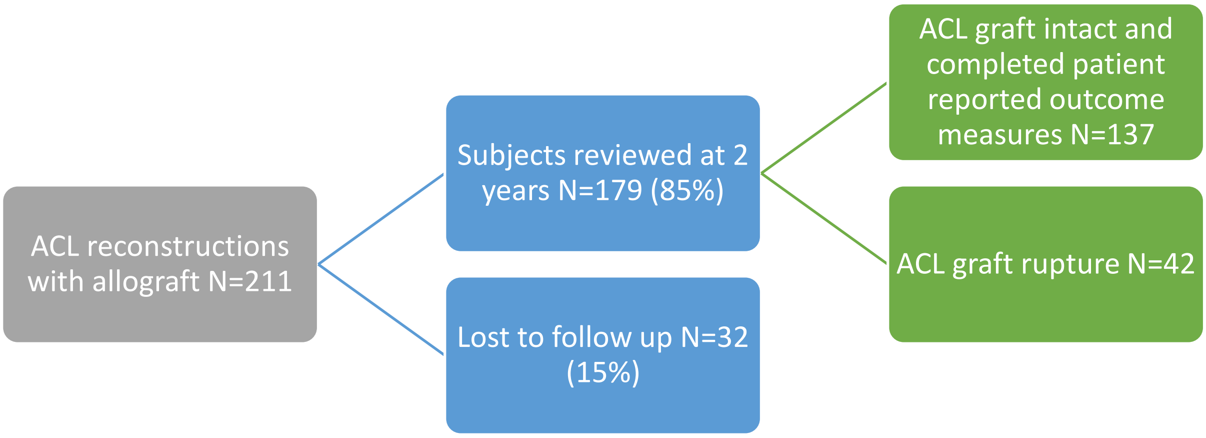
At a minimum of 24 months (range 24-36 months), subjects were assessed with a subjective questionnaire which included any further knee injuries, return to sport and the subjective IKDC Knee Score.

Statistical analysis was performed with SPSS software for Windows (IBM, Armonk, NY). Statistical significance was set at $P = 0.05$. Comparison of variables between groups was analyzed with $\chi 2$ tests for categorical data and comparison of continuous variables was determined by Student's t-test.

Results

Between January 2014 and June 2017, 211 subjects, aged 25 or less, underwent primary ACL reconstruction with fresh frozen allograft. 179 subjects (85%) were followed up at a minimum of 24 months post-operative (range 24-36 months). The remaining 32 subjects were unable to be contacted and deemed lost to follow up. Patient reported outcomes were measured on 137 subjects with intact ACL grafts. (Figure 1- participant flow)

Figure 1: Participant Flow



Of the 179 subjects, the average age was 18.6 years (range 13-25 years) and the majority were males (n= 145, 68.7%). The most common sports resulting in the injury were soccer (n= 75, 35.5%), rugby (n= 49, 23.2%), touch football (n= 26, 12%), netball (n= 15, 7%) and basketball (n= 13, 6%).

Overall for all graft types, 42 subjects (23.5%) sustained an ACL graft rupture at a mean time of 19 months (range 5-38 months) post-surgery. Of the 42 ACL graft ruptures, only one subject was determined to have had an atraumatic failure. This subject received an Achilles tendon allograft from a female donor over the age of 50 years and ruptured at nine months post-surgery. The remaining 41 subjects had a graft rupture related to sport or activity. There were 15 graft ruptures within the first year following surgery; ten related to early return to sport, one from jumping at rehab, one from change of direction drills, one fall from skateboard, one fall while skipping and one atraumatic. The Kaplan Meir curve for ACL graft survival according to donor characteristics in shown in Figure 2, and the and according to graft type is shown in Figure 3.

Figure 2: ACL graft survival according to allograft donor characteristics

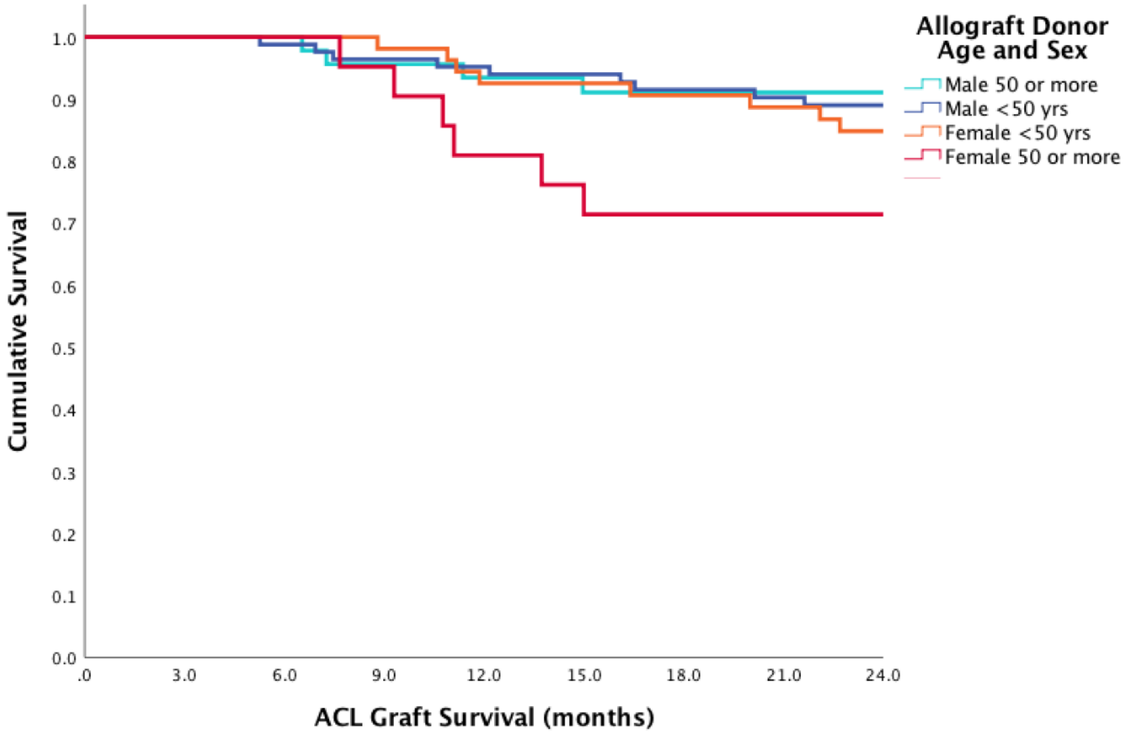
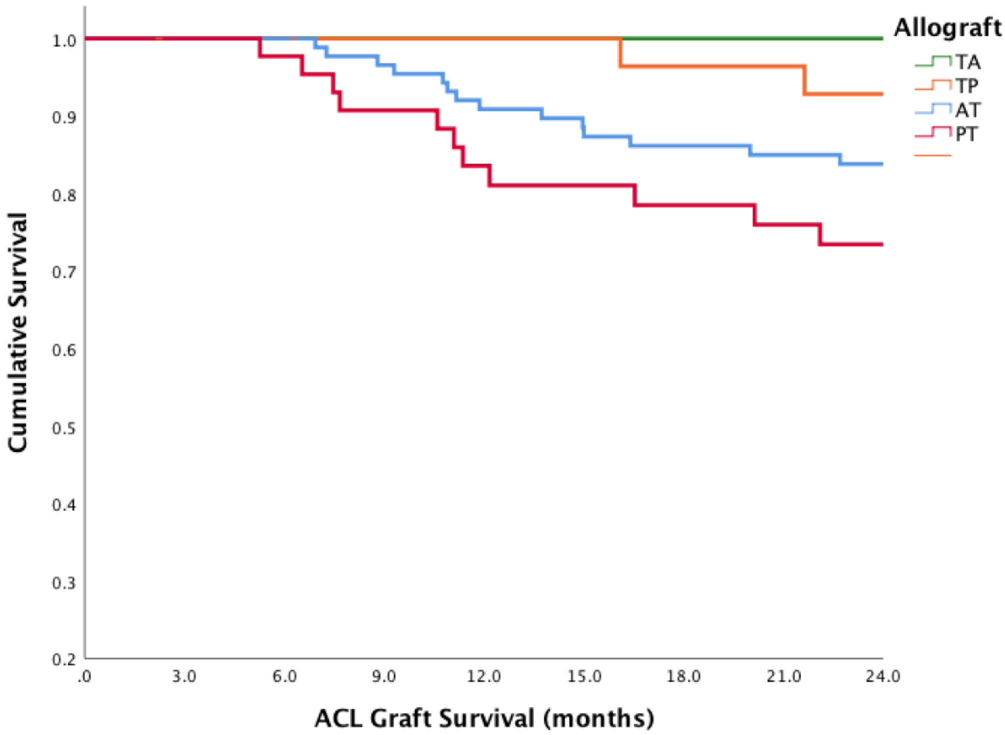


Figure 3: ACL graft survival according to allograft type



*TA – tibialis anterior, TP – tibialis posterior, AT – Achilles Tendon, PT –patellar tendon

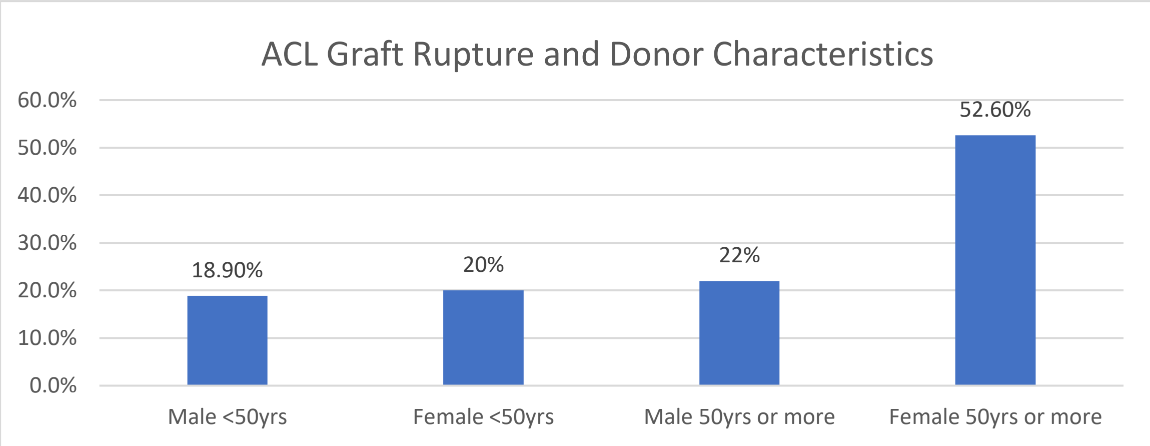
The distribution of the allograft type and rates of ACL graft rupture are shown on Table 2. The most commonly used graft was Achilles tendon (n= 80, 44.7%), followed by patellar tendon and tibialis anterior. Tibialis posterior was the least commonly used. There was found to be a significant difference in the rates of re-injury based on graft type. The patellar tendon had the highest rate of ACL graft rupture (35.1%). When grouped into single stranded grafts (Achilles and patellar tendons) and multi-stranded grafts (tibialis anterior and tibialis posterior tendons), there was found to be a significantly higher rate of rupture amongst the single stranded grafts (29.9% vs. 11% p= 0.003).

Table 2: Graft type and rupture rates

	Achilles	Patellar Tendon	Tibialis Anterior	Tibialis Posterior	TOTAL	P
N	80	37	37	25	179	
ACL graft rupture	22 (27.5%)	13 (35.1%)	3 (8.1%)	4 (16.0%)	42 (24%)	0.027
CACL rupture	7 (8.8%)	3 (8.1%)	4 (10.8%)	3 (12.0%)	17 (9.5%)	0.942

Donor characteristics were divided into four groups: males under 50 years, females under 50 years, males 50 years and over and females 50 years and over. Most grafts were from donor males under 50 years (n= 74), followed by females under 50 years (n= 45), males over 50 years (n= 41) and finally females over 50 years (n=19). The rate of graft rupture was significantly higher from female donors 50 years and over with 52.6% ACL graft rupture (p= 0.017), compared to the other groups. There was no significant difference in graft rupture rates amongst the other groups (Figure 4). The distribution of grafts from females over 50 years was distributed throughout the graft types, 33% (7/21) of the Achilles grafts, 19% (4/21) of the patellar tendon grafts, 19% (4/21) tibialis anterior grafts, 29% (6/21) tibialis posterior grafts (p=0.355).

Figure 4: ACL Graft rupture rates by donor characteristic



A multiple regression analysis was performed to assess the relative contribution of the variables of graft type, donor age and sex and subject age and sex on the rate of ACL graft rupture (Table 3). On multivariant regression analysis, single strand grafts showed at 3.0 times higher odds of ACL graft rupture (95% CI 1.2-7.4 p= 0.018), compared to multi-stranded grafts. There was a 6.7 times greater odds of ACL graft rupture when a graft is used from a female donor 50 years and over (95% CI 1.9-23.3 p=0.003), compared to those donors under 50 years. Male subjects had a 4.6 times greater odds of ACL graft rupture than female subjects.

Table 3: Multivariate analysis of ACL graft rupture by donor gender and age, and graft type.

		N	% Graft Rupture	Odds Ratio	95% CI	p
Donor Graft Type						
	Single strand graft	117	29.9%	3.6	1.3 to 9.9	0.014
	Multi Strand graft	62	11%			
Donor Gender and Age						
	Female 50 or More	19	52.6%	6.7	1.9 to 23.3	0.003
	Male 50 or More	41	22.0%	1.0	0.4 to 2.9	0.942
	Female <50 Years	45	20.0%	1.1	0.4 to 3.0	0.835
	Male < 50 Years	74	18.9%	reference		
Subject Gender						
	Male	145	27%	4.6	1.5 to 14.1	0.007
	Female	77	6%			
Subject Age						
	Age 18 or Less	114	25%	2.2	1.0 to 4.9	0.066
	Age >18 years	65	22%			

There was no significant difference in rates of ACL graft rupture by mode of preparation (0.5% chlorhexidine + 70% alcohol or 320ug/ml gentamicin) (p=0.596).

Graft size was measured in a routine fashion with sizing tube, as the smallest diameter (in 0.5mm increments) through which would pass the entire graft, including the bone blocks on the patellar tendon grafts or whipstitched ends of the single stranded grafts. Given the different shape of the single-strand and multi-strand graft, a comment on intra-articular graft size cannot be accurately made; the sizing reflects the diameter of the femoral tunnel. The intra-articular component of the tibialis anterior and posterior grafts with were measured with a mean size of 8.77mm SD 1.06, and 8.83mm SD 1.06 respectively. The patellar tendon and Achilles tendon grafts were measured based on the bone blocks or whipstitched ends with a mean size of 10.79mm SD 0.57 and 9.45mm SD 0.89.

Subjective analysis by IKDC questionnaire was completed in 137 subjects with intact ACL grafts. There was found to be no difference in the mean IKDC score across the graft types (ANOVA, p=0.404). There was found to be no significant difference between graft type and return to very strenuous activities or return to sport at the same level (Table 5). Similarly, there was no significant difference in mean IKDC score or return to very strenuous activities and sport level between the donor characteristics when grouped by age and sex (Table 6). There was a trend for the group who received grafts from female donors 50 years and over to have lower rates of return to very strenuous activity (44.4%), but this did not reach significance.

Table 5- IKDC Subjective Evaluation and Return to Sports of subjects with intact ACL grafts by donor characteristics

	Female >50 year	Male 50 or more	Female < 50 years	Male < 50 years	p
N	9	32	36	60	
Mean IKDC score/100	82.1	89.5	89.9	91.6	0.120
Participating in very strenuous activities (%)	4 (44.4%)	24 (75%)	27 (75%)	44 (72%)	0.111
Return to sport at same level (%)	5 (55.6%)	17 (53.1%)	24 (66.7%)	43 (71.7%)	0.314

The results indicate that tendon type and donor characteristics are important variables for graft rupture rates. Thus, 'the preferred allograft' may be defined as a multi-strand graft from a male of any age or a female donor under 50 years. Of the 179 subjects, 53 (29.6%) received the 'preferred graft'. ACL graft rupture occurred in four of these 53 subjects (7.5%), compared to ACL graft rupture in 38 of 126 subjects (30.2%) who did not receive the 'preferred graft'.

Discussion

This study evaluated the two-year graft rupture rate for ACL reconstruction with fresh frozen allografts in a young, active population. Although non-irradiated allografts have been shown to be a safe alternative [30], there remains concern and controversy due to high failure rates reported in the literature [15, 18]. However, none of these studies have specifically looked at the allograft characteristics and their influence on ACL graft rupture rates. This study suggests that the characteristics of the allograft play a significant role in rates of ACL graft rupture; in particular, the age and sex of the donor and the allograft morphology.

The most striking finding of this study was the significantly elevated rate of ACL graft rupture in the allografts from female donors age of 50 years and over, with greater than half of the grafts failing within two years. There was 6.7 times increased odds of rupture if the donor tendon was from a female 50 years and over, compared to donor males under 50 years. However, female donors under 50 years and male donors of any age performed equally. The question arises as to what happens to female collagen as estrogen levels fall, and if this makes it an unacceptable graft. It is known that the water content throughout the body decreases with aging, as does the concentration of collagen and the rate of collagen synthesis [2]. Blevins et. al found a decrease in modulus of elasticity of patellar tendon grafts as donor age increased from 17 to 54 [3]. Similarly, it has been found that, for the native ACL, cadaver specimens under 35 years can withstand a load 328% that of cadaver specimens over age 60 [29]. The loss of sex steroid hormones in females over 50 years induces gender-related changes in elastin and collagen metabolism [22]. The ACL graft is a collagen matrix with a structural scaffold on which new cells can integrate and vascularize and ultimately ligamentize [7]. We hypothesise that the hormonal changes in older females may adversely affect the collagen scaffold graft, resulting in an impaired process of ligamentization and subsequently higher rates of ACL graft rupture.

Single stranded grafts (patellar tendon and Achilles tendon) were found to have higher rates of ACL graft rupture compared to multi-strand grafts (tibialis anterior and tibialis posterior). Graft were not randomly allocated but dictated by what was available from the tissue bank. There was a period of several months in which tibialis tendons were difficult to obtain from the bank. Additionally, there was an element of selection bias from the surgeon, in that tendons which required larger tunnel diameters (PT and AT) were used for larger patients, as such there were significantly more male patients who received single stranded grafts (n=102 males vs. n=32 females, p= 0.001). Male subjects had a higher rate of graft rupture (27% vs. 6% females), however, the influence of graft morphology remained significant even when controlled for subject sex in the regression analysis.

When subject sex variable is controlled for, the single strand grafts are still 3.0 times more likely to rupture, than the multi-strand grafts. Possible explanations for this may include the variations in shape of the graft; single strand grafts are ribbon shaped and multi-strand grafts are tubular. This results in a difference in cross-sectional area. A multi-strand, tubular graft measured as 8mm will have a cross sectional area of roughly 50mm^2, however a ribbon graft (average thickness of patellar tendon 3.54mm and Achilles tendon 4.61) [10] will have an area of 28.3-36.9mm^2. It has previously been recognized that there is a strong positive relationship between maximal load to failure and the cross-sectional area of the graft [14]. Another theory could include the shape of the scaffolding on which new cells can grow. Incorporation of new cells is believed to arise from the periphery of the graft and proliferate down the length of the graft [16]. In a multi-strand graft there are several strands on which cells can travel compared to one large strand. This may alter the time to ligamentization and may reflect why within the first 16 months of our study, all graft ruptures were in single strand grafts. The lower ACL graft rupture rate in the multi-strand grafts could also be a result of which tendon was harvested. The Achilles tendon is recognized to have relatively poor vascularity with blood supply predominantly arising from the paratenon and musculotendinous junction [1], comparatively, the tibialis anterior tendon has complete blood supply without any evidence of avascular zones [23], perhaps affecting the overall strength of the tendon. In vivo, the Achilles tendon and patellar tendon are under significant load, and more prone to rupture compared to tibialis anterior tendons, thus there may be greater degenerative changes in these high load tendons. Furthermore, there has been shown to be lower ratios of collagen fibrils to interstitium in patellar tendon compared to other tendon types [13]. Thus, the blood supply in vivo, load through the tendon and the architecture of the tendon being used as a graft may be important to consider. This, however, is all speculation and further research on the properties and structure of the allograft should be considered in the future.

The overall ACL graft rupture rate of the allograft at two years was 23.5%. This rate of re-injuries in a population under 25 years is relatively consistent throughout the literature, regardless of graft type. Wiggins et.al. found on systematic review that the overall rate of graft rupture was 15%, but for athletes under the age of 25, the ACL injury rate was 23% within 5 years [28]. Although we did not directly compare to hamstring autograft in this study, previous studies from the same institution may function as a historical match of this patient population, using the same surgeons, surgical technique and rehabilitation protocol [4, 21]. In a cohort of 673 subjects, with a mean age of 29 years, hamstring tendon autografts have been found to have an overall rate of ACL graft rupture of 11% over 15 years [4], and in a study of 288 adolescents the graft rupture rate was 17% in 15 years [21]. The rate of graft rupture within 2 years was 7% in the adult cohort and 8% in the adolescents. The overall allograft rupture rate in the current study is higher than our autograft cohort, however when the preferred graft characteristics were targeted (multi-stranded, male donor or female donor under 50 years), then the rupture rate of 7.5% at two years is consistent with our previous findings with hamstring autografts.

There was no significant difference in IKDC scores by graft type or donor characteristics. However, in the nine subjects with intact grafts from female donors 50 years and over, only 44.4% returned to participating in very strenuous activities, compared to 72-75% of participants with donor grafts from females aged 50 or younger or males. This appears to be a possible trend and the low number of subjects in the group may prevent it from reaching significance. A larger cohort of patients may help illustrate this difference. A limitation of this study is the lack of objective follow up to determine clinical laxity and possible attenuation of the graft. Objective evaluation was collected on 89 subjects at two year, however given the low rate of follow up was not formally included in the study. Amongst those subjects examined, there was no significant difference in laxity on KT-1000 between the donor sex, age or the morphology of the graft (p=0.823 for age and sex, p=0.415 for morphology).

Along with the surgical bias, the short-term follow-up does not indicate how the allograft will perform in the long-term. Although most re-injuries do occur within the first two years [25], future follow up would certainly be beneficial to determine the outcomes of allografts in the long-term and is planned in this cohort. Furthermore, a more comprehensive evaluation of graft size may reveal a reason for the rates of rupture for the different morphology of the grafts.

Graft choice is a fundamental principle of ACL reconstructive surgery. The ideal graft is one which provides a stable knee, which allows for early rehabilitation and return to level of activity, without causing significant morbidity from graft harvest. This study shows that, when carefully selected, non-irradiated fresh frozen allografts are an acceptable alternative to use in a young active population. When the preferred characteristics are targeted, multi-stranded and from a female donor under 50 years old or a male donor, then the re-injury rates are significantly lower, 7.5% compared to 30.2% in the 'non-preferred' group. This suggests that the characteristics of the donor and the morphology of the allograft are integral components to consider in ACL reconstructive surgery.

Conclusion

Fresh frozen allografts may be an acceptable graft choice for ACL reconstruction in the young, active population when the graft is carefully selected. The age and sex of the donor, and the graft morphology significantly influence the rates of ACL graft rupture. Tendons from female donors over the age of 50 should be avoided given the higher early re-rupture rates compared to donor tendons from males of any age and young females, and multiple strand tendon allografts may be preferable to single strand tendon allografts.

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